CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 103000 S-5215

Trade Name: Botox Injection

Generic Name: onabotulinumtoxinA

Sponsor: Allergan, Inc.

Approval Date: October 15, 2010

Indications: Prophylaxis of headaches in adults with chronic migraine.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 103000/5215

APPROVAL
October 15, 2010

Allergan, Inc.
Attention: Mary O'Sullivan, MPH
Senior Director, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612-1599

Dear Ms. O'Sullivan:

Please refer to your supplemental Biologics License Application (sBLA), dated September 28, 2009, received September 29, 2009, submitted under section 351 of the Public Health Service Act for Botox® (onabotulinumtoxinA) Injection.

We also acknowledge receipt of the following amendments dated:

January 6, 2010	May 3, 2010	July 14, 2010	October 14, 2010
January 26, 2010 (2)	May 4, 2010	September 7, 2010	
March 22, 2010	July 1, 2010	October 6, 2010	
April 9, 2010	July 7, 2010	October 11, 2010	

This "Prior Approval" efficacy supplement to your BLA provides for a new indication for the prophylaxis of headaches in adults with chronic migraine.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm that is identical in content to the enclosed labeling text (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U

CM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 103000/5215.**"

Also within 14 days, amend all pending supplemental applications for this BLA, including pending CBE supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

The SPL will be accessible via publicly available labeling repositories.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 11 years because necessary studies are impossible or highly impracticable. This is because chronic migraine is rare in children under 12 years of age (as chronic migraine typically develops after several years of episodic migraine, which is relatively infrequent below age 12).

We are deferring submission of your pediatric studies for ages 12 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. Deferred pediatric Placebo-Controlled Efficacy and Safety Study under PREA for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include a prospective baseline observation period of at least 4 weeks followed by a double-blind treatment phase of at least 12 weeks. The study must include an adequate evaluation of dose-response. The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities and allow the use of appropriate rescue treatment. The protocol for this study must be submitted as a Special Protocol Assessment (SPA) and receive Division concurrence prior to the initiation of the study.

Final Protocol Submission: March 31, 2011
Study Completion: September 30, 2016
Final Report Submission: September 30, 2017

2. Deferred pediatric 12-month Open-Label Safety Study under PREA for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include at least 300 patients who received two BOTOX treatments at clinically relevant doses over a 6-month period (with at least 100 patients treated at the maximum recommended dose), and at least 100 patients who received four BOTOX treatments at clinically relevant doses over a 12-month period (with at least 60 patients treated at the maximum recommended dose). The study must assess local reactions, distant spread of toxin effects, BOTOX effects on blood glucose, and BOTOX effects on alkaline phosphatase (as a marker of bone metabolism). The safety study must include an adequate evaluation of immunogenicity.

Final Protocol Submission: March 31, 2011
Study Completion: September 30, 2017
Final Report Submission: September 30, 2018

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**".

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Botox® (onabotulinumtoxinA) was originally approved on July 31, 2009 and a REMS modification was approved on March 9, 2010. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of a revised Medication Guide which includes the addition of the indication for which you are seeking approval.

Your proposed modified REMS, submitted on October 6, 2010 and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on July 31, 2009.

There are no changes to the REMS assessment plan described in our July 31, 2009 letter.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must

include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 103000
REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 103000-PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to CDERMedWathSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please contact Ms. Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Package Insert
REMS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103000\5215

FILING ISSUES

Allergan
Attention: Mary O'Sullivan, MPH
2525 Dupont Dr
PO Box 19534
Irvine, CA 92623-9534

DEC 10 2009

Dear Ms. O'Sullivan:

Please refer to the supplement to your biologics license application (BLA), dated September 28, 2009, received September 29, 2009, submitted under section 351 of the Public Health Service Act for Botox (onabotulinumtoxinA). Also refer to our filing letter dated November 25, 2009.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

We also request that you submit the following information:

1. Please provide a justification for the muscle groups injected, the number of sites injected per muscle and the amount per injection used in the Phase 3 trials.

2. Please provide complete explanation of training and quality assurance of investigator's injection technique for Protocols 79 and 80.

3. Please provide tabulation and listing of all concomitant drugs used by patients enrolled in the individual Phase 3 trials and the Pooled Phase 3 trials during the DBPC phase.

4. Please code and tabulate, using MedDRA SMQ, all reports of drug ineffectiveness, lack of efficacy and similar reports including such information found in the "other" field for discontinuation for patients in the Phase 3 trials. Please include patient listing by study and treatment assignment for the events included in the SMQ for lack of efficacy that include the timing of the event with regard to the most recent treatment cycle and the associated outcome.

5. Please describe and provide copies of any materials used to guide patients on post-injection care and behavior.

6. Please provide "all cause, all events" tables for Protocols 37, 509, 38, 39, 79, 80 using MedDRA lower level term (LLT) and preferred term (PT). Prepare a table using the LLT term and the PT term for each individual trial. Please provide the aggregate tables, similar to the tables in the ISS, using the LLT.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 103000\5215

FILING ISSUES

Allergan
Attention: Mary O'Sullivan, MPH
2525 Dupont Dr
PO Box 19534
Irvine, CA 92623-9534

NOV 2 5 2009

Dear Ms. O'Sullivan:

Please refer to your biologics license application (BLA) dated September 28, 2009, received September 29, 2009, submitted under section 351 of the Public Health Service Act for Botox (onabotulinumtoxinA).

We have completed an initial review of your application for onabotulinumtoxinA to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The user fee goal date is July 30, 2010. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

Your request for priority review is denied, as several drug products are already approved for the prophylaxis of migraine headache, without any restriction regarding the frequency of headache events. Your proposed indication constitutes only a subset of the approved indication, and your application does not contain evidence supporting that onabotulinumtoxinA provides a significant improvement compared to marketed products.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 9, 2010.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We note that you have submitted a request for a full waiver of pediatric studies, and are reviewing your request.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

LABELING

BLA STN 103000/5215 – FDA APPROVED LABELING TEXT

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.

BOTOX (onabotulinumtoxinA)
Initial U.S. Approval: 1989

WARNING: Distant Spread of Toxin Effect
See full prescribing information for complete boxed warning.
The effects of **BOTOX** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

RECENT MAJOR CHANGES
- Indications and Usage, Chronic Migraine (1.1) 10/2010
- Indications and Usage, Upper Limb Spasticity (1.2) 3/2010
- Dosage and Administration, Chronic Migraine (2.2) 10/2010
- Dosage and Administration, Upper Limb Spasticity (2.3) 3/2010
- Warnings and Precautions (5.3, 5.6, 5.9) 3/2010

INDICATIONS AND USAGE
BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) (1.1)
- Treatment of upper limb spasticity in adult patients (1.2)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.3)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.4)
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.5)
- Treatment of strabismus in patients ≥12 years of age (1.5)

Important limitations:
- Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month).
- Safety and effectiveness of **BOTOX** have not been established for the treatment of upper limb spasticity in pediatric patients, and for the treatment of lower limb spasticity in adult and pediatric patients.
- Safety and effectiveness of **BOTOX** for hyperhidrosis in body areas other than axillary have not been established.

DOSAGE AND ADMINISTRATION
- Indication specific dosage and administration recommendations should be followed; Do not exceed a total dose of 360 Units administered every 12 to 16 weeks or at longer intervals (2)
- See Preparation and Dilution Technique for instructions on **BOTOX** reconstitution, storage, and preparation before injection (2.1)
- Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.2)
- Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.3)
- Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients (2.4)
- Axillary Hyperhidrosis: 50 Units per axilla (2.5)
- Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.6)
- Strabismus: 1.25 Units-2.5 Units initially in any one muscle (2.7)

DOSAGE FORMS AND STRENGTHS
Single-use, sterile 50 Units, 100 Units, or 200 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection (3)

CONTRAINDICATIONS
- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.3, 6.2)
- Infection at the proposed injection site (4.2)

WARNINGS AND PRECAUTIONS
- Potency Units of **BOTOX** not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death (5.2)
- Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties (5.2, 5.4)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.4, 5.6)
- Corneal exposure and ulceration (5.7)
- Retrobulbar hemorrhages and compromised retinal circulation (5.8)
- Bronchitis and upper respiratory tract infections in patients treated for upper limb spasticity (5.9)

ADVERSE REACTIONS
In controlled studies, the most commonly observed adverse reactions (≥5% and >placebo) were:
- Chronic Migraine: neck pain, headache (6.1)
- Spasticity: pain in extremity (6.1)
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis (6.1)
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Patients receiving concomitant treatment of **BOTOX** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of **BOTOX** may be potentiated (7)

USE IN SPECIFIC POPULATIONS
- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the prophylaxis of headaches in chronic migraine, the treatment of upper limb spasticity and axillary hyperhidrosis, in patients under 16 years of age for the treatment of cervical dystonia, and in patients under 12 years of age for the treatment of blepharospasm and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

1 INDICATIONS AND USAGE

1.1 Chronic Migraine

BOTOX (onabotulinumtoxinA) for injection is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

Important limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

1.2 Upper Limb Spasticity

BOTOX is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

Important limitations
Safety and effectiveness of **BOTOX** have not been established for the treatment of other upper limb muscle groups, or for the treatment of lower limb spasticity. Safety and effectiveness of **BOTOX** have not been established for the treatment of spasticity in pediatric patients under age 18 years. **BOTOX** has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with **BOTOX** is not intended to substitute for usual standard of care rehabilitation regimens.

1.3 Cervical Dystonia
BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.4 Primary Axillary Hyperhidrosis
BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Important limitations
The safety and effectiveness of **BOTOX** for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive **BOTOX** for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of **BOTOX** have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

1.5 Blepharospasm and Strabismus
BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

2 DOSAGE AND ADMINISTRATION
The potency Units of **BOTOX** (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of **BOTOX** cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method */see Warnings and Precautions (5.1) and Description (11)].*

Injection specific dosage and administration recommendations should be followed. In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

The safe and effective use of **BOTOX** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX** must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyographic techniques is also required for treatment of strabismus and of upper limb spasticity, and may be useful for the treatment of cervical dystonia.

Use caution when **BOTOX** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

2.1 Preparation and Dilution Technique
BOTOX is supplied in single-use 50 Units, 100 Units, and 200 Units per vial. Prior to injection, reconstitute each vacuum-dried vial of **BOTOX** with sterile, non-preserved 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe (Dilution Table), and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix **BOTOX** with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. **BOTOX** should be administered within 24 hours after reconstitution. During this time period, reconstituted **BOTOX** should be stored in a refrigerator (2° to 8°C).

Dilution Instructions for BOTOX Vials (50 Units, 100 Units, and 200 Units)

Diluent* Added to 50 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 200 Unit Vial	Resulting Dose Units per 0.1 mL
1 mL	5 Units	1 mL	10 Units	1 mL	20 Units
2 mL	2.5 Units	2 mL	5 Units	2 mL	10 Units
4 mL	1.25 Units	4 mL	2.5 Units	4 mL	5 Units
		8 mL	1.25 Units	8 mL	2.5 Units
				10 mL	2 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the **BOTOX** dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

An injection of **BOTOX** is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile, needle and syringe should be used to enter the vial on each occasion for removal of **BOTOX**.

Reconstituted **BOTOX** should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

2.2 Chronic Migraine

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL (see Dilution Table). The recommended dose for treating chronic migraine is 155 Units administered intramuscularly (IM) using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams and Table 1 below. A 1 inch needle may be needed in the neck region for patients with thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck. The recommended re-treatment schedule is every 12 weeks.

Recommended injection sites for chronic migraine:

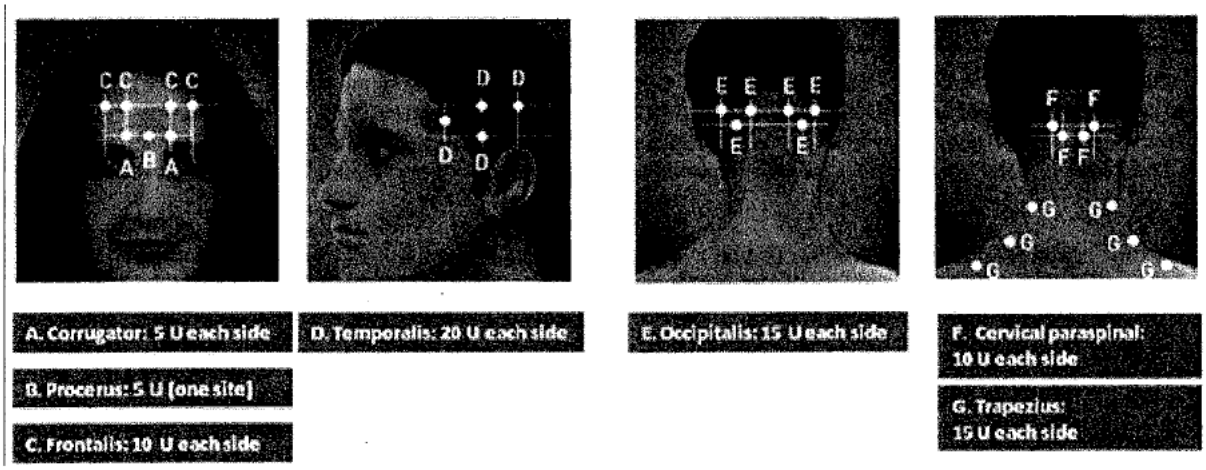


Table 1: BOTOX Dosing by Muscle for Chronic Migraine

Head/Neck Area	Recommended Dose (Number of Sites[a])
Frontalis[b]	20 Units divided in 4 sites
Corrugator[b]	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis[b]	30 Units divided in 6 sites
Temporalis[b]	40 Units divided in 8 sites
Trapezius[b]	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group[b]	20 Units divided in 4 sites
Total Dose:	**155 Units divided in 31 sites**

[a] Each IM injection site = 0.1 mL = 5 Units BOTOX
[b] Dose distributed bilaterally

2.3 Upper Limb Spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, or adverse event history with **BOTOX**. In clinical trials, doses ranging from 75 Units to 360 Units were divided among selected muscles at a given treatment session.

Table 2: BOTOX Dosing by Muscle for Upper Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Biceps Brachii	100 Units-200 Units divided in 4 sites
Flexor Carpi Radialis	12.5 Units-50 Units in 1 site
Flexor Carpi Ulnaris	12.5 Units-50 Units in 1 site
Flexor Digitorum Profundus	30 Units-50 Units in 1 site
Flexor Digitorum Sublimis	30 Units-50 Units in 1 site

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with 0.9% non-preserved sterile saline (see Dilution Table). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance or nerve stimulation techniques is recommended.

Repeat **BOTOX** treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of **BOTOX** and muscles to be injected.

2.4 Cervical Dystonia

The phase 3 study enrolled patients who had extended histories of receiving and tolerating **BOTOX** injections, with prior individualized adjustment of dose. The mean **BOTOX** dose administered to patients in the phase 3 study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The **BOTOX** dose was divided among the affected muscles *[see Clinical Studies (14.3)]*. Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of **BOTOX** should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscle to 100 Units or less may decrease the occurrence of dysphagia *[see Warnings and Precautions (5.2, 5.4, 5.5)]*.

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with 0.9% non-preserved sterile saline, depending on volume and number of injection sites desired to achieve treatment objectives (see Dilution Table). In general, no more than 50 Units per site should be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial

muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the phase 3 study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

2.5 Primary Axillary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Dilution Table). Using a 30 gauge needle, 50 Units of **BOTOX** (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

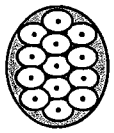
Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine-Starch Test Procedure:

Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks, etc. for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 1:

Figure 1:



Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface, with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject **BOTOX** directly through the ink mark to avoid a permanent tattoo effect.

2.6 Blepharospasm

For blepharospasm, reconstituted **BOTOX** is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units-2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Dilution Table).

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient, usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. Some tolerance may be found when **BOTOX** is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of **BOTOX** treatment for blepharospasm in a 30-day period should not exceed 200 Units.

2.7 Strabismus

BOTOX is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for **BOTOX** injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

Note: The volume of **BOTOX** injected for treatment of strabismus should be between 0.05-0.15 mL per muscle.

The initial listed doses of the reconstituted **BOTOX** *[see Dosage and Administration (2.1)]* typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

I. Initial doses in Units. Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
   A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
   B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
   C. For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

II. Subsequent doses for residual or recurrent strabismus.
   A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
   B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
   C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
   D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
   E. The maximum recommended dose as a single injection for any one muscle is 25 Units.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Dilution Table).

3 DOSAGE FORMS AND STRENGTHS

Single-use, sterile 50 Units, 100 Units, or 200 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection *[see Dosage and Administration (2.1)]*.

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions (5.3)]*.

4.2 Infection at the Injection Site(s)

BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [*see Description (11)*].

5.2 Spread of Toxin Effect

Postmarketing safety data from **BOTOX** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of the symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including

spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX/BOTOX Cosmetic** at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX** for blepharospasm at the recommended dose (30 Units and below), strabismus, or for chronic migraine at the labeled doses have been reported.

5.3 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of **BOTOX** should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

5.4 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved *[see Warnings and Precautions (5.2)]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

5.5 Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX** *[see Adverse Reactions (6.1)]*.

5.6 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity

Patients with compromised respiratory status treated with **BOTOX** for upper limb spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients with stable reduced pulmonary function (defined as FEV_1 40-80% of predicted value and $FEV_1/FVC \leq 0.75$), the event rate in change of Forced Vital Capacity $\geq 15\%$ or $\geq 20\%$ was generally greater in patients treated with **BOTOX** than in patients treated with placebo (see Table 3).

Table 3: Event rate per patient treatment cycle among patients with reduced lung function who experienced at least a 15% or 20% decrease in forced vital capacity from baseline at Week 1, 6, 12 post-injection with up to two treatment cycles with BOTOX or placebo

	BOTOX 360 Units		BOTOX 240 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX** *[see Warnings and Precautions (5.9)]*.

5.7 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

Reduced blinking from **BOTOX** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

5.8 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of **BOTOX** for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

5.9 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with **BOTOX** (3% at 251Units-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX** (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%).

5.10 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

6 ADVERSE REACTIONS

The following adverse reactions to **BOTOX** (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Contraindications (4.1) and Warnings and Precautions (5.3)]*
- Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia *[see Warnings and Precautions (5.4)]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions (5.9)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

BOTOX and **BOTOX Cosmetic** contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse events observed with the use of **BOTOX Cosmetic** also have the potential to be observed with the use of **BOTOX** and vice-versa.

In general, adverse events occur within the first week following injection of **BOTOX** and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions (5.2)]*.

Chronic Migraine
In double-blind placebo controlled chronic migraine pivotal efficacy trials (Study 1 and Study 2), the discontinuation rate was 12% in the **BOTOX**-treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the **BOTOX** group and 1% in the placebo group. The most frequent adverse events leading to discontinuation in the **BOTOX** group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis.

The most frequently reported adverse reactions following injection of **BOTOX** for chronic migraine appear in Table 4.

Table 4: Adverse Reactions Reported by ≥2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body Systems	BOTOX 155 Units-195 Units (N=687)	Placebo (N=692)
Nervous system disorders		
Headache	32 (5%)	22 (3%)
Migraine	26 (4%)	18 (3%)
Facial paresis	15 (2%)	0 (0%)
Eye disorders		
Eyelid ptosis	25 (4%)	2 (<1%)
Infections & Infestations		
Bronchitis	17 (3%)	11 (2%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (9%)	19 (3%)
Musculoskeletal stiffness	25 (4%)	6 (1%)
Muscular weakness	24 (4%)	2 (<1%)
Myalgia	21 (3%)	6 (1%)
Musculoskeletal pain	18 (3%)	10 (1%)
Muscle spasms	13 (2%)	6 (1%)
General disorders and administration site conditions		
Injection site pain	23 (3%)	14 (2%)
Vascular Disorders		
Hypertension	11 (2%)	7 (1%)

Other adverse events that occurred more frequently in the BOTOX group compared to the placebo group at a frequency less than 1% and potentially **BOTOX** related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of **BOTOX**-treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Upper Limb Spasticity
The most frequently reported adverse reactions following injection of **BOTOX** for adult spasticity appear in Table 5.

Table 5: Adverse Reactions Reported by ≥2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Adult Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX 251Units-360 Units (N=115)	BOTOX 150 Units-250 Units (N=188)	BOTOX <150 Units (N=54)	Placebo (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions				
Fatigue	4 (3%)	4 (2%)	1 (2%)	0
Infections and infestations				
Bronchitis	4 (3%)	4 (2%)	0	2 (1%)

Adverse Reactions by Body System	BOTOX 251Units-360 Units (N=115)	BOTOX 150 Units-250 Units (N=188)	BOTOX <150 Units (N=54)	Placebo (N=182)
Musculoskeletal and connective tissue disorders				
Pain in extremity	7 (6%)	10 (5%)	5 (9%)	8 (4%)
Muscular weakness	0	7 (4%)	1 (2%)	2 (1%)

Cervical Dystonia
In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of **BOTOX**, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of **BOTOX** resulting from the spread of the toxin outside the injected muscles *[see Warnings and Precautions (5.2, 5.4)]*.

The most common severe adverse event associated with the use of **BOTOX** injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea *[see Warnings and Precautions (5.2, 5.4)]*. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms *[see Warnings and Precautions (5.4)]*.

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of **BOTOX** for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis
The most frequently reported adverse events (3-10% of adult patients) following injection of **BOTOX** in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to **BOTOX** 50 Units and 110 patients exposed to **BOTOX** 75 Units in each axilla.

Blepharospasm
In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured **BOTOX**, the most frequently reported treatment-related adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder, reduced blinking from **BOTOX** injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus
Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of **BOTOX**. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%.

The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

6.2 Post-Marketing Experience

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions (5.3, 5.4)]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events, not already addressed elsewhere in the package insert, have been reported since the drug has been marketed: abdominal pain; anorexia; brachial plexopathy; diarrhea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoaesthesia; localized numbness; malaise; myalgia; paresthesia; pyrexia; radiculopathy; skin rash (including erythema multiforme, and psoriasiform eruption); tinnitus; vertigo; visual disturbances; and vomiting.

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to botulinum toxin.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX** treatment by inactivating the biological activity of the toxin.

In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of **BOTOX**, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to **BOTOX** therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to **BOTOX** therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), and no patients among 406 migraine patients with analyzed specimens showed the presence of neutralizing antibodies.

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to **BOTOX** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. For these reasons, comparison of the incidence of neutralizing activity to **BOTOX** with the incidence reported to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that **BOTOX** injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with **BOTOX** (onabotulinumtoxinA) for injection.

Co-administration of **BOTOX** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

Use of anticholinergic drugs after administration of **BOTOX** may potentiate systemic anticholinergic effects.

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX**.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. **BOTOX** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When **BOTOX** (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 1½ times the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

When **BOTOX** was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the average high human dose based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 3 times the average high human dose based on Units/kg.

8.3 Nursing Mothers

It is not known whether **BOTOX** is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **BOTOX** is administered to a nursing woman.

8.4 Pediatric Use

Prophylaxis of Headaches in Chronic Migraine

Safety and effectiveness in patients below the age of 18 years have not been established.

Spasticity

Safety and effectiveness in patients below the age of 18 years have not been established.

Cervical Dystonia

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Blepharospasm and Strabismus

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Axillary Hyperhidrosis

Safety and effectiveness in patients below the age of 18 years have not been established.

8.5 Geriatric Use

Clinical studies of **BOTOX** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Excessive doses of **BOTOX** (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis *[see Boxed Warning and Warnings and Precautions (5.2, 5.4)]*. Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

11 DESCRIPTION

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain Clostridium botulinum type A, and intended for intramuscular and intradermal use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

One Unit of **BOTOX** corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method utilized for performing the assay is specific to Allergan's product, **BOTOX**. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols for the various mouse LD_{50} assays, Units of biological activity of **BOTOX** cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes preclude extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of **BOTOX** is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of **BOTOX** contains either 50 Units of Clostridium botulinum type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride; 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride; or 200 Units of Clostridium botulinum type A neurotoxin complex, 1 mg of Albumin Human, and 1.8 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, **BOTOX** produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by **BOTOX**.

When injected intradermally, **BOTOX** produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

12.3 Pharmacokinetics

Using currently available analytical technology, it is not possible to detect **BOTOX** in the peripheral blood following intramuscular injection at the recommended doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals have not been performed to evaluate the carcinogenic potential of **BOTOX**.

Mutagenesis

BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicologic assays.

Impairment of Fertility
In fertility studies of **BOTOX** (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

14 CLINICAL STUDIES

14.1 Chronic Migraine
BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had ≥15 headache days lasting 4 hours or more, with ≥50% being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units **BOTOX** injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. **BOTOX** treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 6).

Table 6: Week 24 Key Efficacy Variables for Study 1 and Study 2

Efficacy per 28 days	Study 1		Study 2	
	BOTOX (N=341)	**Placebo (N=338)**	**BOTOX (N=347)**	**Placebo (N=358)**
Change from baseline in frequency of headache days	-7.8*	-6.4	-9.2*	-6.9
Change from baseline in total cumulative hours of headache on headache days	-107*	-70	-134*	-95

* Significantly different from placebo ($p \leq 0.05$)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 2), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 3), compared to placebo-treated patients.

Figure 2: Mean Change from Baseline in Number of Headache Days for Study 1

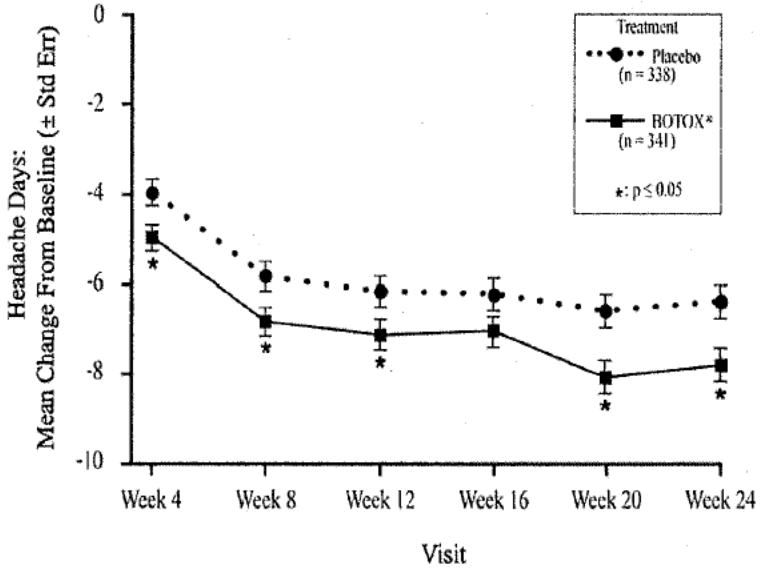
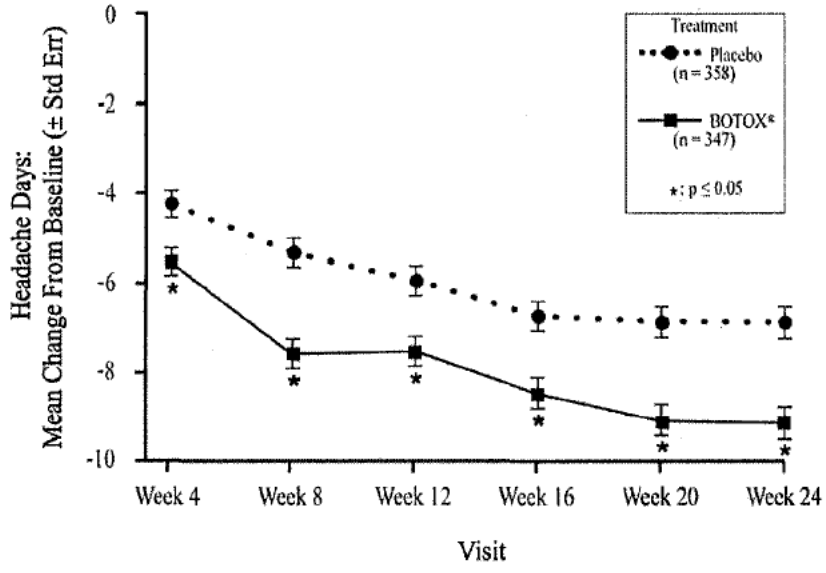


Figure 3: Mean Change from Baseline in Number of Headache Days for Study 2



14.2 Upper Limb Spasticity

The efficacy and safety of **BOTOX** for the treatment of upper limb spasticity were evaluated in three randomized, multi-center, double-blind, placebo-controlled studies.

Study 1 included 126 patients (64 **BOTOX** and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. **BOTOX** (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 7). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 7: Study Medication Dose and Injection Sites in Study 1

Muscles Injected	Volume (mL)	BOTOX (Units)	Number of Injection Sites
Wrist			
Flexor Carpi Radialis	1	50	1
Flexor Carpi Ulnaris	1	50	1
Finger			
Flexor Digitorum Profundus	1	50	1
Flexor Digitorum Sublimis	1	50	1
Thumb			
Adductor Pollicis[a]	0.4	20	1
Flexor Pollicis Longus[a]	0.4	20	1

[a] injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Possible scores range from 0 to 4:
0 = No increase in muscle tone (none)
1 = Slight increase in muscle tone, giving a 'catch' when the limb was moved in flexion or extension (mild)
2 = More marked increase in muscle tone but affected limb is easily flexed (moderate)
3 = Considerable increase in muscle tone - passive movement difficult (severe)
4 = Limb rigid in flexion or extension (very severe).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 8.

Table 8: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

	BOTOX (N=64)	**Placebo (N=62)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†[a]	-2.0*	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††[b]	-1.0*	0.0
Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale††[c]	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment††	2.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[b] **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[c] **BOTOX** injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of **BOTOX** with placebo and included 91 patients [**BOTOX** 360 Units (N=21), **BOTOX** 180 Units (N=23), **BOTOX** 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. **BOTOX** and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 9).

Table 9: Study Medication Dose and Injection Sites in Study 2 and Study 3

	Total Dose				
Muscles Injected	**BOTOX low dose (90 Units)**	**BOTOX mid dose (180 Units)**	**BOTOX high dose (360 Units)**	**Volume (mL) per site**	**Injection Sites (n)**
Wrist					
Flexor Carpi Ulnaris	10 Units	20 Units	40 Units	0.4	1
Flexor Carpi Radialis	15 Units	30 Units	60 Units	0.6	1
Finger					
Flexor Digitorum Profundus	7.5 Units	15 Units	30 Units	0.3	1
Flexor Digitorum Sublimis	7.5 Units	15 Units	30 Units	0.3	1
Elbow					
Biceps Brachii	50 Units	100 Units	200 Units	0.5	4

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 10.

Table 10: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2

	BOTOX low dose (90 Units) (N=21)	**BOTOX mid dose (180 Units) (N=23)**	**BOTOX high dose (360 Units) (N=21)**	**Placebo (N=26)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†[b]	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††[c]	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale††[d]	-0.5	-1.0*	-0.5[a]	-0.5
Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] $p=0.053$
[b] Total dose of **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of **BOTOX** injected into biceps brachii muscle

Study 3 compared 3 doses of **BOTOX** with placebo and enrolled 88 patients [**BOTOX** 360 Units (N=23), **BOTOX** 180 Units (N=23), **BOTOX** 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. **BOTOX** and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 9).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 11.

Table 11: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

	BOTOX low dose (90 Units) (N=23)	**BOTOX mid dose (180 Units) (N=21)**	**BOTOX high dose (360 Units) (N=22)**	**Placebo (N=19)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†[b]	-1.0	-1.0	-1.5*	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††[c]	-1.0	-1.0	-1.0*	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale†[d]	-0.5	-0.5	-1.0*	-0.5

† Primary endpoint at Week 4
†† Secondary endpoints at Week 4
* Significantly different from placebo ($p \leq 0.05$)
[b] Total dose of **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles

[c] Total dose of **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of **BOTOX** injected into biceps brachii muscle

14.3 Cervical Dystonia

A phase 3 randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received **BOTOX** in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of **BOTOX**. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the **BOTOX** group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 12.

Table 12: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

	Placebo (N=82)	BOTOX (N=88)	95% CI on Difference
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3)[a,b]
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%)[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2)[c]
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0)[c]

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.
[c] Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

There were several randomized studies conducted prior to the phase 3 study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of **BOTOX**.

In the phase 3 study the median total **BOTOX** dose in patients randomized to receive **BOTOX** (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 13. The total dose and muscles selected were tailored to meet individual patient needs.

Table 13: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

Muscle	Number of Patients Treated in this Muscle (N=88)	Mean % Dose per Muscle	Mid-Range of % Dose per Muscle*
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

*The mid-range of dose is calculated as the 25th to 75th percentiles.

14.4 Primary Axillary Hyperhidrosis

The efficacy and safety of **BOTOX** for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities". A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of **BOTOX**, 75 Units of **BOTOX**, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both **BOTOX** groups than in the placebo group ($p<0.001$), but was not significantly different between the two **BOTOX** doses (see Table 14).

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in **BOTOX**-treated patients with either dose was 201 days. Among those who received a second **BOTOX** injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of **BOTOX** (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the **BOTOX** group and 36% (28/78) in the placebo group, $p<0.001$. The difference in percentage of responders between **BOTOX** and placebo was 55% (95% CI=43.3, 65.9).

Table 14: Study 1 - Study Outcomes

Treatment Response	BOTOX 50 Units (N=104)	BOTOX 75 Units (N=110)	Placebo (N=108)	BOTOX 50-placebo (95% CI)	BOTOX 75-placebo (95% CI)
HDSS Score change ≥2 (n)[a]	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production % (n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

[a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

14.5 Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of **BOTOX** at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

14.6 Strabismus

Six hundred seventy-seven patients with strabismus treated with one or more injections of **BOTOX** were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX is supplied in a single-use vial in the following sizes:
50 Units NDC 0023-3920-50
100 Units NDC 0023-1145-01
200 Units NDC 0023-3921-02

Vials of **BOTOX** have a holographic film on the vial label that contains the name "Allergan" within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/lot area.) If you do not see the lines of rainbow color or the name "Allergan", do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

Storage

Unopened vials of **BOTOX** should be stored in a refrigerator (2° to 8°C) for up to 36 months for the 100 Units vial or up to 24 months for the 50 Units and 200 Units vial. Do not use after the expiration date on the vial. Administer **BOTOX** within 24 hours of reconstitution; during this period reconstituted **BOTOX** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX** should be clear, colorless, and free of particulate matter.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully, as is done with all medical waste.

Rx Only

17 PATIENT COUNSELING INFORMATION

Provide a copy of the Medication Guide and review the contents with the patient.

17.1 Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

Patients should be advised to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens *[see Boxed Warning and Warnings and Precautions (5.2, 5.4)]*.

17.2 Ability to Operate Machinery or Vehicles

Patients should be counseled that if loss of strength, muscle weakness, blurred vision, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

17.3 Medication Guide

MEDICATION GUIDE
BOTOX®
BOTOX® Cosmetic
(Boe-tox)
(onabotulinumtoxinA)
for Injection

Read the Medication Guide that comes with **BOTOX** or **BOTOX Cosmetic** before you start using it and each time it is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

What is the most important information I should know about BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

- **Problems swallowing, speaking, or breathing. These problems can happen hours to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.
- People with certain breathing problems may need to use muscles in their neck to help them breathe. These patients may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
    - loss of strength and muscle weakness all over the body
    - double vision
    - blurred vision and drooping eyelids
    - hoarseness or change or loss of voice (dysphonia)
    - trouble saying words clearly (dysarthria)
    - loss of bladder control
    - trouble breathing
    - trouble swallowing

These symptoms can happen hours to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic**.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX** or **BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines.

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:

- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary).

It is not known whether **BOTOX** is safe or effective in patients younger than:
- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX and BOTOX Cosmetic** are safe or effective to prevent headaches in patients with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

Who should not take BOTOX or BOTOX Cosmetic?

Do not take **BOTOX** or **BOTOX Cosmetic** if you:
- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc®, Dysport®, or Xeomin®*
- have a skin infection at the planned injection site

What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?

Tell your doctor about all your medical conditions, including if you have:
- a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- a breathing problem, such as asthma or emphysema
- swallowing problems
- bleeding problems
- plans to have surgery
- had surgery on your face
- weakness of your forehead muscles, such as trouble raising your eyebrows
- drooping eyelids
- any other change in the way your face normally looks
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*® (rimabotulinumtoxinB), *Dysport*® (abobotulinumtoxinA), or *Xeomin*® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles or skin.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.

What should I avoid while taking BOTOX or BOTOX Cosmetic?

BOTOX and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, or vision problems within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic. If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about BOTOX and BOTOX Cosmetic:
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that

is written for healthcare professionals. For more information about **BOTOX** and **BOTOX Cosmetic** call Allergan at 1-800-433-8871 or go to www.botox.com.

What are the ingredients in BOTOX and BOTOX Cosmetic?
Active ingredient: botulinum toxin type A
Inactive ingredients: human albumin and sodium chloride

Issued: 10/2010

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc.
2525 Dupont Dr.
Irvine, CA 92612

U.S. Patents 6,974,578; 6,683,049; and 6,896,886

Myobloc® is a registered trademark of Solstice Neurosciences, Inc.
Dysport® is a registered trademark of Ipsen Biopharm Limited Company.
Xeomin® is a registered trademark of Merz Pharma GmbH & Co KGaA.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

OFFICE DIRECTOR MEMO

Pkg

MEMORANDUM

DATE: October 10, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, BLA 103000/5215

SUBJECT: Action Memo for BLA 103000/5215, for the use of Botox (onabotulinumtoxinA) Injection as prophylaxis for patients with chronic migraine

BLA 103000/5215, for the use of Botox (onabotulinumtoxinA) Injection as prophylaxis for patients with chronic migraine, was submitted by Allergan, Inc., on 9/28/09. The application includes the results of two randomized controlled trials in patients with chronic migraine (Studies 79 and 80), as well as safety data.

Botox is currently approved for the treatment of blepharospasm, cervical dystonia, strabismus, hyperhidrosis, and upper limb spasticity. The current submission has been reviewed by Dr. Suhail Kasim, medical reviewer, Dr. Xiang Ling, statistician, Dr. Cheryl Graham, safety reviewer, Dr. Sally Yasuda, safety team leader, Dr. Antoine El-Hage, Division of Scientific Investigations, Walter Fava and Dr. Marcia Britt, Division of Medication Error Prevention and Analysis, Steve Morin, Division of Risk Management, Drs. Quynh-Van Tran and Beth Carr, Division of Drug Marketing, Advertising, and Communications, Jeanine Best, Pediatric and Maternal Health Staff, and Dr. Eric Bastings, neurology team leader.

The review team recommends that the application be approved.

I agree.

As noted by the clinical team, the sponsor had performed numerous controlled trials in patients with various headache syndromes (e.g., episodic migraine, chronic daily headache), none of which demonstrated a beneficial effect of Botox compared to placebo. Nonetheless, the applicant, based on sub-group analyses of patients with chronic migraine headache in several of these studies, decided to perform prospective studies in this latter population.

Effectiveness

As noted by the review team, patients with chronic migraine enrolled in these two trials (Studies 79 and 80) had a history of headaches for at least 15 days/month, with the headaches lasting at least 4 hours/day, and at least 50% of the

headaches must have met criteria for migraine or probable migraine. Further, patients had to have had had least 4 distinct headache episodes/month.

The design of studies 79 and 80 were essential identical, with Study 79 performed in the US and Canada, and Study 80 performed in the US, Germany, Canada, the UK, Croatia, and Switzerland.

As discussed by Drs. Kasim and Bastings, the sponsor chose as the primary outcome in Study 79 the change in the frequency of headache episodes. However, in discussions with the Agency before the study started, we had argued strongly that the primary outcome should be the change in frequency in headache days, for the reasons described by Dr. Bastings. Nonetheless, the sponsor chose headache events as the primary outcome, with headache days, as well as other outcomes, as secondary.

When Study 79 was analyzed, the change in headache events did not reach statistical significance. As a result, the sponsor changed the primary outcome in Study 80 (which was almost completed, but still blinded) to change in headache days (in the protocol, the primary outcome in this study was also change in headache events).

Briefly, in these studies, patients were randomized to receive 2 courses of treatment: either Botox on Day 0 and at Week 12, or placebo on Day 0 and at Week 12. Each treatment course consisted of injections in 7 muscle groups, with a total of at least 155 units. Additional doses up to a total of 195 units could be given at the discretion of the investigator (see Dr. Kasim's Table 24, page 56 for details about the dose/injection site). The 155 unit dose was to be divided into 31 injections; the higher dose could be given in up to 39 injections.

Patients were not permitted to receive other prophylactic treatments.

The primary outcome was the change in headache events in Study 79 and change in headache days in Study 80 for Weeks 20-24. That is, the study consisted of a 24 week observation period, with the primary outcomes being assessed in the last 4 weeks (which represented the 4 week period beginning 20 weeks after the initial treatment and 8 weeks after the second treatment). The primary outcomes were also assessed every 4 weeks. In both studies, other outcomes were also assessed at this (and other) time periods, including the frequency of migraine/probably migraine days, and the frequency of probable migraine/migraine episodes.

As described by the review team, in Study 79, the between-treatment difference on the primary outcome (change in headache events) did not reach significance at any time point. In Study 80, the primary outcome (change in headache days) reached significance at all time points (Weeks 4, 8, 12, 16, 20, and 24), and very robustly ($p<0.001$ at all time points save week 4; $p=0.002$). Importantly, the

between-treatment contrasts for change of headache days in Study 79 (a secondary outcome in this study, but, as described earlier, the Agency's recommendation for primary in this study), reached significance at all time points, except at Week 16 (p=0.08), and, especially at Week 24 (the protocol specified time point for the primary analysis; p=0.006).

In addition, the change in the number of probable migraine/migraine days reached statistical significance at all time points in both studies (see Dr. Kasim's Table 30, page 72). Further, the change in the number of moderate/severe headaches reached significance at all time points in both studies except at Week 16 in Study 79; p=0.09; see Dr. Kasim's Table 31, page 73).

An analysis of only those patients who received 155 units was performed. This represented about 50% of the patients in Study 79, and about 61% of the patients in Study 80. The change in frequency of headache days reached significance in both studies, as did the cumulative number of hours of headache on headache days (see Dr. Kasim's Table 43, page 87-8).

Safety

The safety data submitted in this application included data from the multiple trials described above, and consisted of 3235 patients who received at least one dose of Botox. A total of 1300 patients received at least 155 Units every 12 weeks; 518 patients received at least 5 treatments every 12 weeks (patients in Studies 79 and 80 were permitted to receive up to 3 additional open-label treatments). A total of 1997 patients with chronic daily headache or chronic migraine received at least one dose of Botox. A total of 132 patients received 3 treatments of at least 200 units every 12 weeks. A total of 687 patients received Botox in Studies 79 and 80 compared to 692 placebo patients.

There were no deaths in patients treated with Botox.

In Studies 79 and 80, 33/687 (4.8%) of Botox and 16/692 (2.3%) of patients experienced a serious adverse event (SAE), with most of the imbalances in neoplasms and migraine (0.6% vs 0.1%). In the combined Phase 3 experience, 13/3235 (4.2%) had an SAE. In pooled placebo controlled studies, 83/2532 (3.3%) of Botox treated and 36/1544 (2.3%) had an SAE with migraine, headache, and depression reported more frequently on Botox compared to placebo. There were 5 SAE reports of migraine headache.

In pooled Phase 3 controlled trials, 12% of Botox and 10% of placebo patients discontinued treatment due to an adverse event. In Studies 79 and 80, 26/687 (3.8%) of Botox and 8/692 (1.2%) of placebo patients discontinued due to an adverse event. In the Botox patients, migraine, headache, and weakness were reported in 3 patients each. Similar events led to discontinuation in the open-label phase.

In pooled Phase 3 studies, 34/1544 (2.2%) of placebo and 658/2532 (25.9%) of Botox-treated patients had at least one event that corresponded to at least one term that could have been related to the spread of the toxin. The vast majority of these events represented local effects (e.g., ptosis, diplopia, dysarthria, dysphagia, etc.). A total of 10 Botox and 2 placebo patients experienced dyspnea (of the Botox patients, one had a positive re-challenge, and 9 did not experience dyspnea again with repeated dosing). A total of 9% of Botox and 0.5% of placebo patients, but only 5 patients had weakness outside of the muscles injected.

Other adverse events were similar to those already known to be caused by Botox.

Currently, a REMS exists for Botox (because of the existing Medication Guide). The medication guide will be updated to include the new indication, and the sponsor will issue a Dear Health Care Practitioner letter describing the risks of the treatment. These elements (Med Guide and letter, the latter constituting a Communication Plan) constitute the revised REMS. In addition, the sponsor will undertake an extensive educational campaign to instruct practitioners in the correct dosing of patients with chronic migraine, given the rather complex (7 muscle groups, (b) (4) 32 injection sites) treatment for this new indication.

Comments

The sponsor has submitted the results of two controlled trials that clearly establish substantial evidence of effectiveness for Botox as prophylaxis of migraine in patients with chronic migraine (at least 15 headache days a month with at least 4 hours of headache/headache day. Although the between-treatment difference on the prospectively designated primary outcome in Study 79 did not reach statistical significance, the analysis of the primary outcome that we had strongly recommended be chosen (headache days) did reach clear significance in that study, and that finding was replicated, prospectively, in Study 80. In addition, numerous relevant secondary outcomes in both studies reached clear, unequivocal significance. Further, the sponsor has submitted sufficient exposure to the effective dose, and no new adverse events not previously known to be associated with the use of Botox have been seen.

Given the considerations described above, I will issue the attached Approval letter, with appended product labeling, with which the sponsor and we have agreed.

10/15/10

Russell Katz, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	103000/5215
Applicant	Allergan
Date of Submission	September 29, 2009
PDUFA Goal Date	October 29, 2010
Proprietary Name / Established (USAN) names	BOTOX (onabotulinumtoxinA)
Dosage forms / Strength	Intramuscular injection
Proposed Indication(s)	Prophylaxis of Headaches in Adults with Chronic Migraine
Recommended:	Approval

1. Introduction

OnabotulinumtoxinA (BOTOX) is an acetylcholine release inhibitor and a neuromuscular blocking agent currently approved for the treatment of hyperhidrosis, cervical dystonia, strabismus, blepharospasm, upper limb spasticity. In this supplemental BLA, the sponsor is proposing a new indication: prophylaxis of headaches in adults with chronic migraine.

The application was reviewed by the following FDA staff:

Project Manager: Lana Chen, Pharm.D.
Clinical Safety: Cheryl Graham, MD and Sally Yasuda, Pharm.D.
Clinical Efficacy: Suhail Kasim, MD.
Statistics: Xiang Ling, Ph.D., Kun Jin, Ph.D., and Kooros Mahjoob, Ph.D.
DRISK (Med Guide): Steve Morin, RN, BSN, LaShawn Griffiths, MSHS-PH, BSN, RN, and Mary Willy, Ph.D.
DRISK (REMS): Marcia Britt, Ph.D., Kendra Worthy, Pharm.D., Suzanne Robottom, Pharm.D, and Claudia Karwoski, Pharm.D.
DMEPA: Walter Fava RPh, MSEd and Denise P. Toyer, Pharm.D.
DDMAC: Quynh-Van Tran, PharmD, BCPP and Beth Carr, PharmD
Maternal Health: Jeanine Best, MSN, RN, PNP, Karen Feibus, MD, and Lisa Mathis, MD.
DSI: Antoine EI-Hage, Ph.D, and Tejashr Purohit-Sheth, M.D.

2. Background

As discussed by Dr. Kasim, a number of treatments are approved for the prophylaxis of migraine. These include beta blockers propanolol and timolol, and epilepsy drugs topiramate and divalproex sodium. Historically, migraine prophylaxis studies have been conducted in patients who have 14 migraine headache days or less (i.e. "episodic" migraine), mostly with the goal to making it easier to identify discrete migraine attacks and better quantify the treatment effect in clinical trials. The indication for migraine prophylactic drugs has, however, not been limited to patients experiencing a specific number of migraine attacks, and these drugs are de facto approved for patients who have a headache on more than 14 days per month. In recent years, the concept of chronic migraine, i.e. migraine patients experiencing headache on more than 14 days per month, has been increasingly recognized, and identified as an debilitating form of migraine in need of specific attention.

Allergan first evaluated BOTOX for the treatment of episodic migraine, in seven controlled studies, which all failed to demonstrate a significant clinical effect. Allergan later focused on the treatment of chronic migraine, and the studies part of that development program are the object of the current supplement. Because Allergan studies were conducted while the international headache society (IHS) diagnostic criteria for chronic migraine were evolving, inclusion criteria in chronic migraine BOTOX studies were not strictly based on IHS criteria[1], but they are similar. Allergan studied migraineurs with ≥15 headache days per 4 week period. To be counted as a headache day, the patient had to experience ≥4 hours of continuous headache, and ≥50% of headache days had to fulfill IHS criteria for migraine or probable migraine[2]. In addition, patients had to experience ≥4 distinct headache episodes each lasting ≥4 hours.

The primary endpoint used in the pivotal chronic migraine studies was the object of discussions between FDA and Allergan. FDA strongly recommended that Allergan evaluate "headache days" as the primary efficacy endpoint, as opposed to the "frequency of headache episodes". FDA was concerned that in patients with frequent headache, that outcome would be unreliable, as the duration of discrete episodes may vary wildly (e.g. an episode could last as little as 4 hours or as long as 27 days). FDA indicated that if the "frequency of headache episodes" endpoint indicated success, but the "headache days" endpoint did not, interpretation of the study results would be difficult. Allergan opted nevertheless to use headache episodes as a primary endpoint in the first pivotal trial, Study 191622-079. As discussed below, BOTOX failed to be superior to placebo for the frequency of headache episodes in that study,

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1 A formal definition for chronic migraine was first introduced in 2000 in the 2nd edition of the International Headache Classification. Because the original criteria were felt to be too restrictive, the International Headache Society Classification Committee published in 2006 new proposed criteria for the diagnosis of chronic migraine. These are as follows: A. Headache (tension-type and/or migraine) on ≥ 15 days per month for at least 3 months; B. Occurring in a patient who has had at least five attacks fulfilling criteria for Migraine without aura; C. On ≥ 8 days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura (1) has at least two of a–d: (a) unilateral location (b) pulsating quality (c) moderate or severe pain intensity (d) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs); and at least one of a or b (a) nausea and/or vomiting (b) photophobia and phonophobia (2) Treated and relieved by triptan(s) or ergot before the expected development of C1 above. D. No medication overuse and not attributed to another causative disorder.

2 See IHS classification for definition of migraine and probable migraine at http://ihs-classification.org/en/

but most secondary endpoints, including the frequency of headache days, had nominal p values under 0.05. Therefore, the sponsor requested a modification of the primary endpoint in their second pivotal study (Study 191622-080), from the frequency of headache episodes to the frequency of headache days[3].

3. CMC/Device

No new CMC information in this efficacy supplement.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information in this efficacy supplement.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information in this efficacy supplement.

6. Clinical Microbiology

No new clinical microbiology information in this efficacy supplement.

7. Clinical/Statistical- Efficacy

As discussed by Dr. Kasim and Dr. Ling, the primary evidence of efficacy was based on two 24-week phase 3 randomized, multicenter placebo-controlled studies (Study 191622-079 and 191622-080) in patients with chronic migraine. For both studies, the original primary efficacy endpoint was the change from baseline in the frequency of headache episodes[4] in the 28-day period ending with Week 24, and the original key secondary efficacy measure was the change

[3] The IHS published in 2008 new Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. These guidelines note that "depending on the nature of the study, there are several different endpoints that may be considered as a primary endpoint. Selection of the primary endpoint must be done a priori and should depend on study objective. It is recommended that the primary endpoint include headache days with moderate or severe intensity, migraine days or frequency of migraine episodes.
A. Number of headache days with moderate or severe intensity: A headache day with moderate or severe intensity is defined as a day with headache pain that lasts ≥4 h with a peak severity of moderate or severe intensity, or of any severity or duration if the subject takes and responds to a triptan or ergot.
B. Number of migraine days, i.e. days with migraine or probable migraine.
C. Number of migraine episodes: In studies that include subjects who have pain-free periods, the number of migraine episodes may be considered as a primary end-point. The duration of pain-free periods between episodes must be predefined. This endpoint should not be used in trials including subjects with continuous headache."

[4] A headache episode was defined as an episode with headache lasting at least 4 continuous hours (with no duration limit).

from baseline in the frequency of headache days[5]. As discussed above, after completion of Study 079 and prior to database lock and treatment unblinding for Study 080, the primary endpoint for Study 080 was changed to frequency of headache days.

Table 1 shows the primary efficacy results, as analyzed by Dr. Ling. Nominal p values were very low in both studies for the "headache days" endpoint, but the contrast for the "headache episodes" endpoint in Study 079 was not significant.

Table 1: Primary efficacy results in pivotal chronic migraine studies

	Study 079			Study 080		
	BOTOX (N=341)	Placebo (N=338)	p	BOTOX	Placebo	p
Headache episodes	-5.36	-4.99	0.34	-5.60	-4.87	0.0034
Headache days	-7.81	-6.40	0.006	-9.21	-6.92	<0.0001

As discussed by Dr. Ling, Allergan selected the endpoint of "frequency of headache episodes" against FDA advice. FDA expressed concern that it would be difficult to distinguish between two or three shorter headaches occurring back to back vs. one headache with duration of several days. In other words, the proposed endpoint lacked sensitivity in identifying an effect by which patients may continue to have about the same number of headache episodes, but of shorter duration. Considering that the frequency of headache days is the FDA preferred endpoint, that contrasts on that endpoint have low p values in both studies, and that results on multiple secondary endpoints are supportive (see Table 2), I agree that Study 079 and Study 080 provide substantial evidence of efficacy of BOTOX for the treatment of chronic migraine.

Secondary endpoints are supportive of the primary efficacy results. In Study 079, beside the frequency of headache days, secondary endpoints included the frequency of migraine/probable migraine days per 28 day period, the frequency of migraine/probable migraine[6] episodes per 28 day period, and the frequency of acute headache pain medication intakes per 28 day period. Dr. Ling notes that a statistical method to control the type I error rate for the secondary endpoints was not prespecified for Study 079. In Study 080, secondary endpoints included frequency of migraine/probable migraine days, frequency of moderate/severe headache days; total cumulative hours of headache occurring on headache days, proportion of patients with severe headache impact test (HIT-6) category scores, and frequency of headache episodes. In Study 080, the above secondary endpoints were tested sequentially in the stated order to control the type 1 error rate for multiple secondary endpoints.

Table 2: Prespecified secondary endpoints in pivotal studies (prespecified secondary endpoints in each respective study are bolded)

	Study 079			Study 080		
	BOTOX (N=341)	Placebo (N=338)	p	BOTOX	Placebo	p
Frequency of migraine/probable migraine days	**-7.6**	**-6.0**	**0.002**	**-8.8**	**-6.5**	**<0.001**
Frequency of migraine/probable migraine episodes	**-5.0**	**-4.5**	**0.206**	**-5.6**	**-4.6**	**0.003**

[5] A headache day was defined as a day (00:00 to 23:59) with 4 or more continuous hours of headache.
[6] See IHS classification document for definition of migraine and of probable migraine

	Study 079			Study 080		
	BOTOX (N=341)	Placebo (N=338)	p	BOTOX	Placebo	p
Frequency of moderate/severe headache days	-7.2	-5.8	0.004[a]	**-8.8**	**-6.0**	**<0.001**
Frequency of acute headache pain medication intakes	**-10.1**	**-9.8**	**0.795**	-9.7	-8.1	0.132
Total cumulative hours of headache on headache days	-106.7	-70.4	0.003 [a]	**-134**	**-95**	**<0.001**
Proportion of patients "Severely impacted" on Severe Headache Impact Test (HIT-6)	68.9	79.9	<0.001 [a]	**66.3%**	**91.6%**	**0.003**

a: post-hoc analysis

It is also important to emphasize that nominal p values under 0.05 (and favoring BOTOX) were seen at most to all time points for the headache days endpoint in both studies, and for the secondary endpoints that are listed with p values under 0.05 in Table 2.

Finally, as discussed by Dr. Kasim, optional additional injections of BOTOX (additional dose of 40 U) or placebo could be administered unilaterally or bilaterally using a "follow-the-pain" paradigm in up to 8 injection sites. There was no requirement for the optional injections to be consistently administered across treatment visits, and no clear decision rule as to which patients could be eligible for the extra dose. Instead, this was left to the "clinician's best judgment on the potential benefit of additional doses in the specified muscles". As the trial was not designed to assess whether that "follow the pain" paradigm provided any benefit over the "fixed dose" paradigm, it is impossible to assess whether administering the extra 40 Units of BOTOX is justified. Considering the known dose-dependent toxicity of this product, the sponsor should provide evidence of the "follow the pain" paradigm's benefit before this can be considered for inclusion in labeling. To assess whether efficacy was preserved in the "fixed dose" patient subgroup, I requested an analysis of the primary efficacy endpoint in patients who received fixed doses of BOTOX at both injection sessions. Table 3 shows that nominal p values remained under 0.05 in both studies for the frequency of headache days endpoint. On the other hand, nominal p values were above 0.05 for most contrasts in the subgroup of patients who received an extra dose at one or both injection cycles (see Table 42 of Dr. Kasim's review).

Table 3: Subgroup efficacy analysis in patients who received a fixed 155U dose for Both Treatments during the Double Blind Phase in Study 079 and Study 080 (adapted from Table 43 of Dr. Kasim's review).

Efficacy variable (per 28 days)	**191622-079**			**191622-080**		
	BOTOX (N=126)	**PLACEBO (N=126)**	**p-value**	**BOTOX (N=166)**	**PLACEBO (N=182)**	**p-value**
Frequency of HA Days[A]	-8.5	-6.7	0.0378	-10.0	-7.0	<0.0001
Frequency of HA Episodes[B]	-6.3	-5.6	0.3211	-6.2	-4.8	0.0073
Total cumulative hours of headache on HA days	-109.4	-67.8	0.0178	-144.0	-91.4	<0.0001

[A] Primary End-point 191622-080, [B] Primary End-point 191622-079

8. Safety

Dr. Cheryl Graham conducted the clinical safety review, under the supervision of Dr. Sally Yasuda. I agree with Dr. Yasuda's conclusions described in her memorandum, and I refer the reader to that document for a discussion of the key safety findings. The safety database included not only studies in chronic migraine patients, but also studies in episodic migraine, tension-type headache, and chronic daily headache patients. Safety data were examined both for the entire pooled database of the various headache indications, and for a database limited to chronic migraine studies only. My discussion below will focus on the double-blind portion of chronic migraine studies[7], as no additional significant safety findings were identified in the "entire pooled database" or in the open-label phase of chronic migraine studies. As noted by Dr. Graham and Yasuda, BOTOX exposure in the safety database is adequate, with the exception of limited data at total doses of 155 Units or higher.

Deaths

There was a single death in the safety database, with no suspect relationship to the study drug.

Serious adverse events

During the double blind controlled portion of the chronic migraine trials, 4.8% (33/687) of BOTOX-treated subjects and 2.3% (16/692) of placebo-treated subjects reported a SAE. The SAES that occurred more frequently on BOTOX than on placebo include Neoplasms (1% vs. 0.3%), Nervous system disorders (1.3% vs. 0.3%)[8], and Infections & infestations (1% vs. 0.7%). The review of individual SAEs did not demonstrate any clear pattern. Dr. Graham reviewed all cases of neoplasia and did not find a cancer risk associated with BOTOX.

Adverse dropouts

During the double blind controlled portion of the chronic migraine trials, 3.8% (26/687) of BOTOX treated subjects and 1.2% (8/692) of placebo-treated subjects had adverse events leading to discontinuation. In the BOTOX group, events that occurred in at least 2 subjects include neck pain (4 subjects), muscular weakness, headache, migraine (each in 3 subjects), eyelid ptosis and breast cancer (each in 2 subjects). Of these events, only headache and migraine were reported in the placebo group, in one patient each. Neck pain, muscle weakness, and eyelid ptosis can easily be attributed to BOTOX. Headache and migraine were of course also examined in the primary endpoint of both chronic migraine trials, and the superiority of BOTOX over placebo on that endpoint largely dismisses the finding (even though it is possible that a few patients have a paradoxical increase in headaches after BOTOX treatment). A role of BOTOX in the cases of neoplasia does not appear plausible. Dr. Graham and Dr. Yasuda also discuss a case of bilateral pneumonia in a patient who received BOTOX. I agree that a role of BOTOX can not be ruled out, but there is no clear pattern for dropouts related to pulmonary infections on BOTOX. There was also a case of adverse dropout on BOTOX for shortness of breath (with positive rechallenge).

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[7] Double-blind portion included 2 injection cycles (24 weeks), after what patients were eligible to an additional 3 injections in a 32-week open-label phase

8 Main contributor to the BOTOX/placebo difference was migraine (0.6% vs. 0.1%)

Spread of toxin effects

Spread of toxin effects is a concern with all botulinum toxin products, and is the object of a black box warning. Spread of toxin effect was assessed by the sponsor using a search based on a specific set of MedDRA terms. As discussed by Dr. Graham and Yasuda, of the 4076 subjects included in the analysis, 34/1544 (2.2%) placebo-treated subjects and 658/2532 (25.9%) BOTOX treated subjects had an adverse event report corresponding to a least one of the spread of toxin effect terms. Most terms corresponded to expected adverse reactions at the site of injection, but several did not. These include dyspnea, aspiration pneumonia, respiratory failure, muscular weakness, bradycardia, urinary retention, and constipation. Dr. Graham was able to dismiss the cases of respiratory failure, aspiration pneumonia and urinary retention. Dyspnea was reported in 10 subjects treated with BOTOX and 2 with placebo, and a relationship to BOTOX treatment is likely (this event is already described in labeling). There were 228 reports of muscular weakness in patients receiving BOTOX (9%), compared to only 7 in placebo (0.5%). This is expected, considering BOTOX mechanism of action. It is reassuring that only 5 of these reports in BOTOX treated subjects involved muscle weakness outside the muscles injected, with only 1 considered by Dr. Graham as potentially related to BOTOX treatment (lower extremity weakness). Dr. Graham and Yasuda also discuss that the cases of constipation were largely confounded, but a role of BOTOX can not be ruled out.

Common adverse events

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 4. Most of these adverse reactions can be easily explained by the mechanism of action of BOTOX.

Table 4: Adverse Reactions Reported by ≥2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body Systems	BOTOX 155 Units-195 Units (N=687)	Placebo (N=692)
Nervous system disorders		
Headache	32 (5%)	22 (3%)
Migraine	26 (4%)	18 (3%)
Facial paresis	15 (2%)	0 (0%)
Eye disorders		
Eyelid ptosis	25 (4%)	2 (<1%)
Infections & Infestations		
Bronchitis	17 (3%)	11 (2%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (9%)	19 (3%)
Musculoskeletal stiffness	25 (4%)	6 (1%)
Muscular weakness	24 (4%)	2 (<1%)
Myalgia	21 (3%)	6 (1%)
Musculoskeletal pain	18 (3%)	10 (1%)
Muscle spasms	13 (2%)	6 (1%)
General disorders and administration site conditions		
Injection site pain	23 (3%)	14 (2%)
Vascular Disorders		
Hypertension	11 (2%)	7 (1%)

The numerically higher incidence of hypertension and muscle spasms are more difficult to interpret, but the difference between BOTOX and placebo is numerically small.

Other adverse events that occurred more frequently in the BOTOX group compared to the placebo group, at a frequency less that 1%, and potentially BOTOX related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX-treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Overall, Dr. Graham and Dr. Yasuda did not identify safety concerns that would preclude approval.

9. Advisory Committee Meeting

No advisory committee meeting was held, as this supplement is for a new indication of an already approved product, and there is no unique issue for which external expertise was needed.

10. Pediatrics

The division's plan to issue a partial waiver for patients 0-11 years and deferral for patients 12 to 17 years of age was reviewed by the PeRC PREA Subcommittee on June 30, 2010. The PeRC agreed with the Division's plan.
The division is waiving the pediatric study requirement for ages 0 to 11 years because necessary studies are impossible or highly impracticable. This is because chronic migraine is rare in children under 12 years of age (as chronic migraine typically develops after several years of episodic migraine, which is relatively infrequent below age 12).

The division is deferring submission of pediatric studies for ages 12 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The division is requiring the following studies:

1. Deferred pediatric Placebo-Controlled Efficacy and Safety Study under PREA for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include a prospective baseline observation period of at least 4 weeks followed by a double-blind treatment phase of at least 12 weeks. The study must include an adequate evaluation of dose-response. The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities and allow the use of appropriate rescue treatment. The protocol for this study must be submitted as a Special Protocol Assessment (SPA) and receive Division concurrence prior to the initiation of the study.

2. Deferred pediatric 12-month Open-Label Safety Study under PREA for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include

at least 300 patients who received two BOTOX treatments at clinically relevant doses over a 6-month period (with at least 100 patients treated at the maximum recommended dose), and at least 100 patients who received four BOTOX treatments at clinically relevant doses over a 12-month period (with at least 60 patients treated at the maximum recommended dose). The study must assess local reactions, distant spread of toxin effects, BOTOX effects on blood glucose, and BOTOX effects on alkaline phosphatase (as a marker of bone metabolism). The safety study must include an adequate evaluation of immunogenicity.

11. Other Relevant Regulatory Issues

DSI

Three domestic clinical investigators and one foreign investigator were inspected by DSI. Overall, DSI found the data submitted from these sites acceptable.

REMS

BOTOX has had an existing REMS since 2009, to address the risk(s) of medication errors related to the lack of interchangeability of BOTOX units and the spread of toxin effect beyond the injection site. The REMS consists of a Medication Guide, a Communication Plan (Dear Healthcare Provider Letter disseminated within 6 weeks of REMS approval), and a Timetable for Submission of Assessments (18 months, 3 years, and 7 years) of the REMS. The sponsor proposed some changes to the existing REMS to adapt it to the new chronic migraine indication. DRISK reviewed the modified REMS.

DRISK notes that the addition of the prophylaxis of headaches in adults with chronic migraine indication to the BOTOX label has impact on the approved REMS, warranting changes to the text of the Medication Guide and modifying the communication plan to include a revised Dear Healthcare Provider Letter (DHCPL) distributed to additional healthcare provider specialties not previously targeted. Headache specialists, neurologists, and pain management specialists will receive the DHCPL within 6 weeks of REMS approval. Allergan will use professional societies such as the American Headache Society, the American Academy of Neurology, and the American Board of Pain Medicine as sources for obtaining information on the appropriate prescribers. (b) (4) DRISK reviewed the revised REMS, and recommended some changes, which were adopted by the sponsor. DRISK recommended that the Timetable for Submission of Assessments of the REMS should remain consistent with the timetable in the original REMS approval, and emphasized that the assessment methodology will need to be revised to include the additional specialties included in the modified REMS communication plan.

Maternal Health
The maternal health team (MHT) was consulted regarding the need for a post-marketing requirement for a pregnancy registry. I agree with MHT recommendation not to require such a registry. MHT also made recommendations regarding other possible studies, and alignment was reached not to require these studies (also see Dr. Yasuda's memo).

12. Labeling

Labeling was updated to include the new indication. Specifically, the following sections were modified:

- Indications and Usage, Chronic Migraine (1.1)
- Dosage and Administration, Chronic Migraine (2.2)
- Adverse reactions (6.1)

Dr. Kasim, Graham and Yasuda reviewed the clinical safety and efficacy sections of labeling. Mr. Fava, from DMEPA, also reviewed the professional insert (PI) and provided labeling comments, which were implemented.

The Medication Guide was updated to include the new indication. This was reviewed by OSE/DRISK.

DDMAC also provided comments for the PI and Medication Guide.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
I recommend approval.

Risk Benefit Assessment
BOTOX was shown to reduce the number of headache days in patients with chronic migraine, with a treatment effect, compared to placebo, of about 2-3 additional days without headache lasting 4 hours or more in a 28-day period. Secondary endpoints also support a treatment effect of about 35-40 additional headache-free hours (on headache days, i.e. days with headache lasting 4 hour or more) in a 28-day period. That effect is, in my opinion, clinically significant. There are no new safety findings identified in the extensive database. The well known adverse reactions of botulinum toxin products were however also seen in this development program. These include dyspnea, and muscular weakness, mostly in the area of injection (with more distant effects in infrequent cases). Spread of toxin effect is already the object of a black box warning, and I believe that labeling along with the REMS described below will adequately manage the risks of this treatment. It will also be very important that the sponsor educates prescribers on how to identify patients candidates for this treatment, and how to administer the drug, as chronic migraine is a relatively new concept, and prescribers for this new indication will largely be different from those administering the drug for already approved indications.

Recommendation for Postmarketing Risk Management Activities
The existing REMS was modified to accommodate the new indication. The REMS consists of a Medication Guide, a Communication Plan (Dear Healthcare Provider Letter to be disseminated within 6 weeks of REMS approval), and a Timetable for Submission of Assessments (18 months, 3 years, and 7 years) of the REMS. The revised Dear Healthcare Provider Letter (DHCPL) will be distributed to additional healthcare provider specialties not previously targeted, including headache specialists, neurologists, and pain management specialists.

Recommendation for other Postmarketing Study Requirement
None.

CENTER FOR DRUG EVALUATION AND RESEARCH

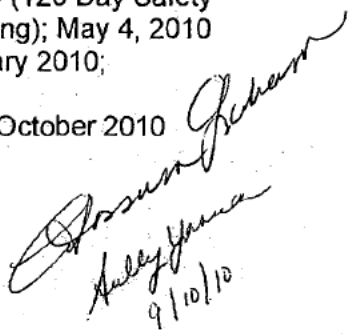
APPLICATION NUMBER:

BLA 103000 S-5215

MEDICAL REVIEW(S)

CLINICAL REVIEW (Safety Only)

Application Type	BLA Supplement
Application Number(s)	STN BL 103000/5215
Priority or Standard	Standard
Submit Date(s)	28 September 2009; 6 January 2010 (Safety Amendment); 26 January 2010 (Response to Questions); 26 January 2010 (120 Day Safety Update); 9 April 2010 (Labeling); May 4, 2010
Received Date(s)	28 September 2009; 6 January 2010; 26January 2010
PDUFA Goal Date	31July 2010 extended to 29 October 2010
Division / Office	DNP/ODE1
Reviewer Name(s)	Cheryl Fossum Graham MD
Review Completion Date	09 September 2010
Established Name	Onabotulinumtoxin A
(Proposed) Trade Name	BOTOX®
Therapeutic Class	Neuromuscular blocking agent
Applicant	Allergan
Formulation(s)	Each single use vial contains 50 or 100 units of *Clostridium botulinum* toxin type A neurotoxin complex in a sterile, vacuum-dried form without preservative.
Dosing Regimen	The recommended dilution is 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL. The recommended dose for treating chronic migraine is 155 Units (b) (4) administered intramuscularly (IM) using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per each site. Injections should be divided across 7 specific head/neck muscle areas.
Indication(s)	Prophylaxis of headaches in adults with chronic migraine
Intended Population(s)	Adults with chronic migraine defined as greater than 15 headaches days per month of which 50% or greater are migraine or probable migraine



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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This supplemental application contained adequate safety data for review. No safety concerns were identified that would preclude approval. However there are risk mitigation, labeling and post-market study recommendations in Section 1.2 and Section 1.3.

1.2 Risk Benefit Assessment

Deferred to Cross Discipline Team Leader review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

1. (b) (4)
2. The proposed physician label should contain explicit wording about exacerbation of migraine, usually occurring shortly after a BTA dose.

1.4 Recommendations for Postmarket Requirements and Commitments

1. None

2 Introduction and Regulatory Background

2.1 Product Information

Onabotulinumtoxin A (BTA) is an approved product in the United States. Please refer to section 2.6 for relevant background information.

2.2 Tables of Currently Available Treatments for Proposed Indications

Onabotulinumtoxin A (BTA) is an approved product in the United States. Please refer to section 2.6 for relevant background information.

2.3 Availability of Proposed Active Ingredient in the United States

Onabotulinumtoxin A (BTA) is an approved product in the United States. Please refer to section 2.6 for relevant background information.

2.4 Important Safety Issues With Consideration to Related Drugs

Onabotulinumtoxin A (BTA) is an approved product in the United States. Please refer to section 2.6 for relevant background information.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The pre-sBLA meeting was held on June 11, 2009. At that meeting there were several items related to the content and format of the proposed submission that were specific to the safety sections. The item and a summary of the FDA response are included below.

- Long term safety exposure; the sponsor asked if 500 patients exposed for 48 weeks or more was sufficient. The FDA responded that at least 40% of patients should receive the highest dose recommended for marketing. The sponsor responded that about 50% of patients in the Phase 3 trials got the minimum dose of 155 units and about 50% got a least one additional injections with a mean dose of 165 units.
- Format for ISS; the FDA had a number of requests for improving the reporting plan for the ISS. The FDA also accepted the coding scheme for converting reports coded with COSTART to MedDRA.
- CRFs and Narratives: the sponsor proposed including only narratives for serious adverse events and excluding non-serious discontinuations. The FDA disagreed with this approach and requested narratives for deaths, discontinuations and serious adverse events for all Phase 3 and Phase 2 chronic headache studies.

Other advice from the FDA included cross-referencing to the cervical dystonia data for high dose safety and providing a justification for not referencing safety data collected in the episodic migraine population.

2.6 Other Relevant Background Information

Safety Findings from Previously Approved Indications

Onabotulinumtoxin A (BTA) was designated an orphan drug product on March 22, 1984 for the treatment of strabismus associated with dystonia in adults (patients 12 years of

age and above) and under a separate designation on the same date for the treatment of blepharospasm associated with dystonia in adults (patients 12 years of age and above). BTA was approved for both indications on December 29, 1989. BTA received designation as an orphan product for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia on August 20, 1986 and was approved for this indication on December 21, 2000. (b) (4)

Since the original BLA approval on December 29, 1989, BTA has been supplemented with both orphan and non-orphan indications so that it is currently approved for six indications. The five medical indications for BOTOX in the Prescribing Information (PI) approved on March 9, 2010 [1] and the cosmetic indication with labeling approved on April 12, 2002 are listed below followed by a summary of the safety database description and the most common adverse events contained in the PI.

1. *treatment of blepharospasm associated with dystonia in patients ≥12 years of age*
2. *treatment of strabismus in patients ≥ 12 years of age*
   - Approved; 29 December 1989; orphan product designation
   - These indications are supported primarily by open label studies that included over 1000 exposures for blepharospasm and 667 patients with strabismus. The blepharospasm adverse reaction data in the PI makes a distinction about the source of safety data, suggesting that a previous formulation of BTA probably supported the safety and efficacy of this indication. The current PI reads: "In a study of blepharospasm patients who received an average dose per eye of 33 units (injected at 3-5 sites) of currently manufactured BOTOX, the most frequently reported treatment-related adverse reactions were ptosis (20.8%), superficial punctuate keratitis (6.3%), and eye dryness (6.3%)." The adverse reaction information for strabismus references 2058 adults who received a total of 3650 injection with a 15.7% rate of ptosis and 16.9% rate of vertical deviation. Only the blepharospasm dosing instructions contains information about potential re-dosing (every 3 months) and maximum cumulative dose (200 units in a 30 day period). The rationale for the blepharospasm dosing limitations includes the potential for tolerance.

3. treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain

- Approved; 21 December 2000; orphan product designation

[1] http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory
[2] http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/botuall041202LB.pdf

- This indication is supported by a single phase 3 randomized, multi-center, double-blind, placebo controlled trial in which 88 known responder patients received a single administration of BTA with 10 weeks follow up. The median total dose was 236 units with 25th to 75th percentile of 198-300 units. While as many as 7 muscles could be injected; 38 were injected in 3 muscles, 28 in 4 muscles, 5 in 5 muscles, 5 in 2 muscles. Most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%) and headache (11%).

4. treatment of glabellar lines

- Approved; 12 April 2002; BOTOX Cosmetic
- This indication is supported by two phase 3 randomized, multi-center, double-blind, placebo-controlled trials in which 405 patients received a single 20 unit administration of BTA injected as 4 unit increments into 5 sites in the corrugator and procerus muscle. The adverse events reported more frequently in BTA treated patients than placebo treated patients were blepharoptosis (3% v 0%), nausea (3% v 2%), muscle weakness (2% v 0), pain in face (2% v 1%), and skin tightness, dyspepsia, tooth disorder, hypertension (all 1% v 0%).

5.treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients

- Approved; 19 July 2004
- This indication is supported by two randomized, multi-center, double-blind, placebo-controlled studies. The combined single dose BTA exposure in these controlled studies was 346 patients receiving 50 units in each axilla and 110 patients receiving 75 units in each axilla. Administration of BTA is intradermal at 10-15 sites in each axilla (2.5 -5 units per site). The most frequent adverse events (3-10%) included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

6. upper limb spasticity

- Approved; 9 March 2010
- This indication is supported by three randomized, multi-center, double-blind, placebo-controlled studies. The combined single dose BTA exposure in the pooled data from these controlled studies was 115 patients receiving 251-360 units, 188 patients receiving 150-250 units, 54 receiving < 150 units, and 182 patients receiving placebo. Single injections in wrist muscles (flexor carpi radialis, flexor carpi ulnaris) ranged from 10 – 60 units in a volume of 0.6 – 1ml; single finger injections (flexor digitorum profundus, flexor digitorum sublimis) ranged from 7.5 – 50 units in a volume of 0.3 – 1 ml; single thumb injections (adductor pollicis, flexor policis longus) were 20 units in a volume of 0.4 ml; elbow injections (biceps brachii) ranged from 50-200 units as 4 injections of 0.5 ml each. The most common adverse events are listed in Table 1 as it appears in the current PI.

Table 1: Adverse Reactions Reported by > 2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Adult Spasticity Double-Blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX 251-360 Units (N=115)	BOTOX 150-250 Units (N=188)	BOTOX <150 Units (N=54)	Placebo (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions				
Fatigue	4(3%)	4 (2%)	1 (2%)	0
Infections and infestations				
Bronchitis	4 (3%)	4 (2%)	0	2(1%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	7(6%)	10 (5%)	5 (9%)	8 (4%)
Muscular weakness	0	7 (4%)	1 (2%)	2 (1%)

Among the six indications the highest total single unit dose mentioned in the current BOTOX® Prescribing Information is 360 units distributed across muscles of the wrist, finger, and elbow for treatment of adult upper limb spasticity. However, for muscles of the head and neck region (most relevant to the chronic migraine indication) the highest total single dose is 300 units for the treatment of cervical dystonia.

Since the submission of this supplemental BLA on September 28, 2009, an indication for treatment of adult spasticity was approved on March 9, 2010 that required conversion of the format and content of the BOTOX label to conform with the new Physician Labeling Rule. A BOXED WARNING regarding Distant Spread of Toxin Effect was retained from the previous version of the label.

Distant Spread of Toxin Effect
Postmarketing reports indicate that the effects of **BOTOX®** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have occurred at doses comparable to those used to treat cervical dystonia and at lower doses.

The WARNINGS and PRECAUTIONS section of the label was expanded to include the following items:

5.1 Lack of Interchangeability between Botulinum Toxin Products
5.2 Spread of Toxin
5.3 Hypersensitivity Reactions
5.4 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia
5.5 Pre-existing Neuromuscular Disorders
5.6 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity
5.7 Corneal Exposure and Ulceration in Patients Treated with BOTOX for blepharospasm
5.8 Retrobulbar Hemorrhage in Patients Treated with BOTOX for Strabismus
5.9 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
5.10 Human Albumin and Transmission of Viral Diseases

In addition to the BOXED WARNING and the addition of items to the WARNINGS AND PRECAUTIONS section, general information about the adverse effects of BOTOX was included in the ADVERSE REACTION section.

In general, adverse events occur within the first week following injection of BOTOX and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.
Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin.

It is in the context of the extensive revision of the PI for BOTOX occurring 6 months after this supplement was submitted that this review was completed.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Safety Review

This safety review is dependent on the identification, reporting, coding and analysis of elicited adverse events in Phase 2 and 3 trials. Objective measures of safety such as clinical laboratory data, electrocardiograms, pulmonary function studies, X-rays and other potential biomarkers for organ toxicity were not included in the trials contributing to the safety database. Thus the quality and integrity of the safety database is synonymous with adverse event reporting.

The intensity and consistency of the adverse event data collection and analysis across all the clinical trials included in the sBLA is not optimal. With the exception of the Phase 3 clinical trials, the adverse events that caused subjects to discontinue from a trial were not consistently collected and/or recorded in the CRF and thus were not analyzed in the ISS. Based on random cross checking between database and CRF in the individual trials data, reconciliation was not always done, or was done at different times resulting in discrepancies between tables and listings in the individual trial reports and tables in the ISE and ISS. While not a major quality issue for assessment of the Phase 3 clinical trials, it is considered a potential indicator of other potential quality issues.

The use of different adverse event coding systems for the Phase 3 clinical trials and the ISS compared to all the Phase 2 clinical trials is addressed by the sponsor as an operational issue within the ISS even though the conversion, especially for anatomically specific adverse events like muscle weakness and myalgia, demand some specificity with regard to local injections of BTA. Neither COSTART nor the preferred term of MedDRA provides the specificity needed for anatomical sites and the two dictionaries code the verbatim adverse events to different terms. The sponsor was asked to provide tabulations of adverse events in the Phase 3 trials using the lower level MedDRA terms in order to provide more specificity for the anatomical location.

While none of the data management/quality issues presented major impediments to assessing the safety of BTA for CM, they did result in additional time spent cross checking CRFs, narratives, listings and tables of major interest.

3.2 Compliance with Good Clinical Practices

A separate review of the efficacy portion of this supplemental application was done. Please refer to the Efficacy Review for this information.

3.3 Financial Disclosures

A separate review of the efficacy portion of this supplemental application was done. Please refer to the Efficacy Review for this information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Onabotulinumtoxin A (BTA) is an approved product in the United States. This supplemental application referenced previously approved submissions to this BLA for this section.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Onabotulinumtoxin A (BTA) is an approved product in the United States. This supplemental application referenced previously approved submissions to this BLA for nonclinical pharmacokinetics and toxicology. The Pharmacologist's review contains an assessment of additional pharmacology studies.

4.4 Clinical Pharmacology

Onabotulinumtoxin A (BTA) is an approved product in the United States. This supplemental application referenced previously approved submissions to this BLA for this section.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

See Section 7.1

5.2 Review Strategy

Safety Review

This supplement to the BOTOX®, onabotulinumtoxin A, (BTA) biologics license application (BLA) requests an indication for the prophylaxis of headaches in adults with chronic migraine (CM). The recommended dose is (b) (4)f 31 intramuscular injections of 5 units (0.1ml) each in 7 different muscles bilaterally in the head and neck region for a total of 155 units (b) (4) . Injections may be repeated as frequently as every 3 months. The sponsor's proposed text for the DOSAGE AND ADMINISTRATION section for this new indication is included below. (b) (4)

Table 2: Dosing by Muscle for Chronic Migraine

(b) (4)

[redacted]

[a] Each IM injection site = 0.1 mL = 5 Units **BOTOX®**
[b] Dose distributed bilaterally

Chronic migraine (CM) is potentially a very large target population if BTA is approved for this indication. However, the number of CM patients exposed at the dose and using the injection scheme proposed in the label is relatively small and reflects only the Phase 3 clinical trials (N=1300). The major focus of this review for purposes of labeling for CM is based on the results of the combined Phase 3 trials (Protocols 79 and 80). Results from Protocol 039, a Phase 2 trial using a somewhat different dose and injection scheme, are included throughout the review to expand the relevant safety experience.

Protocol 39 is a fixed dose comparison study of 0, 75, 150 and 225 units of BTA with the highest doses bracketing the dose range used in the Phase 3 trials. It uses the same treatment cycle interval as the Phase 3 trials and was done in a chronic daily headache population (CDH). Protocol 38 was a flexible dose Phase 2 trial. The pooled safety results of Protocols 79, 80, 38, and 39 represent the relevant aggregate experience in CM/CDH (N=1997).

As noted in Section 3.1, there was no systematic collection of clinical laboratory samples, and no protocol required electrocardiograms, pulmonary function testing, or other common safety measurements. Therefore, the assessment of safety is dependent on the reporting, codification and aggregation of elicited adverse events. For this reason, examination of adverse event reports in the CM/CDH patient population, down to a frequency of ≥1%, was done.

The adverse event profile for previously approved BTA indications is informative with regard to expected common adverse events in a CM population. (See Section 2.6) The indications for strabismus, blepharospasm and glabellar lines are treated with injections to the facial area and are associated with eyelid ptosis, facial pain and facial muscle weakness. In contrast the cervical dystonia indication depends on BTA injections to the neck region with the most frequent adverse events being dysphagia, upper respiratory infection, neck pain and headache. The CM indication involves injections to both the facial and the neck region. Thus, it was anticipated at the outset of this review that the adverse event profile for CM would be a blend of previously reported events for the already approved indications.

The search for serious known or unexpected reports of adverse events was based on review of deaths and serious adverse events that resulted in discontinuation from the study. Because the dosing and injection scheme in the Phase 2 trials was different from the Phase 3 trials, the most relevant serious reports to a CM population were derived from the results of Protocol 038, 039, 079 and 080.

5.3 Discussion of Individual Studies/Clinical Trials

See Efficacy Review

6 Review of Efficacy

Efficacy Summary

A separate review of the efficacy portion of this supplemental application was done. Please refer to the Efficacy Review for information in Section 6.

7 Review of Safety

Safety Summary

This supplement to the BOTOX®, onabotulinumtoxin A, (BTA) biologics license application (BLA) requests an indication for the prophylaxis of headaches in adults with chronic migraine. The recommended dose is (b) (4) 31 intramuscular injections of 5 units (0.1ml) each in 7 different muscles bilaterally in the head and neck region for a total of 155 units (b) (4) Injections may be repeated as frequently as every 3 months.

The number of single treatment exposures to BTA reported in the integrated summary of safety in this sBLA is greater than 3000 with 1997 exposures in patients with either chronic migraine (CM) or chronic daily headache (CDH). The number of single dose exposures in CM/CDH patients using greater than 200 units of BTA exceeds 250, while the number of exposures between 150 and 200 units was 1550. There were 132 patients who received three consecutive cycles of >200 units of BTA for CM/CDH [See ISS Table 2-4.2].

In the Phase 3 trials where the dose and injection scheme (b) (4), there were a total of 1300 patients with at least 1 treatment with BTA, 1092 with at least 3 treatment cycles and 518 with 5 treatment cycles. Twenty seven (27) of 518 patients in the Phase 3 clinical trials received ≥ 4 consecutive cycles (48 weeks of exposure) to 195 units of BTA [See Amendment dated May 4, 2010].

There were no deaths reported in BTA-treated patients in the overall integrated safety database (N=3235). The number of serious adverse events and adverse drop outs in the Phase 3 trials was approximately 4% in the BTA-treated group and about 2% more than placebo treated patients.

The integrated safety database conforms to the ICH-E1A Guidance for exposure of 1500 patients' total, 100 for a minimum of 1 year at the dose intended for clinical use, and 300-600 for 6 months. It contains the results of 11 controlled trials in nine different exposure groups with 3,235 patients receiving at least one injection of BTA. A total of 1300 patients received BTA using the dosing regimen (b) (4) with 518 having exposure for greater than one year (5 treatments on a 12 week cycle). There are data on an additional 453 patients who received a total single dose greater than the maximum (b) (4) (See Section 7.2.1)

Safety Issue #1: Dose and Injection Scheme Compliance

The development program in headache (episodic migraine, chronic migraine, chronic daily headache and chronic tension-type headache) has included a variety of dose and injection schemes. (See Table 6) The majority of the Phase 2 trials, regardless of indication, did not demonstrate efficacy and had adverse event rates that exceeded the rates found in the Phase 3 trials in chronic migraine headache. (See Table 43) It is likely that the margin between acceptable efficacy and unacceptable adverse effects is very narrow in the headache population tested with BTA. The Phase 3 trials used a different dose and injection scheme from all previous trials and appear to have effectively decreased the frequency of the most common dose related adverse effects and achieved sufficient separation of the dose response for efficacy from the dose response for toxicity to demonstrate statistically significant evidence of efficacy. However, the placebo response rate is high compared to trials conducted with other drugs approved for migraine prophylaxis (See Section 7.7) making the actual drug effect a small incremental improvement over a large background placebo rate. For a treatment that has a small drug effect, the minimization of adverse effects is important. Thus strict compliance with the dose and injection scheme used in the Phase 3 trials is considered vital to achieving even a small efficacy effect and minimizing dose related adverse effects.

Recommendation: The sponsor should be required to assure proper training of all healthcare professionals intending to use BTA for the prevention of headaches associated with CM. This requirement would be an extension of the current REMS in place for Botox®. (See Section 7.7)

Safety Issue #2: Regional and Distant Spread of Toxin

As discussed below, the dose per injection (units/ml) and the number of sites injected per muscle appear to be critical to reducing the risk of toxin-related adverse effects related to the particular muscle group injected as well as regional or distant spread of the toxin to other muscles. In the fixed dose comparison Phase 2 trials (Protocol 039 and 509) where total doses equivalent to and above those used in the Phase 3 trials (Protocols 079 and 080) were administered, the frequency of dose related adverse effects was greater than reported in the Phase 3 trials and indicative of either functional paralysis of an individual muscle or potential regional spread of the BTA.

Dysphagia is a BTA induced adverse event frequently reported when BTA is administered to muscles of the neck (in contrast to facial muscles). Therefore it is a good indicator of the ability of the choice of a particular dose and injection

scheme to reduce its occurrence. In Protocols 039 (a placebo-controlled fixed dose comparison trial in patients with chronic daily headache) and 509 (a placebo-controlled fixed dose comparison trial in patients with episodic migraine) the incidence of dysphagia in the 150 unit dose group was 3.6% (6/168) and 2.4% (3/125), respectively compared to 0.7% (5/687) in the Phase 3 trials where the mean total dose was 165 units. For the 150 unit dose in Protocol 039 and 509, the trapezius muscle was injected at 4 sites (2 sites in the left and right muscle) at a dose of 10 units/0.2 ml and a total of 40 units. In the Phase 3 trials (Protocol 079 and 080) the trapezius muscle was injected with 5 units/0.1 ml at a minimum of 6 sites and a maximum of 10 sites distributed bilaterally for a total of 30 to 50 units. Thus the number of injection sites was essentially doubled and the dose per injection was halved in the Phase 3 trials in order to achieve approximately the same total dose. Adjustments in the injection scheme for other neck muscles also occurred prior to initiation of the Phase 3 trials. While a direct cause and effect between the dosing scheme and the occurrence of particular adverse effects with BTA is difficult to definitively establish, the reduction in the reporting frequency for dysphagia in the Phase 3 trials is significant and reasonably attributable to the change in dose per injection and number of injection sites.

As noted in Safety Issue #1, the role of strict compliance with the dose and injection scheme used in the Phase 3 trials appears to be critical in reducing the likelihood of either functional paralysis of a specific muscle or regional spread of toxin.

Recommendation: See Safety Issue #1.

Safety Issue #3: Exacerbation of Migraine

Reports of migraine/headache episodes are the major efficacy focus of this sBLA, so migraine/headache would ordinarily be reported as part of the efficacy assessment and not as an adverse event unless the event was serious and was required to be reported separately as a serious adverse event (SAE). In Section 7.3.5 there is a review of the imbalance in serious adverse events reports of migraine between the BTA and the placebo group in the combined Phase 3 trials (079 & 080). During the double-blind portion of the Phase 3 trials nine (1.3%) of the BTA treated patients were either hospitalized and/or discontinued because of a serious/severe migraine headache compared to two (0.3%) placebo treated patients. Exacerbation of migraine has been previously reported with triptans [1]; although, the current PI for triptans does not appear to have information on this phenomenon.

Recommendation: The proposed PI should contain explicit wording about exacerbation of migraine, usually occurring shortly after a BTA dose.

Other safety issues that were explored as part of this review included the occurrence of vision and eye effects due to ptosis, potential effects on pregnancy maintenance and outcome, frequency of neutralizing antibodies, hypersensitivity reactions and the occurrence of potentially serious previously unrecognized adverse events. The PI approved on March 13, 2010 during the pendency of this review included a new precaution for patients regarding driving or engaging in hazardous activities if vision or muscle strength was impaired. A request was made to the Maternal Health Team of the Pediatric and Maternal Health Staff for advice on an appropriate response to the pregnancy data from the Phase 3 trials and is discussed in Section 7.6.2. The incidence of hypersensitivity reactions was low in the integrated safety database and the occurrence of neutralizing antibodies was well below the rate currently stated in the PI. No new life-threatening adverse events surfaced in this population as a result of this safety reivew.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Nine placebo controlled trials were submitted in the sBLA. One additional study (027) relevant to a dose response assessment was identified through a literature search and (b) (4) It has been included in this safety review as appropriate, but the data were not integrated into the ISS. Table 3 identifies all placebo controlled trials (N=10) considered in this review and includes pertinent design information. With the exception of Protocol 509, the majority of the sites and patients in these trials were recruited in North America.

Table 3: Placebo Controlled Clinical Trials of BTA for Safety Evaluation (N=10)

Trial ID	Dates	Population	N	Dose Design	Doses	Duration (12 week Cycle)
005	January 1998 to September 1998	EM (2-8/ month)	123	Fixed Dose	0, 25, 75	1
009	January 1999 to November 1999	EM (4-8/ month	232	Fixed Dose /Variable muscle group	6 to 25 depending on muscles injected	1
024 with extensions 026, 036[3]	March 1999 to April 2000	EM (4-8/ month)	418	Fixed Dose	0, 7.5, 25, 50	1
027[4]	January 2000 to February 2001	CTTH (≥ 15 HA days/ month)	300	Fixed Dose	0, 50, 86Usub, 100, 100Usub, 150	1
037	March 2001 to June 2004	EM (4-15/ month)	369	Flexible Dose	105 to 260	3
509	June 2001 to January 2004	EM (4-15/ month)	495	Fixed Dose	0, 75, 150, 225	3
038	June 2001 to October 2003	CDH (≥ 16 HA days per month)	355	Flexible Dose	105 to 260	3
039	July 2001 to November 2003	CDH (≥ 16 HA days per month)	702	Fixed Dose	0, 75, 150, 225	3
079 with 3 cycle extension	February 2006 to July 2008	CM (≥ 15 HA days per month)	679	Fixed Dose with option	155 with option to 195	2 (plus 3 open label)
080 with 3 cycle extension	March 2006 to August 2008	CM (≥ 15 HA days per month)	705	Fixed Dose with option	155 with option to 195	2 (plus 3 open label)

EM = episodic migraine; CDH = chronic daily headache; CTTH = chronic tension-type headache; CM = chronic migraine; Usub = mix of placebo and BTA depending on muscle group

3 The sponsor considered 024, 026 and 036 separate trials for efficacy analysis; however, the same patients were continued on different doses of BTA in the 026 and 036 extensions of 024.
4 Results of this clinical trial were not included in the Integrated Summary of Safety submitted by the sponsor.

7.1.2 Categorization of Adverse Events

MedDRA version 11.0 was used to code all adverse events for the pooled safety analyses. However, only the two Phase 3 clinical trials (079 and 080) used MedDRA to code the adverse events in the primary study reports. All the Phase 2 clinical trials were coded using a modified COSTART dictionary. The adverse events from the Phase 2 trials were converted to MedDRA version 11.0 based on the COSTART codes.

All integrated safety tables of adverse events were based on the MedDRA preferred term (PT). During the review of these tables it became apparent that using the PT did not provide sufficient detail about the anatomical location of the most common adverse events (e.g., muscle weakness, muscle tightness, myalgia, etc.). The sponsor was asked to rerun key adverse event tables for the pooled Phase 3 clinical trials using the MedDRA lower level term (LLT).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

A total of 11 randomized controlled trials (RCTs) are included in the BLA supplement ISS. The trials included in the various pooled safety analysis are based on indication; chronic migraine (CM), chronic daily headache (CDH) or episodic migraine (EM). Table 4 summarizes the number of patients included in each pooled analysis.

For safety review purposes the pooling of data according to indication is not as useful as the dose and injection scheme used in the individual trials. In subsequent sections of this review, results of the individual studies have been separated into matching dosing schemes to better understand the adverse event profile of BTA.

Table 4: Summary of exposures for each pooled safety population

	DBPC Exposure			Open Label Exposure			
	BTA	**Placebo**	**Total**	**BTA/ BTA**	**Placebo/ BTA**	**Total**	**Any BTA Exposure**
Phase 3 CM	687	692	1379	592	613	1205	1300
CM/CDH	1384	1052	2436	NA	NA	NA	1997
CM/CDH/EM	2532	1544	4076	NA	NA	NA	3235

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The integrated safety database conforms to the ICH-E1A Guidance for exposure, although, as noted below, the numbers of patients receiving the highest recommended dose for a year is small. Because the highest dose could only be achieved if a patient was treated with the maximum allowable dose to the occipital, temporal and trapezius muscles, very few patients actually received 195 units of BTA for 5 cycles. Repeat dosing of BTA for the treatment of CM is not recommended sooner than every 12 weeks for other approved indications for BTA and was the re-treatment interval for CM used in the Phase 3 trials. Therefore, in the absence of evidence of an increase in adverse events over time suggestive of carryover or cumulative BTA effects, each BTA exposure can be considered as independent of the previous or the succeeding doses. Section 7.5.2 presents data supporting the position that there is no evidence supporting an adverse carryover or cumulative effect of BTA after repeat dosing.

The number of single treatment exposures to BTA in patients with CM or CDH was 1997. The number of single dose exposures in CM/CDH patients using greater than 200 units of BTA exceeds 250, while the number of exposures between 150 and 200 units was 1550. There were 132 patients who received three consecutive cycles of >200 units of BTA for CM/CDH [See ISS Table 2-4.2].

In the Phase 3 trials (b) (4) there were a total of 1300 patients with at least 1 treatment with BTA, 1092 with at least 3 treatment cycles and 518 with 5 treatment cycles. Twenty-seven (27) of 518 patients in the Phase 3 clinical trials received ≥ 4 consecutive cycles (48 weeks of exposure) to 195 units of BTA [See amendment dated May 4, 2010].

In the overall integrated safety database there were 3235 patients with CM, CDH or EM who received at least one dose of BTA ranging from a total single dose of 6 units to 260 units

Exposure Assessment

Exposure to BTA can be measured by the number of treatment cycles based on repeat dosing every 12 weeks, by the total dose injected in each treatment cycle, by the dose per muscle group, by the number of injections per muscles, and by the combination of muscle groups injected as specified by the protocol. Table 5 summarizes the duration of exposure by the number of treatment cycles in the pooled Phase 3 trials (079 and

080), the pooled Phase 2 trials in CDH (038 and 039) and the combined Phase 2 and 3 trials in a CM/CDH population.

Table 5: Duration of BTA Exposure by Treatment Cycle (every 12 weeks)

Trial ID	1 cycle	2 cycles	3 cycles	4 cycles	5 cycles
079 & 080 DBPC only	687	625	NA	NA	NA
079 & 080 DBPC plus extension	1300	1180	1092	558	518
039 & 038 DBPC	697	402	356	NA	NA
TOTAL DBPC 038, 039, 079, 080	1384	1027	356	NA	NA
Any exposure in 038, 039, 079, 080	1997	1582	1448	558	518

A different dosing scheme was used in each of the Phase 2 trials (038 and 039) conducted in a CDH population, and both of the Phase 2 trials are different from the Phase 3 trials with regard to the dosing scheme. The dosing scheme in the Phase 2 trials in the CDH population (038 & 039) is similar to the dosing scheme used in two Phase 2 trials conducted in EM patients (037 & 509). Table 6 summarizes the dosing scheme in the Phase 3 trials and the four Phase 2 trials in migraine patients (CM and EM). All of the trials were RCTs with a placebo arm. The two Phase 3 trials had 2 blinded treatment cycles compared to 3 blinded treatment cycles in the Phase 2 trials.

For the pooled Phase 3 trials the minimum total BTA dose was 155 units injected at 31 protocol specified sites for 7 muscle groups bilaterally (except procerus muscle). An additional 40 units could be injected in 3 of the 7 muscles groups (see Table 6). The dose administered to patients in the Phase 3 trials receiving at least one treatment cycle (N=1300) and those receiving 5 treatment cycles (N=518) is summarized in Table 7 by total units, units per kilogram and number of sites injected.

Table 6: Randomized placebo controlled multi-treatment cycle trials of BTA; Comparison of dosing scheme

	Protocols 79 & 80		**Protocols 39 & 509**		**Protocols 38 & 37**	
	Phase 3 CM Trials; 2 DBPC treatment cycles		**Phase 2 CDH & EM Trials; 3 DBPC treatment cycles**		**Phase 2 CDH & EM Trials; 3 DBPC treatment cycles**	
Design	fixed dose to 155 plus option to increase to 195		fixed dose comparison with a 75, 150 & 225 dose included in trial		flexible dosing	
Dose	155-195		150 (mid-dose)		105-260	
Units of BTA per Muscle/ Muscle Group (number of injections)						
Required:	Left side	Right side	Left side	Right side	Left side	Right side
Frontal	10 (2)	10 (2)	10 (2)	10 (2)	25-40	
Corrugator	5 (1)	5 (1)	5 (1)	5 (1)	---	---
Procerus	5 (1)		---	---	---	---
Occipital	15 (3)	15 (3)	10 (1)	10 (1)	10	10
Temporal	20 (4)	20 (4)	10 (2)	10 (2)	10-25	10-25
Trapezius	15 (3)	15 (3)	20 (2)	20 (2)	10-30	10-30
Cervical / Paraspinal	10 (2)	10 (2)	20 (2)	20 (2)	10-20	10-20
Minimum Total	**155 (31)**		**150 (20)**		**105-210 (23-58)**	
Optional:						
Occipital[5]	5 (1)	5 (1)				
Temporal	5 (1)	5 (1)				
Trapezius[6]	10 (2)	10(2)				
Masseter					0-25	0-25
Maximum additional	40 (8)					
Maximum total	**195 (39)**		**150 (20)**		**105-260 (23-58)**	

[5] Protocol 79/80; optional site of injection could be injected unilaterally by muscle group; however, not more than 2 additional injections (10 units) could be given for this muscle group
[6] Protocol 79/80; optional site of injection could be injected unilaterally by muscle group; however, not more that 4 additional injections (20 units) could be given for this muscle group.

Table 7: Pooled Phase 3 Trials; Total Dose by Treatment Cycle for 1st and 5th Cycle

Measurement variable		BTA; at least one treatment (N=1300)	BTA; five treatments (N=518)
Units of BTA	Mean SD Median Range	164.3 13.43 155.0 15-195[7]	164.8 13.24 155.0 155-195
Units/kg	Mean SD Median Range <2 2-4 >4	2.3 0.58 2.3 0-4 388 (29.8%) 905 (69.6%) 7 (0.5%)	2.3 0.56 2.3 1-4 149 (28.8%) 367 (70.9%) 2 (0.4%)
Injection Sites	Mean SD Median Range	32.9 2.69 31.0 3-39	33.0 2.65 31.0 31-39
Days to next treatment cycle	Mean SD Median Range	87.3 17.73 85.0 5-273	87.0 5.32 85.0 64-121

[7] There were 16 patients who had 19 injections outside of the protocol specified BTA dose of 155-195 units.

As noted in Section 7.4, there is very little evidence of a carryover effect from one treatment cycle to another with regard to common adverse events. Some adverse events are associated with every injection (e.g. neck pain) while most only occur with the first injection and are most likely tolerated on subsequent injections. Therefore it would be reasonable to assess exposure as though each injection (treatment cycle) were independent of the other. Since in the Phase 3 trials there was fixed dosing (up to 155 units) and flexible dosing from >155 units to 195 units, an exposure by dose received analysis is included in Table 8 . The time intervals in Table 8 represent actual time between doses (as opposed to treatment cycle) but suggest that of the 1711 BTA treatments given in the pooled Phase 3 trials, more than half (51%) were at the lowest dose of 155 units and about 7% were at the highest dose of 195 units.

Table 8: Pooled Phase 3 Trials; Duration of exposure for number (%) patients by acutal doses received

Duration	Number (%) Patients by Actual Doses Received (Units)				
	BTA < 155	BTA 155	BTA 156 – 194	BTA ≥ 195	Placebo
DBPC Exposure					
	N = 2	N = 434	N = 322	N = 58	N = 694
< 12 Weeks	2 (100.0%)	37 (8.5%)	32 (9.9%)	2 (3.4%)	27 (3.9%)
12 to < 24 Weeks	0 (0.0%)	143 (32.9%)	135 (41.9%)	33 (56.9%)	96 (13.8%)
≥ 24 Weeks	0 (0.0%)	254 (58.5%)	155 (48.1%)	23 (39.7%)	571 (82.3%)
Open-label Exposure					
	N = 13	N = 760	N = 618	N = 107	NA
< 12 Weeks	5 (38.5%)	77 (10.1%)	78 (12.6%)	14 (13.1%)	NA
12 to < 24 Weeks	7 (53.8%)	193 (25.4%)	191 (30.9%)	38 (35.5%)	NA
24 to < 36 Weeks	0 (0.0%)	429 (56.4%)	322 (52.1%)	49 (45.8%)	NA
≥ 36 Weeks	1 (7.7%)	61 (8.0%)	27 (4.4%)	6 (5.6%)	NA
Any BOTOX® Exposure					
	N = 15	N = 875	N = 697	N = 124	NA
< 12 Weeks	7 (46.7%)	84 (9.6%)	75 (10.8%)	14 (11.3%)	NA
12 to < 24 Weeks	7 (46.7%)	198 (22.6%)	193 (27.7%)	39 (31.5%)	NA
24 to < 36 Weeks	0 (0.0%)	285 (32.6%)	214 (30.7%)	35 (28.2%)	NA
36 to < 48 Weeks	1 (6.7%)	95 (10.9%)	87 (12.5%)	15 (12.1%)	NA
≥ 48 Weeks	0 (0.0%)	213 (24.3%)	128 (18.4%)	21 (16.9%)	NA

Source: Module 5.3.5.3 ISS Tables 2-10.1, 2-10.2, 2-10.3
Treatment duration was calculated for each patient by summing the treatment cycle durations within each dose group, whether or not the treatment cycles in that dose group were consecutive. Patients were counted for each dose group received; therefore, a patient may appear in more than one column.

Demographics of Trial Population

The patient population recruited for the CM studies were predominantly middle aged, slightly overweight, Caucasian women with a background of chronic conditions including allergies, depression and musculoskeletal conditions. No experience in elderly or in adolescent migraine patients is included in the integrated safety database. All trials excluded patients with any significant medical condition including conditions that could be aggravated by the use of BTA. Potential subjects were excluded if they had a significant psychiatric disorder or any other type of headache or head/neck disorder such as temporomandibular pain that could interfere with assessment of migraine.

Table 9 and Table 10 summarize the baseline demographics and medical conditions of the pooled Phase 3 clinical trial participants and the pooled Phase 2 and Phase 3 controlled clinical trials in CM and CDH

The population included in the Phase 2/3 trials of CM and CDH characterizes the safety of BTA in the group of patients most likely to experience chronic migraine. However, there is only a modest amount of data in adult men, little data in elderly patients of either gender, and no data in patients less than 18 years old. Because safety, and probably efficacy as well, is dose and injection site dependent, it is not possible to extrapolate the safety in this limited population to other populations not represented in the combined Phase 3 trials.

Table 9: Baseline Demographics of Pooled Phase 3 and Phase 2/3 CM/CDH Trials

	Pooled Phase 3 CM Trials		**Pooled Phase 2/3 CM/CDH Trials**	
	BTA/BTA	Placebo/BTA	BTA	Placebo
	N=687	N=692	N=1384	N=1052
Age in years; mean (range)	41.1 (18-65)	41.5 (18-65)	42.1 (18-65)	42.3 (18-65)
Age < 40 years	293 (42.6%)	287 (41.5%)	532 (38.4%)	414 (39.4%)
Age ≥ 40 years	394 (57.4%)	405 (58.5%)	852 (61.6%)	638 (60.6%)
≥ 60 years	27 (3.9 %)	30 (4.3%)	-------	---------
Sex: Male	84 (12.2%)	103 (14.9%)	188 (13.6%)	174 (16.5%)
Female	603 (87.8%)	589 (85.1%)	1196 (86.4%)	878 (83.5%)
Race: Caucasian	616 (89.7%)	626 (90.5%)	1262 (91.2%)	952 (90.5%)
Non-Caucasian	71 (10.3%)	66 (9.5%)	122 (8.8%)	100 (9.5%)
BMI; Mean (range)	26.7 (16-68)	27.2 (15-51)	26.6 (16-68)	26.9 (12-69)
Median	25.5	25.8	25.4	25.7

Table 10: Baseline Medical Characteristics of Pooled Phase 3 and Phase 2/3 CM/CDH Trials[8]

	Pooled Phase 3 CM Trials		Pooled Phase 2/3 CM/CDH Trials	
	BTA/BTA	Placebo/BTA	BTA	Placebo
	N=687	N=692	N=1384	N=1052
Concurrent Conditions (>10% of patients at baseline):				
allergies			16.5%	9.5%
anxiety	---	---	---	----
back pain	13.2%	13.0%	---	----
contraception	13.7%	13.0%	9.0%	10.9%
depression	18.0%	16.6%	11.8%	17.6%
drug sensitivities	23.9%	26.7%	12.9%	9.3%
drug hypersensitivity	---	---	9.8%	10.6%
ear, nose & throat	19.7%	16.2%	18.6%	12.7%
gastrointestinal	---	---	20.2%	12.6%
GERD	11.2%	11.6%	---	---
gynecologic	----	-----	26.7%	17.9%
insomnia	16.6%	18.6%	8.2%	12.3%
musculoskeletal	----	----	25.4%	16.3%
neurological	----	----	10.9%	6.1%
psychiatric	----	----	21.7%	16.2%
pulmonary	----	----	10.0%	5.4%
seasonal allergy	20.8%	21.8%	10.3%	14.4%
tonsillitis	11.2%	7.2%	---	---
Pre-Study HA Prophylactic Medications:				
None	37.9%	34.7%	46.2%	42.1%
Beta blocker	29.5%	31.4%	20.5%	24.9%
Calcium channel blocker	15.1%	13.4%	11.0%	12.0%
Anti-convulsant	45.6%	49.0%	33.5%	38.5%
Anti-depressant	36.5%	35.7%	29.4%	31.6%
Other	26.1%	24.9%	----	----

[8] Different coding dictionaries were used for the Phase 3 trials and the Phase 2 trials resulting in different groupings of coding terms for the Medical History

7.2.2 Explorations for Dose Response

The sponsor provided an assessment of dose response based on the total single BTA dose received at the first treatment cycle in the combined Phase 2 and Phase 3 trials in CM/CDH. Dose groups explored were <150 units, 150-200 units and > 200 units. Because over 99% of the patients in the Phase 3 trials received a dose between 150 and 200 units and because the dose scheme (see Table 6) for the Phase 3 trials was entirely different from the Phase 2 trials, no dose response was identified when the Phase 2 and Phase 3 trials were pooled. No other discussion of dose response was provided by the sponsor.

The sponsor's exploration of a dose response for adverse events is considered inadequate. Furthermore, there is no discussion within the ISS justifying the dosing scheme chosen for the Phase 3 trials based on the Phase 2 safety experience. In fact, the entire development program in headache, when reviewed retrospectively, is a search for a dosing scheme and a population where the placebo response and associated adverse events could be convincingly separated from the overlapping wanted and unwanted effects of BTA. An extensive review of the evolution of dosing schemes based on adverse events is presented in Section 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

Testing for neutralizing antibodies was conducted using the mouse protection assay (MPA). The results of this testing are reviewed in Section 7.4.6. No other special animal or *in vitro* testing was done, nor was any need for additional testing identified during this review.

7.2.4 Routine Clinical Testing

Only adverse event data were collected at clinic visits between baseline and study exit for all the clinical trials included in this sBLA. Vital sign and clinical laboratory data were generally not collected at the interval visits or at the time of repeat dosing. Vital signs and clinical laboratory data were collected at baseline and upon exit from the trial. No ECG data were collected.

On the basis of the adverse event reporting, no specific clinical testing was identified during the course of this review as being necessary for the safe use of BTA. An assessment of the limited laboratory testing that was done can be found in Section 7.4.2.

7.2.5 Metabolic, Clearance, and Interaction Workup

BTA is injected directly into specific muscles and acts directly on the neuromuscular junctions in that muscle. No systemic circulation is expected. The pharmacodynamic effect of BTA on the injected muscle has been described in previous submissions and appears to have duration of about 3 months. The retreatment period for the use of BTA in CM is every 12 weeks, consistent with this duration.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The regional and distant spread of botulinum toxin from the site of injection has been previously identified as a class issue for all products containing any of the subtypes of botulinum toxin. None of the other botulinum toxin products are approved for use in the prophylaxis of migraine or other headache types, but there are published reports of clinical trial results involving other products for use in headaches. As appropriate the adverse events from the published trials with other products are incorporated into the discussion of the major safety results.

7.3 Major Safety Results

7.3.1 Deaths

Only 1 death was reported among the 4076 clinical trial enrollees from the 11 trials included in the sBLA. A placebo treated patient in a Phase 2 trial (038) died. The patient (3224-4711) was a 60-year-old Caucasian male with no significant past medical history, who suffered a syncopal episode and stopped breathing on day 271 of the study (54 days after the third treatment with placebo). The sudden death was considered due to 'cardiac irregularity.' This event was not considered to be related to study treatment by the investigator.

7.3.2 Nonfatal Serious Adverse Events

There were a total of 3235 patients treated with a least one dose of BTA included in the integrated safety database submitted in this sBLA. There were 136 (4.2%) of these patients for whom a nonfatal serious adverse event was reported. The Sponsor's narratives for these patients were reviewed to determine potential drug relatedness. Upon review of the narratives for these 136 patients, it was determined that the cases were heavily confounded by pre-existing medical conditions, concomitant medications, and a history of previous hospitalizations. Attribution of the reported serious adverse event was more likely to a pre-existing condition or an unrelated intercurrent event. Most of the patients with a report of a serious adverse event continued in the study. Thus case by case causality assessment was not productive of a signal of a serious event potentially due to BTA.

Because review and causality assessment of individual case reports of serious adverse events was not particularly helpful, the safety database for the pooled double blind placebo (DBPC) controlled trials was examined. The pooled DBPC safety base (see **Table 11**) was reviewed for potential imbalances in event reporting. Nonfatal serious adverse events occurred in 3.3% (83/2532) of patients treated with BTA compared to 2.3% (36/1544) placebo treated. Most of the imbalance in nonfatal serious adverse event reports could be accounted for by imbalances in events occurring in the neoplasm category, nervous system disorders, gastrointestinal system disorders, and psychiatric disorders system organ classes (SOCs). Only reports coded to migraine, headache, and depression/ major depression occurred more frequently in the BTA treated group compared to the placebo treated patients. These cases are discussed in Section 7.3.3. as discontinuations, in Section 7.3.5 as special safety concerns and in Section 7.6.1 as cases of malignant neoplasms.

One nonfatal serious adverse event occurring in a BTA treated patient, a report of intractable migraine, was considered possibly treatment related by the investigator.

Exacerbation of migraine is discussed in more detail in Section 7.3.5. The sponsor's brief summary of this case is included below.

> Patient 10024-50090 (BOTOX® group), a 44-year-old Caucasian female in study 191622-080, reported intractable migraine (preferred term: migraine; Module 5.3.5.1, Report 191622-080, Table 14.3-1; Listing 16.2.7-3), which was the only serious adverse event reported during DBPC exposure that was considered to be treatment-related by the investigator (Module 5.3.5.3, ISS Table 3-1.1). She received the first treatment with 165 U BOTOX® on (b) (4) and symptoms began 7 days later. She was hospitalized on (b) (4) due to worsening severe headaches and her treatment included dihydroergotamine, a patient controlled analgesia pump, and high dose steroids. The following day, Valium® was also added for a recurrence of chronic trapezius muscle spasm. She was discontinued from the study due to the event, which resolved 4 days later without sequelae.

Table 11: All DBPC Exposure; Number (%) of patients with a nonfatal serious adverse event reported by 2 or more patients in either treatment group

Serious Adverse Event (Preferred Term)	BTA (N = 2532)	Placebo (N = 1544)
OVERALL	83 (3.3%)	36 (2.3%)
Gastrointestinal Disorders	**9 (0.4%)**	**3 (0.2%)**
Abdominal pain	2 (0.1%)	1 (0.1%)
Hepatobiliary Disorders	**4 (0.2%)**	**1 (0.1%)**
Cholelithiasis	2 (0.1%)	1 (0.1%)
Infections & Infestations	**13 (0.5%)**	**9 (0.6%)**
Pneumonia	3 (0.1%)	2 (0.1%)
Appendicitis	2 (0.1%)	1 (0.1%)
Gastroenteritis	0 (0.0%)	2 (0.1%)
Musculoskeletal & Connective Tissue Disorders	**6 (0.2%)**	**3 (0.2%)**
Intervertebral disc protrusion	2 (0.1%)	3 (0.2%)
Neoplasms Benign, Malignant & Unspecified (Including Cysts & Polyps)	**9 (0.4%)**	**3 (0.2%)**
Uterine leiomyoma	3 (0.1%)	1 (0.1%)
Breast cancer	2 (0.1%)	1 (0.1%)
Nervous System Disorders	**17 (0.7%)**	**4 (0.3%)**
Migraine	5 (0.2%)	1 (0.1%)
Headache	4 (0.2%)	0 (0.0%)
Psychiatric Disorders	**5 (0.2%)**	**0 (0.0%)**
Depression	2 (0.1%)	0 (0.0%)
Major Depression	2 (0.1%)	0 (0.0%)
Reproductive System & Breast Disorders	**7 (0.3%)**	**4 (0.3%)**
Endometriosis	1 (0.0%)	3 (0.2%)

The pooled Phase 3 trials safety database was examined for imbalances in the reporting of serious adverse events. This database is not diluted by the inclusion of single dose BTA trials which is a potential problem with the data included in **Table 11**. During the DBPC portion of the Phase 3 trials a total of 33 (4.8%) BTA treated patients and 16 (2.3%) placebo treated patients reported a serious adverse event. Table 12 summarizes the system organ class and preferred MedDRA terms where two or more reports occurred. Consistent with the findings in the overall DBPC safety database, the imbalances in reporting occurred in the infection, neoplasm and nervous system groups However, unlike the larger database, pneumonia occurred in two BTA patients versus only one in the placebo group, suggesting a potential exacerbation by BTA of this event. Pneumonia and other respiratory disorders are examined more closely in Section 7.3.3 and 7.3.5.

Table 12: Pooled Phase 3 Trials: DBPC Exposure; Number (%) of Patients with Serious Adverse Event Reported by ≥2 patients in either treatment group

		Treatment Group	
MedDRA System Organ Class	**MedDRA Preferred Term**	**BTA N = 687**	**Placebo N=692**
Overall		**33 (4.8%)**	**16 (2.3%)**
Infections & Infestations		**7 (1.0%)**	**5 (0.7%)**
	Pneumonia	2 (0.3%)	1 (0.1%)
	Gastroenteritis	0	2 (0.3%)
Neoplasms Benign, Malignant & Unspecified (Including Cysts & Polyps)		**7 (1.0%)**	**2 (0.3%)**
	Breast cancer	2 (0.3%)	0
	Uterine leiomyoma	2 (0.3%)	0
Nervous System Disorders		**9 (1.3%)**	**2 (0.3%)**
	Migraine	4 (0.6%)	1 (0.1%)

ISS Table 3-20.1

The DBPC portion of the Phase 3 trials was only two treatment cycles in length. The majority of the placebo treated patients were treated with BTA for up to 3 treatment cycles in the open label extension. Therefore the open label BTA exposure of 3 treatment cycles provides a more extensive collection of serious adverse events. Roughly half of the patients included in Table 12 received two treatment cycles of BTA

before entering the open label portion of the study (BTA/BTA) while the other half received placebo and the BTA (PLC/BTA).

Table 13: Pooled Phase 3 Trials: Open Label Exposure; Number (%) of patients with serious adverse event reported by ≥ 2 patients in either treatment group

		Treatment Group	
MedDRA System Organ Class	**MedDRA Preferred Term**	**BTA/BTA N = 592**	**PLC/BTA N=613**
Overall		**27 (4.6%)**	**19 (3.1%)**
General Disorders & Administration Site Conditions		**3 (0.5%)**	**0**
	Non-cardiac chest pain	3 (0.5%)	0
Neoplasms Benign, Malignant & Unspecified (Including Cysts & Polyps)		**4 (0.7%)**	**4 (0.7%)**
	Uterine leiomyoma	3 (0.5%)	0
	Squamous cell carcinoma	0	2 (0.3%)
Nervous System Disorders		**6 (1.0%)**	**1 (0.2%)**
	Migraine	4 (0.7%)	0

A total of 1300 patients received at least one dose of BTA in the Phase 3 trials. Based on the combined exposures during the DBPC and the open label portion of the trial, there were 75 (5.8%) patients with a report of a serious adverse event. The MedDRA preferred terms for which two or more reports occurred are summarized in Table 14 in descending frequency.

Table 14: Pooled Phase 3 Trials; Any BTA Exposure: Number (%) of patients with serious adverse events reported by ≥ 2 patients

MedDRA Preferred Term	Any BTA (N=1300)
Overall	**75 (5.8%)**
Migraine	8 (0.6%)
Uterine leiomyoma	5 (0.4%)
Pneumonia	4 (0.3%)
Non-cardiac chest pain	4 (0.3%)
Breast cancer	3 (0.2%)
Small intestinal obstruction	2 (0.2%)
Intervertebral disc protrusion	2 (0.2%)
Basal cell carcinoma	2 (0.2%)
Squamous cell carcinoma	2 (0.2%)
Depression	2 (0.2%)

Brief narratives for the patients included in Table 12, Table 13, and Table 14 can be found in Section 7.3.3, 7.3.5 and 7.6.1 where these serious adverse events are explored in more detail.

7.3.3 Dropouts and/or Discontinuations

This section focuses on the discontinuations that occurred in the pooled Phase 3 trials. The design of the CRF for the Phase 2 trials in this sBLA did not capture the adverse event leading to discontinuation. Since this data was not consistently recorded, it is not evaluable in an integrated manner. Only the report of results for Protocol 039 was reviewed in detail with regard to discontinuations due to an adverse event.

Pooled Phase 3 Trials

Table 15 summarizes the disposition of all randomized patients in the pooled Phase 3 trials (Protocols 079 and 080). The "all randomized" dataset contains 5 more patients than the "exposed" data set used for safety analysis. However, the pattern of discontinuations between the two datasets should not be remarkably dissimilar. During the double-blind portion of the trial the largest proportion of patients were discontinued for adverse events, personal reasons, lost to follow up or other.

Table 15: Pooled Phase 3 Trials; Patient Disposition

	Treatment Group	
Disposition	**BTA/BTA**	**PLC/BTA**
Enrolled	688*	696 *
Completed double-blind phase (week 24)	607 (88.2%)	629 (90.4%)
Discontinued prior to week 24	81 (11.8%)	67 (9.6%)
Adverse events	19 (2.8%)	5 (0.7%)
Lack of efficacy	5 (0.7%)	1 (0.1%)
Pregnancy	3 (0.4%)	2 (0.3%)
Lost to follow-up	13 (1.9%)	23 (3.3%)
Personal reasons	19 (2.8%)	16 (2.3%)
Protocol violations	1 (0.1%)	3 (0.4%)
Other	21 (3.1%)	17 (2.4%)
Completed open-label phase (week 56) and entire study	513 (74.6%)	492 (70.7%)
Discontinued entire study	175 (25.4%)	204 (29.3%)
Adverse events	38 (5.5%)	26 (3.7%)
Lack of efficacy	16 (2.3%)	21 (3.0%)
Pregnancy	6 (0.9%)	6 (0.9%)
Lost to follow-up	24 (3.5%)	52 (7.5%)
Personal reasons	41 (6.0%)	37 (5.3%)
Protocol violations	4 (0.6%)	7 (1.0%)
Other	46 (6.7%)	55 (7.9%)

* This is an ITT dataset analysis. Five of the randomized patients never received treatment and therefore do no appear in the safety analysis dataset.; ISE Table 1-1

Because the other category was the most frequent reason for discontinuation, the data listings of discontinuations for Protocols 079 and 080 (Table 16.2.1) were examined for additional information in the "specify reason" section to identify potential adverse events imbedded in the discontinuation categories. The most frequent reason for a discontinuation listed as other was lack of efficacy. Section 7.3.5 of this review contains an expanded discussion of the underreporting of lack of efficacy. Additional information was not found for discontinuations classified as lost to follow-up or personal reasons.

There is disagreement between the ISE and ISS tables (Table 15 and Table 16 respectively) with regard to the proportion of patients discontinued due to an adverse

event. Because the ISS tables report a higher number of such discontinuations, the remainder of this section uses the ISS analyses.

During the blinded portion (2 treatment cycles) of the Phase 3 trials (Protocols 079 and 080) discontinuations attributed to an adverse event were 3.8% (26/687) and 1.2% (8/692) in the BTA and placebo group respectively. Regardless of the body system associated with the adverse event prompting discontinuation, the frequency was greater in the BTA group compared to the placebo group.

Table 16 summarizes the discontinuations due to adverse events in both the blinded and the open label exposure portions of the Phase 3 trials. Noteworthy are the early discontinuations occurring in both phases of the trial due to neck pain, muscular weakness, migraine and headache. Pain and weakness are well documented adverse events associated with other BTA indications (See Section 2.6) and are associated with the particular muscle or group of muscles injected. Migraine and headache were efficacy endpoints for the trial. With the exception of migraine and headaches considered a serious adverse event or leading to discontinuation, the most reliable data on the frequency and extent of migraine and headache are part of the efficacy evaluation. During the open label exposure, when the placebo-treated patients began open label treatment with BTA, the frequency of discontinuations for neck pain, muscular weakness, migraine and headache increased compared to the BTA experienced patients.

Table 16: Pooled Phase 3 Trials; Adverse events leading to discontinuation of ≥ 2 patients

MedDRA System Organ Class MedDRA Preferred Term	Treatment Group	
Blinded Exposure	**BTA N = 687**	**Placebo N = 692**
OVERALL	**26 (3.8%)**	**8 (1.2%)**
Eye Disorders	**2 (0.3%)**	**0 (0.0%)**
Eyelid ptosis	2 (0.3%)	0 (0.0%)
Musculoskeletal & Connective Tissue Disorders	**8 (1.2%)**	**1 (0.1%)**
Neck pain	4 (0.6%)	0 (0.0%)
Muscular weakness	3 (0.4%)	0 (0.0%)
Neoplasms Benign, Malignant & Unspecified (Including Cysts & Polyps)	**2 (0.3%)**	**1 (0.1%)**
Breast cancer	2 (0.3%)	0 (0.0%)
Nervous System Disorders	**10 (1.5%)**	**2 (0.3%)**
Headache	3 (0.4%)	1 (0.1%)
Migraine	3 (0.4%)	1 (0.1%)
Open-label Exposure	**BTA/BTA N = 592**	**Placebo/BTA N = 613**
OVERALL	**13 (2.2%)**	**18 (2.9%)**
Musculoskeletal & Connective Tissue Disorders	**6 (1.0%)**	**9 (1.5%)**
Neck pain	1 (0.2%)	4 (0.7%)
Muscle spasms	2 (0.3%)	2 (0.3%)
Muscular weakness	0 (0.0%)	3 (0.5%)
Joint stiffness	2 (0.3%)	0 (0.0%)
Muscle tightness	0 (0.0%)	2 (0.3%)
Musculoskeletal pain	0 (0.0%)	2 (0.3%)
Nervous System Disorders	**4 (0.7%)**	**6 (1.0%)**
Headache	1 (0.2%)	2 (0.3%)
Migraine	1 (0.2%)	2 (0.3%)

ISS Table 3-21.1

Table 17 summarizes the adverse event information about each of the discontinuations that occurred in the pooled Phase 3 trials organized according to severity and type of adverse event. Overall there were 56 of 1300 patient (4.3%) exposed to BTA that discontinued treatment during either the blinded or the open label portion of the pooled Phase 3 trials. Using the MedDRA Preferred Term for coding these discontinuations the most frequent reasons were neck pain (0.6%), migraine (0.5%), headache (0.5%), muscular weakness (0.5%) and eyelid ptosis (0.3%).

In order to obtain the most comprehensive information on the 56 patients discontinued for an adverse event, the listings of discontinuation in the report of Protocols 079 and 080 were reviewed (Listing 16.2.7-5) as well as the narratives for each of the patients. The majority of the adverse events occurred within several weeks of receiving a dose of BTA, many within a couple of days. Approximately half of the adverse events occurred after the first dose of BTA. Over half were attributed by the investigator to BTA during the blinded and open label portion of the trial driven principally by adverse events previously associated with the use of BTA such as neck pain and muscle weakness.

The dose of BTA received by patients discontinuing BTA was 155 units for all treatment cycles in about half the cases with the rest receiving a variety of doses between 155 and 190 units depending on the investigator's and patient's ability to isolate the muscles associated with pain. Only one of the discontinuations occurred in a patient receiving only 195 units of BTA; 10056-11476 who received 4 treatment cycles of BTA before being discontinued for worsening headaches. Two other patients (10042-50853 and 10030-50697) received 195 units for at least one treatment cycle.

Table 17: Phase 3 Trials 079 and 080; Patients discontinued for an adverse event

Site-Patient ID/ Listing 16.2.7-5	Age/ Gender	BTA Dose	# of BTA doses	Days post-dose	Severity/ Related to Drug*	SER	Adverse Events
10005-51032/Y	28/F	155	1	14	severe/ No	Yes	pleurisy; bilateral **pneumonia**
10003-50677/Y	30/F	155	3	1	severe/ Yes	No	**Neck pain**; also experienced severe neck and face pain after Treatment #2
10003-50608/Y	54/F	155	1 OL	1	severe/ Yes	No	**neck pain**
10031-50279/Y	64/M	155-160	4 OL	10	severe/ Yes	No	**stiffness of neck muscles**; bilateral stiffness of shoulder muscles; stiffness of upper back muscles; first episode occurred after Treatment #3 but persisted with dose reduction in Treatment #4
10003-50227/Y	43/F	175	2 OL	30	severe/ Yes	No	**body aches**; occurred after each treatment
10031-50639/Y	43/F	155	3 OL	4	severe/ Yes	No	**jaw pain** and limited jaw range of motion
10005-51103/Y	23/F	155	2	2	severe/ Yes	Yes	**worsening of migraine**; **jaw locking** open due to muscular weakness; also experienced less severe jaw locking 10 days after Treatment #1
10024-50090/Y	44/F	165	1	7	severe/ Yes	Yes	**intractable migraine**
10031-50736/Y	35/F	175	1	1	severe/ No	No	**worsening of migraine**
10026-51567/Y	46/F	155	2 OL	1	severe/ No	No	**increased headache and viral syndrome**
11401-50716/Y	59/M	165-185	4 OL	5	severe/ No	No	**exacerbation of migraine**
10014-10498/Y	50/F	165	1	76	severe/ Yes	No	**increased amount of headaches** and neck pain
10029-10203/Y	39/F	155	2	33	severe/ No	No	**increasing headaches**
11305-10654/Y	64/M	175	1	29	severe/ No	No	**worsening headache**
11307-10470/Y	52/F	175	1 OL	1	severe/ Yes	No	**increased headache severity;** flu-like symptoms; bilateral arm weakness; shoulder and neck pain; nausea and vomiting
10056-11476/Y	52/F	195	4 OL	42	severe/ Yes	No	**worsening of headache severity**
10033-50627/Y	46/F	185	5 OL	16	severe/ No	Yes	**brain tumor, malignant**
10042-51408/Y	60/F	155	2	75	severe/ No	Yes	**breast cancer**
12504-51270/Y	57/F	155	1	6	severe/ No	Yes	**breast cancer**

Site-Patient ID/ Listing 16.2.7-5	Age/ Gender	BTA Dose	# of BTA doses	Days post-dose	Severity/ Related to Drug*	SER	Adverse Events
10047-50749/Y	39/F	165	1 OL	23	severe/ No	Yes	**exacerbation of depression** with suicidal ideation; history of depression, obsessive/compulsive disorder and anxiety
10029-10921/Y	45/F	160	1	41	severe/ No	Yes	**major depression**; history of manic depression
10009-11590/Y	32/M	155	1	1	severe/ No	No	**explosive disorder and confusion**
10042-50853/Y	46/F	155-195	4 OL	39	severe/ No	Yes	**tachycardia**
10026-10609/Y	46/M	185	1	18	severe/ No	Yes	right carotid artery occlusion; **right cerebral infarction**
10027-10686/Y	32/F	105-155	2		severe/ No	No	**injection site pain** after Treatment #1 and refused further treatment after partial Treatment #2
10027-11410/Y	42/F	180	4 OL	1	severe/ Yes	No	**injection site pain**; dizziness
10015-50408/Y	54/F	155	1	63	moderate/ Yes	No	**tightness in forehead**
10019-50404/Y	32/F	155	2	2	moderate/ Yes	No	bilateral **neck muscle weakness** and neck extensor weakness
10030-50697/Y	29/F	155-195	4 OL	10	moderate/ No	No	**worsening of neck soreness**; first experienced after treatment #2 with persistence until discontinuation
10049-51268/Y	41/F	185	1 OL	7	moderate/ Yes	No	**weakness of cervical muscles** (difficult to lift head up from forward leaning position)
10005-51016/Y	23/F	165	1 OL	10	moderate/ Yes	No	localized **muscular weakness**
10006-50952/Y	32/F	155-165	3 OL	23	moderate/ Yes	No	**tightness back of head/spasm back of head** (coded as TENSION HEADACHE/MUSCLE SPASMS); also had head and shoulder tightness after Treatment #1
10034-10433/Y	33/F	165	1	2	moderate/ No	No	**worsening cervical pain** and muscle spasms
10010-10937/Y	53/F	155	1	1	moderate/ Yes	No	**heavy neck** (coded as MUSCLE WEAKNESS)
11306-51573/Y	65/F	155-175	4 OL	6	moderate/ Yes	No	**worsened constipation**; reported abdominal pain with previous treatments

Site-Patient ID/ Listing 16.2.7-5	Age/ Gender	BTA Dose	# of BTA doses	Days post-dose	Severity/ Related to Drug*	SER	Adverse Events
10024-50748/Y	56/M	165	1 OL	6	moderate/ Yes	No	**skin tightness** above both eyebrows
10041-51358/Y	42/F	155	1 OL	1	moderate/ Yes	No	**pain in shoulder and neck**
10025-11042/Y	47/F	155	4 OL	33	moderate/ No	No	**neck spasm**
10038-10103/Y	49/F	175	2 OL	6	moderate/ Yes	No	dysphagia; **tightness in the back of the neck**
10001-10814/Y	48/F	190	2 OL	1	moderate/ No	No	**back pain**; shoulder pain; neck pain
10034-10704/Y	44/F	155	2 OL	2	moderate/ Yes	No	**exacerbation of dizziness**; heavy feeling in head; worsening of neck pain
10008-10979/Y	59/F	165	1	69	moderate/ No	Yes	**atrial fibrillation and syncope**; 10 year history of syncope
10015-50282/Y	54/F	155-185	3 OL	2	moderate/ Yes	No	**non-cardiac chest pain**; dyspnea; also had dyspnea after previous treatments
10025-11194/Y	57/F	155	1	12	moderate/ No	No	**worsening hypertension** attributed to overuse of Relpax
10019-11145/Y	64/M	155	2	65	moderate/ No	No	**right upper extremity numbness**; attributed to carpal tunnel syndrome
11301-50560/N	39/F	155	1 OL	1	moderate/ Yes	No	**increase in migraine**
10039-10731/Y	51/F	155	1 OL	1	moderate/ Yes	No	**worsening of migraine**; injection site pain/bruising; neck pain/spasms; dry mouth
10030-50968/Y	25/F	155	1 OL	1	moderate/ Yes	No	**blurred vision**
10048-50821/Y	47/F	165	2 OL	7	moderate/ Yes	No	right **eyelid ptosis**; reported eyelid ptosis after Treatment #1 as well
10026-50287/Y	62/F	160	1	1	mild/ Yes	No	bilateral **eyelid ptosis** (coded as FACIAL PARESIS)
10043-51485/Y	54/F	155	1	1	mild/ Yes	No	bilateral **eyelid ptosis**

Site-Patient ID/ Listing 16.2.7-5	Age/ Gender	BTA Dose	# of BTA doses	Days post-dose	Severity/ Related to Drug*	SER	Adverse Events
10014-50756/Y	25/F	155	4 OL	7	mild/ Yes	No	left **eyelid ptosis**
10001-11170/Y	24/F	190	1	13	mild/ Yes	No	**eyelid ptosis**
10023-50236/Y	42/F	155-160	2 OL	2	mild/ Yes	No	**paresthesia** of face and rash on forehead; reported paresthesia after Treatment #1
10048-10912/N	48/F	165-187	3	40	mild/ No	No	**whiplash injury**; began after motorcycle accident following TRT #2
10007-10307/Y	41/F	155-165	4 OL	13	mild/ Yes	No	difficulty closing jaw due to **jaw stiffness**; developed after TRT #3 and persisted after TRT #4
10007-50355/Y	45/F	0	1	1	severe/ Yes	No	left head pain
10047-50583/Y	44/F	0	2	14	severe/ No	Yes	pulmonary sarcoidosis
11301-10960/Y	43/F	0	1	56	severe/ Yes	No	worsening of migraines
10050-51553/Y	47/F	0	2	60	moderate/ No	No	hives related to adhesives applied after surgery for varicose veins
10009-10571/Y	38/F	0	2	78	moderate/ No	No	temporo-mandibular joint syndrome
11307-11016/Y	53/F	0	1	7	moderate/ No	No	worsening of anxiety and panic attacks
11307-51059/Y	23/F	0	2	76	mild/ No	Yes	thrombocytopenia; family history of idiopathic thrombocytopenia
10026-51100/Y	32/F	0	1	48	mild/ No	Yes	papillary thyroid cancer

*Related as assessed by investigator; ISS Listing 16.2.7-5 and Table 13.3; OL = open label; SER= serious; Y=yes; N=No

Exacerbation of migraine is explored more fully in Section 7.3.5. The cases of cancer are discussed in Section 7.6.1. The sponsor's short narratives for the other serious and severe cases of pneumonia, depression, tachycardia, and cerebral infarction are included below.

- Patient 10005-51032, a 28-year-old Caucasian female in study191622-080, had **bilateral pneumonia**. She received her first dose of 155 U of BOTOX® on 08 February 2007. On (b) (6), she was hospitalized with pneumonia after failing outpatient therapy for bronchitis. Her treatment included cefepime, Zyvox®, Albuterol®, guaifenesin, and pantoprazole, and she was discharged on (b) (6). The investigator did not consider the event to be related to BOTOX®.
- Patient 10047-50749 a 40-year-old Caucasian female with history of depression, obsessive compulsive disorder, and anxiety in study 191622-080, reported **worsening of depression**. She received her third dose (and first dose of 165 U of BOTOX® on (b) (6). On (b) (6) (i.e., 23 days later), she was admitted to the hospital with depression, suicidal ideation, and bipolar disorder. She was treated and released on (b) (6) The investigator did not consider this event to be related to BOTOX®.
- Patient 10029-10921 a 45-year-old black female in study 191622-079 with a history of manic depression, auditory hallucinations, and a suicide attempt, reported **depression** with psychotic features. She received the first dose of 160 U of BOTOX® on 28 November 2006. She had been psychiatrically stable for approximately 2 years, but had stopped taking her medications. On an unreported date, she developed hallucinations and went to an emergency department on (b) (6). She was admitted to the psychiatric ward on (b) (6) treated, and discharged on (b) (6) The investigator did not consider the event to be related to BOTOX®.
- Patient 10042-50853, a 47-year-old Caucasian female with a history of anxiety, mild depression, and adult attention deficit disorder in study 191622-080, had **tachycardia**. She received her fourth dose of 195 U of BOTOX® on (b) (6) On (b) (6), 39 days later, she presented to the emergency department with tachycardia. She was admitted and catheterized, which revealed normal cardiac anatomy and normal ejection fraction. She was discharged on (b) (6) The investigator did not consider this event to be related to BOTOX®.
- Patient 10026-10609, a 46-year-old Caucasian male in study 191622-079 with a history of hypertension, hypercholesterolemia, myocardial infarction, and femoral bypass, had a right carotid occlusion/right hemispheric **cerebral infarction**. He received the first dose of 185 U of BOTOX® on (b) (6). Twenty days later, on (b) (6) he was hospitalized after developing left-sided weakness. He was diagnosed with complete right carotid occlusion and right hemispheric infarction. He gradually improved and was transferred to a

rehabilitation center. The investigator did not consider these events to be related to BOTOX®.

None of these cases was considered attributable to BTA exposure by the investigator or the sponsor. After view of the narratives for the cases of depression, tachycardia and cerebral infarction, the adverse event could be reasonably attributed to pre-existing conditions. However, the case of pneumonia (10005-51032) could potentially be explained by the action of BTA on respiratory muscles .

Case 10005-51032 describes a 28 year old white female with a normal BMI who was enrolled in Protocol 080, randomized to received BTA and received her first dose of 155 units of BTA on (b) (6) Two weeks after receiving her first dose of BTA the patient was hospitalized with left lower lobe pneumonia. The patient was discontinued from the trial.

The sponsor collected follow up information on this patient as follows :

Additional information received 16-MAR-2007: The patient's symptoms started six weeks prior to hospitalization and consisted of flu-like symptoms with fever of 103 to 104 degrees, chills and generalized malaise. She was diagnosed by her primary care physician as having bronchitis and was treated with prednisone and albuterol, but the patient's symptoms did not improve. **She developed right-sided pleuritic chest pain about a week later and went to the urgent care center[emphasis added]**[9], where she was diagnosed with pneumonia and started on Levaquin for five days and was also given Toradol once. The patient completed her course of antibiotic with still no improvement and once again returned to her primary care physician. She was prescribed doxycycline and Percocet and received Rocephin once. The patient was subsequently hospitalized on (b) (6) On admission, her blood pressure was 114178 mmHg, heart rate was 110 beats/minute, respiratory rate of 12 breaths/minute, temperature of 97.8 degrees and oxygen saturation was 98% on room air. Her white blood cell count (WBC) was 10 (10A9/L). Blood and sputum cultures were both negative. Chest X-ray and computed tomography noted left lower lobe infiltrates with superimposed small nodular components and focal consolidation. The patient was treated with cefepime due to a history of methicillin-resistant Staphylococcus aureus (MRSA), although hospital cultures were negative for MRSA. The patient was also treated with Zyvox. The patient also received Albuterol nebulizer, guaifenesin, influenza vaccine, pantoprazole, Pneumoccocal vaccine, potassium chloride, acetaminophen, enoxaparin, prochlorperazine, and oxycodone. On (b) (6) the patient was afebrile and doing well. Chest X-ray on (b) (6) noted unchanged left lower lobe airspace disease consistent with a clinical history of pneumonia, and her WBC was 5.6 (10A9/L). The patient was discharged on oral Levaquin and Zyvox. She recovered with sequelae and was released from the hospital on (b) (6)

9 The timing is a week after she received her first dose of BTA, NOT a week after the occurrence of flu-like symptoms.

There is some conflict between the narrative provided by the sponsor and the CRF as well as some disingenuous wording in the narrative as noted above. The patient was screened for the trial 4 weeks prior to receiving her first dose of BTA at which time she was afebrile but was noted to have wheezing at the left lower base of her lungs which cleared with coughing. She successfully completed the four week screening/baseline period and was randomized to receive BTA. Two days after receiving her first BTA dose she presented with the right sided pleuritic pain for which was treated with Levaquin and Toradol. The Rocephin and doxycycline was initiated one week after the first BTA dose, and two weeks after the BTA dose she was hospitalized.

This case of pneumonia is possibly related to BTA. While there is some pre-existing evidence of bronchitis and lower left lung symptoms, the signs and symptoms became significantly worse within several days of receiving the first dose of BTA. Additional examination of respiratory adverse events occurring after use of BTA is discussed in Section 7.3.5.

Of note among the mild to moderately severe adverse events associated with discontinuation are the number of discontinuations due to eyelid ptosis. This particularly event, while not serious/severe with regard to its clinical presentation, must be considered a potential safety hazard for the functionality of the patient. While sufficient patient reported information regarding the effect of ptosis on their ability to function is not included in the data provided on these cases, similar cases reported in the postmarketing setting suggest that eyelid ptosis is potentially hazardous to driving and working. (See Section 8)

Phase 2 Trial: Protocol 039

Protocol 039 was a Phase 2 fixed dose, 3 cycle, double-blind comparison of 0, 75, 150 and 225 units of BTA that enrolled a total of 702 patients at 28 US centers. The protocol was amended during the course of the trial from 1 active treatment cycle to 3 active treatment cycles therefore the completion and discontinuation data may not be representative of continuous exposure for all enrolled patients. Nonetheless the discontinuation rate for adverse events is worth examining for the 150 unit and 225 unit BTA dosing group since it exceeds what was reported for the combined Phase 3 trial BTA group; 7.7% and 5.9% versus 3.8%, respectively. A total of 18 patients discontinued at the highest BTA doses compared to three in the combined low dose BTA and placebo group. Table 18 summarizes the subject disposition for Trial 039.

Table 18: Trial 039; Disposition of patients

	BTA 225 U	BTA 150 U	BTA 75 U	Placebo
Enrolled	182	168	174	178

	BTA 225 U	BTA 150 U	BTA 75 U	Placebo
Complete protocol as assigned	100 (74.1%)	102 (78.5%)	94 (70.1%)	91 (65.5%)
Discontinued	35 (25.9%)	28 (21.5%)	40 (29.9%)	48 (34.5%)
Lack of efficacy	17 (12.6%)	7 (5.4%)	11 (8.2%)	28 (20.1%)
Adverse event	8 (5.9%)	10 (7.7%)	2 (1.5%)	1 (0.7%)
Administrative	6 (4.4%)	5 (3.8%)	18 (13.4%)	11 (7.9%)
Protocol violation	0 (0.0%)	1 (0.8%)	1 (0.7%)	0 (0.0%)
Other	3 (2.2%)	4 (3.1%)	7 (5.2%)	7 (5.0%)
Site Terminated	1 (0.7%)	1 (0.8%)	1 (0.7)	1 (0.7%)

The report for Protocol 039 contains no analysis of discontinuations for adverse events. The CRF for each discontinuation was included in the final report for Protocol 039 as well as a listing of patients discontinued because of an adverse event. The CRF and narrative for each patient in the listing discontinued due to an adverse event was reviewed and the adverse events are tabulated in Table 19. It should be noted that the table included in the report for Trial 039 and reproduced here as Table 18 does not match the number of discontinuations included in the Table 19. Based on review of the listing and CRF for each patient, there were 8 discontinuations in the 225 unit dose group for an adverse event, 13 in the 150 unit group, 3 in the 75 unit group and 2 in the placebo group.

Table 19: Trial 039; Patients discontinued for an adverse event

Site-Patient ID	Age/ Gender	BTA Dose	Study Day(Days after BTA dose)	# of BTA doses	Severity	SER	Adverse Events
2322-1054	47/F	225	1	1	moderate	No	band-like pressure around head; neck weakness
2373-1262	61/F	225	1	1	severe	No	pain, soreness in posterior neck; nausea; drooped left eyebrow lid; neck weakness; bilateral eyebrow limited movement
3071-1446	53/F	225	1	1	severe	No	sinus infection, ptosis of left eye; bilateral blepharitis; worsening of headache; facial numbness; severe aching of right eyebrow
3137-1456	29/F	225	1	1	moderate	No	neck weakness; low back pain; difficulty swallowing; URI
3137-1464	47/F	225	1	1	moderate	No	neck pain; occipital pain; nausea; pain at trapezius injection site; difficulty swallowing; right knee pain; neck weakness
3270-2729	34/F	225	1 day after 1st; 3 days after 2nd	2;	moderate	No	neck muscle weakness; neck pain; facial muscle tightening
3270-2738	42/F	225	1	1	moderate	No	shoulder pain; neck pain; shoulder weakness; neck weakness; increased headache pain
3666-1014	45/F	225	48	1	severe	Yes	**hospitalized for bilateral numbness and tingling from shoulders to toes**
2373-1260	53/F	150	1	1	moderate	No	head, neck & shoulder soreness; dysphagia; mid-back pain;
2828-1630	35/F	150	94	2	severe	Yes	**hospitalized for brain abscess secondary to shunt**
2828-2600	33/F	150	2	1	moderate	No	dysphagia; body pain
2830-1712	46/M	150	69	2	moderate	Yes	neck pain; gastric distress; insomnia; **vomited with blood**; pruritus; sore throat; diarrhea; mild elevations of LFTs

Site-Patient ID	Age/ Gender	BTA Dose	Study Day(Days after BTA dose)	# of BTA doses	Severity	SER	Adverse Events
3071-2426	40/F	150	12	1	severe	Yes	**hospitalized for leg weakness, pain, parathesias, migratory polyarthralgias;**
3129-1604	49/F	150	1	1	moderate	No	neck weakness; neck soreness; kidney stones
3130-1690	35/F	150	30	2	moderate	No	depression; loss of forehead wrinkles
3312-1920	51/F	150	7	1	moderate	No	neck sore; neck stiff; injection site bruising
3670-2008	46/F	150	3	1	moderate	No	dysphagia; neck pain; bilateral shoulder pain; nausea
3671-1313	47/F	150	4	1	moderate	No	sore neck; head feels heavy
3672-1213	45/F	150	1	1	mild	No	injection site pain; myalgia at base of neck and back of shoulders; alopecia; URI; anisocoria
3672-2204	42/F	150	7	2	moderate	No	injection site pain; difficulty swallowing; right triceps myalgia; radiculopathy secondary to lumbar herniated disk; ptosis
3700-1645	43/F	150	2	1	moderate	No	worsening of headaches; tension type headache; ptosis; nausea
3270-2737	62/F	75	52	1	mild/ moderate	No	neck weakness; bilateral neck pain; strep throat; shingles in right upper quadrant of head
3672-1218	47/M	75	62	2	severe	No	severe worsening headaches; decreased sensation bilateral at corrugator and temple
3673-1495	23/F	75	3	1	severe	No	severe shoulder and neck pain
3672-1201	58/F	placebo	38	1	moderate	No	injection site pain; URI; worsening headache
3701-1864	40/F	placebo	84	2	severe	Yes	**motor vehicle accident**;

The most frequent reasons for terminating the study are consistent with the overall adverse event profile for this study which is described in Section 7.4.1 Table 31. Most of the adverse events occurred within several days of receiving a BTA dose. The review of the narratives for these discontinuations revealed at least two cases of interest where there is a possible causal relationship to BTA. Both cases involve some unusual motor and sensory nerve findings that might suggest an effect of BTA that is not related to local muscle paralysis. In patient 3071-2426 there are some pre-existing conditions confounding the adverse event that may be relevant to its occurrence; however, the timing of the onset of the new symptoms cannot be ignored.

Patient 3666-1014 is a 46 year old woman who received placebo run-in treatment on October 21 and the first dose of 225 units of BTA on (b) (6). Besides migraine, she had a history of back pain for which she received tramadol and mitral valve prolapse. On (b) (6) (48 days later), the patient complained of "numbness and tingling from shoulder to toes" (hypoesthesia). She was admitted to a hospital, however an MRI of the brain, and lumbar puncture were unremarkable, and no etiology to her symptoms was found. She was incidentally found to have a "low B 12'" although the relationship between this finding and her symptoms is unclear. She was discharged from the hospital on (b) (6). Patient started taking vitamin B 12 and by May 21, 2002, her symptoms reportedly resolved without sequellae, though she now notes a non-serious adverse event: bilateral numbness in the legs and feet. This was also felt to be unrelated to study treatment. In the opinion of the clinical investigator, this adverse event was not related to the study drug.

Patient 3071-2426, a 40 year old Caucasian female with history of seasonal allergies (1987), depression (1995), asthma (1999), intermittent elevated intracranial pressure, fronto-parietal meningioma, head trauma, irritable bowel syndrome, fibromyalgia, hypothyroidism, and multiple drug allergies, was enrolled and received placebo run-in on December 3, 2002. She received her first dose of 150 U BTA on (b) (6) Twelve days after her BTA dose she was hospitalized with a one week history of migratory polyarthralgias, acute low back pain, right foot cellulitis, right leg pain, swelling and paresthesias. Some time in (b) (6), she also complained of urinary retention. There was a question of weakness in the left leg as well. An outpatient MRI scan of the LS spine had revealed a very mild disc bulge and a questionable signal abnormality in the right ilium and area of the SI joint. Her physical examination was limited due to pain, but there was at least 4+/5 strength in the proximal right leg. There appeared to be right foot weakness, as well as weak toe movements. Her reflexes were brisk at the knees, and trace at the left ankle. The reflex was not assessable at the right ankle. Her toes were down-going. Additionally, she appeared to have a possible sensory level deficiency in the upper lumbar region that was slightly asymmetric. She underwent multiple tests, and her EBV IgG and IgM were noted to be elevated. Her ESR varied from 96 to 112. Other rheumatological tests were unremarkable. She had multiple diagnostic tests, which were essentially noncontributory, including a bilateral lower extremity EMG, bilateral lower extremity venous doppler testing, an MRI of the thorax and pelvis, abdominal ultrasound, CT scan of the brain, and a transthoracic echocardiogram. The patient's xrays revealed only nominal left first MTP joint osteoarthritis of the left foot. X-

rays of the left knee showed only mild suprapatellar soft tissue fullness and effusion. Left knee synovial cultures were normal. She was incidentally found to have an elevated TSH of 6.25, and a freeT4 of 1.3. A lumbar puncture was not performed. The patient's pain and strength improved spontaneously, however the etiology of the patient's acute low back pain and lower extremity weakness was unclear at the time of discharge The patient was incidentally found to have a cardiomyopathy of uncertain etiology, although EBV was considered as a possible etiology. The Investigator did not consider the muscular weakness or any of the other reported adverse events related to study drug treatment. The patient discontinued the study on (b) (6) due to these adverse events.

Conclusions on Discontinuations

The frequency of discontinuation for an adverse event was less than 5% for all BTA exposures in the Phase 3 trials compared to about 30% for all reasons. Because the Other category for discontinuations accounted the largest proportion of discontinuations (about 8%) in the Phase 3 trials and appeared to contain may reports of lack of efficacy, the sponsor was asked to reanalyze the Phase 3 trial discontinuations for all instances of lack of efficacy. The results of this re-analysis are discussion in Section 7.3.6.

In both the Phase 3 trials and the dose comparison Phase 2 trial (039) many of the discontinuations were related to adverse events commonly associated with BTA injections for other indications and attributable to the local pharmacological activity of the drug such a muscle pain, weakness, stiffness, or spasm. While some were considered severe in intensity, most occurred within several days of receiving a BTA dose and none resulted in hospitalization. In contrast, there were a number of discontinuations due to severe headaches and migraine which resulted in hospitalization. The serious adverse event reports of headache and migraine occurring in the Phase 3 trials are described more completely in Section 7.3.5.

There were three serious cases leading to discontinuation in which the temporal association with the BTA dose and the subsequent adverse events are possibly related to BTA and pre-existing conditions do not fully explain the subsequent events. A case of pneumonia occurring 2 weeks after the first dose of 155 units of BTA, a case of severe numbness and tingling occurring 6 to 7 weeks after a 225 unit dose of BTA, and a case of migratory arthralgia and weakness occurring 2 weeks after a 150 unit dose of BTA. A viral etiology might be the explanation for any or all of these unusual cases, or they may reflect a secondary spread of toxin effect and /or nerve activity.

7.3.4 Significant Adverse Events

See discussion of specific adverse events of interest in Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

Regional and Distant Spread of Toxin Effect

The sponsor conducted an analysis of the entire safety database using a set of MedDRA codes intended to signal distant spread of toxin effect if it occurred in this patient population. The terms used were intended to capture cases of acute botulinum toxin poisoning based on the clinical presentation of a wound or food-borne poisoning. Forty MedDRA terms were chosen; however only 17 terms were actually associated with reports in the integrated safety database. Table 20 contains the MedDRA terms by symptom of botulism. These terms were identical to the terms used in the spread of toxin analysis recently submitted by the manufacturers of all botulinum toxin products with the exception of the specific term "muscle paresis" that was included in that set of terms and "extraocular muscle paresis" that was not included.

Table 20: MedDRA Version 11.1 Preferred Terms Evaluated for Possible Distant Spread of Toxin

Airway reflexes and breathing
- Aspiration
- Diaphragmatic paralysis
- Dyspnoea *
- Pneumonia aspiration*
- Respiratory arrest
- Respiratory depression
- Respiratory failure*

Weakness, body
- Hyporeflexia
- Hypotonia*
- Muscular weakness*
- Paralysis
- Paralysis flaccid
- Pelvic floor muscle weakness
- Peripheral nerve palsy
- Peripheral paralysis

Ocular manifestations
- Accommodation disorder
- Diplopia*
- Extraocular muscles paresis*
- Eyelid function disorder
- Eyelid ptosis*
- Pupillary reflex impaired
- Vision blurred*

Cranial neuropathies
- Bulbar palsy
- Cranial nerve palsies multiple
- Cranial nerve paralysis
- Facial palsy*
- Facial paresis*
- Paresis cranial nerve

Autonomic manifestations
- Bradycardia*
- Constipation*
- Dry mouth*
- Ileus paralytic
- Urinary retention*

Speech and swallowing
- Dysarthria*
- Dysphagia*
- Dysphonia

Speech disorder
- Vocal cord paralysis
- Vocal cord paresis

Botulism
- Botulism

* Preferred terms reported across patients following placebo or BTA treatment

Of the 4076 patients included in the analysis 34 of 1544 (2.2%) placebo treated patients and 658 of 2532 BTA treated patients (25.9%) had an adverse event report corresponding to at least one of the MedDRA codes in Table 20. In general, the analysis provided no signals that were not already apparent in the analysis of common adverse events described in Section 7.4.1. Ten of the 17 terms with adverse event reports were interpreted by the sponsor as associated with local adverse events including eyelid ptosis, diplopia, vision blurred, extraocular muscle paresis, facial palsy, facial paresis, dysarthria, dysphagia, dry mouth, and hypotonia.

The sponsor reviewed cases in all report categories that appeared inconsistent with local spread, but all were associated with another primary condition or confounded by concomitant drugs. My review of the reports associated with those terms is included below.

The seven remaining terms were dyspnea, aspiration pneumonia, respiratory failure, muscular weakness, bradycardia urinary retention and constipation. One patient had respiratory failure and aspiration pneumonia secondary to a carotid artery occlusion and cerebral infarction. One patient had urinary retention confounded by medical history and the concomitant use of an anticholinergic drug. One patient had bradycardia reported 76 days after receiving a BTA dose.

Fourteen patients reported constipation, 2 patients on placebo (0.1%) and 12 patients on BTA (0.5%). The sponsor was asked to provide more detail on these cases to assess whether the muscle groups and dose of BTA injected were associated with a potential pattern suggesting a causal relationship with BTA. The sponsor's response to this request was received on May 26, 2010 and included additional information on each of the cases. The demographics of the 14 cases were similar to the overall safety database, Of the 12 patients treated with BTA, the average dose was 114 units at the time of the report with a range of 9 to 204 units. The timing of the event was an average of 42 days after the BTA dose with a range of 1-98 days. All reports of constipation occurred as single reports without other events potentially associated with spread of BTA toxin. Three of the 12 BTA cases occurred after the first dose, while the other cases were reported after multiple cycles. The events were generally mild to moderate and were confounded by medical history or concurrent use of medications associated with bowel symptoms including constipation. No positive rechallenge was reported.

Muscular weakness is a common adverse event associated with BTA. There were 228 reports of muscular weakness in patients receiving BTA (9%) and 7 in patients receiving placebo (0.5%). Only 5 of the 228 reports in BTA treated patients involved muscle weakness outside the muscles injected. Only one of the five cases described a patient that I considered potentially related to BTA. This patient (3071-2426) is described in Section 7.3.3 as one of the discontinuations of concern in Protocol 039.

Dyspnea was reported in 10 patients treated with BTA and 2 patients treated with placebo. Dyspnea (breathing difficulties) is included in the current PI for BOTOX as being associated with treatment of cervical dystonia. Since there is overlap between the muscle groups injected for treatment of cervical dystonia and CM, it is not surprising that there are reports of dyspnea in this analysis. The neck muscles serve as accessory muscles during respiration and to the degree that any given patient may be more or less dependent on these muscles for respiration, a BTA injection in one of the muscles could produce symptoms of decreased respiratory function. One of the 10 patients with a positive rechallenge is described here. The other nine patients did not have a recurrence after repeat dosing and all completed the study.

Patient 10015-50282, a 54 year old Caucasian female with history of degenerative joint disease and herniated cervical disc, was enrolled in study 191622-080 and received her first treatment with BTA 185 units. That day she was also treated for a herniated disc with tizanidine (muscle relaxant), which was discontinued the following day. Two days after injection she complained of intermittent moderate shortness of breath and nasal congestion. She received Astelin® nasal spray for the nasal congestion and no treatment for the shortness of breath. The events resolved 15 days later. The Investigator considered both events possibly related to study drug treatment. The patient continued in the study and was treated for a second time with BTA 155 units. Two days later she developed intermittent, moderate shortness of breath which resolved on 37 days later. No treatment was given for the shortness of breath. The Investigator considered the event possibly related to study drug treatment. The patient received a third treatment with BTA 165 units. Two days later she again complained of intermittent, moderate shortness of breath along with moderate non-cardiac chest tightness. No treatment was given for either of these events. The Investigator considered both possibly related to study drug treatment. The patient discontinued the study due to non-cardiac chest pain.

The analysis paradigm for distant spread of botulinum toxin used in this sBLA is intended to detect acute effects of botulinum toxin poisoning. With possible exception of constipation, none of the events that surfaced in this analysis were unexpected. All (b) (4) Further analysis of the cases of constipation generally revealed concurrent conditions that could explain the event, and none of the reported cases included other signs or symptoms of distant spread of toxin.

With the submission of this sBLA there is a new and somewhat different safety consideration which is the signs and symptoms of toxicity after chronic use of BTA. Muscular weakness is reported as an acute adverse event and tends to decrease over time based on presumed tolerance to this local effect. However, other adverse events continue to be reported at about the same rate in every cycle, suggesting that tolerance is not developing. A discussion of time dependent adverse events is presented in Section 7.5.2.

Falls

During the open label exposure period of the pooled Phase 3 trials, there was an excess of falls reported in the chronically treated group (up to 5 treatment cycles) compared to the group that received placebo for 2 of 5 treatment cycles. Falls may be an indicator of cumulative toxicity of BTA related to visual effects, muscular weakness or other potential drug effects culminating in an accidental injury including falls. Therefore the individual reports of the Phase 3 trials were reviewed for information on the patients experiencing falls.

The report of results from Protocol 080 includes 1 fall in the BTA group and 3 in the placebo group during the DBPC phase and 6 falls in the BTA/BTA group and none in the placebo/BTA group during the open label exposure phase. Of the 7 falls in the BTA group, one occurred after the second treatment, 5 occurred about the third treatment, 1 occurred after the fourth treatment. In the placebo/BTA group one occurred after the first treatment and two occurred after the second treatment, none occurred during the BTA treatment phase. One of the falls in the BTA/BTA treatment group was considered severe. Table 21 is a summary of the cases coded as FALL in Trial 080. A search of the patient line listings and comments revealed one additional case of fall in the BTA group in Trial 080.

The report of results from Protocol 079 includes reports of 5 falls in the BTA group and 3 in the placebo group during the DBPC phase; and 2 reports in the BTA/BTA group and 1 in the placebo/BTA group during the open label exposure phase. One each of the reports of a fall in a BTA and a placebo treated patient was considered severe. Table 22 is a summary of the cases coded as FALL in Trial 079.

For combined Phase 3 trials 079 and 080 there were 12 cases of FALL occurring during treatment with BTA excluding cases secondary to syncope or accident (hit by car, fell off horse, etc.) The 12 cases are lightly shaded in Table 21 and Table 22. There were five cases of FALL in patients receiving placebo after their most recent treatment. Two of the BTA cases occurred after the first treatment as did 2 placebo cases. Four cases were reported after the second BTA treatment as were 3 placebo cases. There were 4 reports of FALL after 3 BTA treatments and 2 after four treatments.

The results of Trial 039, a fixed dose comparison study, was examined for instances of FALL in the verbatim reports of adverse events. As noted elsewhere in this review, the adverse events in Trial 039 were coded using a modified COSTART dictionary. COSTART does not have a preferred term called FALL so the verbatim reports from the investigators contained in the individual patient listing were screened for mentions of "fall". Table 23 summarizes those adverse events reports in which "fall" was mentioned. While this analysis of adverse events reported secondary to a fall is suboptimal, there is

no strong suggestion of a dose response and several occurred at time where the contribution of BTA to the fall is unlikely (Day 85 and 91 post-dose).

The distribution of reports of FALL over time with BTA compared to placebo in the combined Phase 3 trials does not suggest a strong trend for an increase with increasing exposure dose of BTA. A examination of adverse events secondary to "fall" in Trial 039 does not suggest a dose response. Therefore, no precautions in the labeling regarding the potential for falls with BTA treatment are recommended at this time

Table 21: Trial 080: Summary of adverse events coded as FALL

Pt ID	Age/ Sex	Drug	Verbatim	Severity	TRT Cycle	Days after injection	Other AEs (TRT cycle)	Comments
100019-50259	43/F	BTA	fall	mild	3	55	neck strain (3); sinusitis (3); diabetes (3); peripheral neuropathy (3)	fall due to imbalance, pt underwent CT scan of head secondary to head trauma, CT showed no intracranial abnormality except for sinus disease
11306-51592	45/F	BTA	fall	mild	2	7	pain to occiput (2); dizziness (2); right eye ptosis (3); right antecubital fossa pain (4)	headache and dizziness after the fall
12502-50700	41/F	BTA	fall	mild	3	1	neurodermatitis (2); frontal sinusitis (5); syncope (3)43	hypotension 1 day after medication, no allergic reaction, prolonged phase of hypotension with one syncope and fall on right side
10033-50410	48/F	BTA	fell down stairs	moderate	3	0	benign breast neoplasm(5); hordeolum (4)	
10048-50739	60/M	BTA	fall from a standing position	moderate	3	23	pain in left ankle (3); right sided neck pain(3); tension headache(3)	pt was hit as a pedestrian in a crosswalk
10022-51291	31/F	BTA	fall onto floor, did not require treatment	severe	3	16	joint dislocation (3); shoulder discomfort(3)	
10043-51130	32/F	BTA	fall	not reported	4	15	broken 5th metatarsal, left foot(4)	AE due to fall...
10007-50480	43/F	plc	fall	mild	2	26	trauma to left index finger (2)	patient tripped on ground
10007-50526	32F	plc	fall	mild	2	25	chest cold (2)	fell on a step
10033-50394	27/F	plc	pt. fell off a high stool	moderate	1	23	fractured left wrist (1); sprained left ankle (1); bruised left side (1)	pt fell off a high stool
Other cases with "fall" mentioned in the investigator verbatim								
10030-51162	41/F	BTA	ligament rupture	moderate	3	74	staph infection in right ear (4); hearing loss right ear (4)	pt complained of tearing ligament in left ankle after slipping and falling

Table 22: Trial 079; Summary of adverse events coded as FALL

Pt ID	Age/ Sex	Drug	Verbatim	Severity	TRT Cycle	Days after injection	Other AEs (TRT cycle)	Comments
10008-10970	59/F	BTA	fall	moderate	1	69	cardiac chest pain (1)	fall secondary to syncope and atrial fibrillation
10010-10225	41/F	BTA	patient fell	moderate	2	16	right frontal sinus head ache (1); back injury (2), neck injury (2); stiff neck post injection (1)	
10019-11145	64/M	BTA	fall	moderate	2	58	right upper extremity numbness, pain (2); carpal tunnel syndrome (2)	new onset neck pain after a fall in his home followed by RUE pain and numbness and tingling
10024-11021	45/F	BTA	slip and fall	moderate	4	49	shoulder stiffness (2); wrist sprain (4); URI (5); GI bleed (5); abdominal pain (5); gastritis (5)	wrist sprain resulted from fall at work after patient slipped on a puddle of water
10029-10391	48/F	BTA	fall	moderate	2	42	neck soreness (1); neck pain (1); acclower back pain (2); disclocated jaw (2); worsening migraine (2)	back pain and joint dislocation due to fall
10040-10579	27/F	BTA	accidental fall	moderate	1	19	right knee torn ligament (1)	ligament rupture due to accidental fall
10015-11006	46/F	BTA	fall	severe	3	57	contusion of right lower back (3); abrasion right elbow (3)	traumatic fall from a horse which resulted in injury to back and elbow
10006-11028	47/F	Plc/ BTA	fall	mild	3 (1st BTA)	11	bronchitis (1); strained lower back muscle (2)	
10039-10731	51/F	Plc	fall	moderate	1	1	neck pain (1); injection site pain (0); dry mouth(3); overactive bladder (3).....	patient fell hitting back, neck and shoulders, did not seek medical care
11301-10795	58/F	Plc	fall on ice	moderate	2	46	hypertension (3)	bruising to breast
10014-10139	57/F	Plc	fall	severe	2	1	stomach flu (1); worsening headache (2); rhinitis (1); asthma (1); syncope (2); ecchymosis (2); head trauma (2)	pt had stomach flue and a syncopal episode and struck her head

Table 23: Trial 039; Summary of cases with mention of FALL in verbatim adverse event report

Pt ID	Age/ Sex	Drug	Verbatim	Severity	TRT Cycle	Days after injection	Other AEs	Comments
2322-1035	51/F	BTA 225	bruised forehead and wrist due to fall	moderate	3	19	bronchitis, torn tendon in left foot	
1667-1079	54/F	BTA 225	tripped and fell causing bruising of right hand and foot	mild	2	50	neck weakness, difficulty swallowing on left side of throat	
3672-1199	35/F	BTA 225	left should and hip pain after fall	moderate	1	85	none	
1672-1202	29/F	BTA 150	pain at sacral region secondary to fall	moderate	1	60	sore throat, photophobia, sleep disturbance	
3672-1206	50/F	BTA 75	unconsciousness secondary to fall	moderate	1	57	knee contusion, facial laceration, TMJ sprain	
3672-2206	39/F	BTA 75	distal radius fracture secondary to fall	moderate	2	11	elbow contusion, knee dysfunction	
3700-1652	61/M	BTA 75	fracture left wrist secondary to fall	severe	1	91	neck rigidity	
3270-2731	22/F	BTA 75	fall on tail bone	moderate	1	25	tail bone pain	
3312-1402	52/F	plc	hip and arm pain secondary to fall	moderate	1	8	arm bruising, difficulty sleeping	
2830-1734	47/F	plc	hematoma resulting from a fall	mild	unk	unk		

Exacerbation of Migraine

The BTA development program for headache prevention is remarkable for the number of Phase 2 studies demonstrating little efficacy and dose-related adverse events suggesting tolerability issues with BTA that did not outweigh any perceived effectiveness. While reviewing discontinuations in the Phase 3 trials, the number of patients hospitalized or discontinuing treatment because of migraine headaches was impressive as were the coded reports and ancillary notes suggesting lack of efficacy. Thus, a more extensive examination of both serious reports of migraine exacerbation and reports of "lack of efficacy" were done. The results of those analyses for migraine are presented in this section followed by an analysis of lack of efficacy in the following section.

In order to identify all cases of serious adverse events reported as migraine including both those reported as serious because of hospitalization and those resulting in discontinuation, the narratives for the Phase 3 trials were searched for all headaches compatible with migraine. Only the Phase 3 trials were explored because of the difference in dose and injection scheme used in the Phase 2 trials.

There were 15 reports of migraine in the BTA treated group and 2 (0.3%) in the placebo group from the pooled Phase 3 trials. Nine (1.3% of the 687 patients exposed to BTA) of the 15 BTA reports occurred during the double-blind phase (Cycle #1 and #2) and are lightly shaded in Table 24. Five of the nine cases discontinued further treatment with BTA. The remaining 6 occurred during the open label extension. Six of the BTA cases in the double blind period and 4 in the open label period were reported within the first week after receiving a BTA treatment with the remaining reported 7 to 9 weeks after a treatment. Since there were only 2 cases in the placebo group, there is insufficient data to characterize the time course for a migraine resulting in hospitalization or discontinuation in the absence of BTA exposure. Narratives for the patients in Table 24 who were hospitalized as a result of the migraine headache can be found in Appendix 9.4.

Exacerbation of migraine has been previously reported with triptans [1]; however, the current PI for triptans does not appear to have information on this phenomenon (b) (4)

Table 24: Pooled Phase 3 Trials; Cases of migraine considered serious or resulting in discontinuation

ID/ Protocol Number	Age/ Sex	SAE	BTA Dose	Cycle	Days post treatment	Treatment	Hosp.	DC from Study
10005-51103/80	23/F	severe worsening of migraine	155 units	2	2	Not reported	No	Yes
10018-51186/80	40/F	worsening migraine	190	2	63	IV fluids, morphine, Phenergan	Yes	No
10024-50090/80	44/F	intractable migraine	165 units	1	7	dihydroergotamine, analgesic NOS, steroids, diazepam	Yes	Yes
10031-50736/80	35/F	severe worsening of migraine	175 units	1	1	nerve block, Elavil	No	Yes
10038-50607/80	33/F	intractable migraine	155	2	49	dihydroergotamine	Yes	No
10041-50555/80	37/F	continuous migraine	155	5	6	dihydroergotamine, metoclopramide, diphenhydramine prochlorperazine, valproate	Yes	No
11410-50716/80	59/M	severe exacerbation of migraine	165	4	5	none	No	Yes
11301-5056-/80	39/F	moderate increase in migraine	155	1	1	none	No	Yes
10005-11539/79	29/F	intractable migraine	155	1	5	dihydroergotamine, Dilaudid, Zofran	Yes	No
10007-11324/79	31/F	status migrainosus	175	4	6	Dilaudid, dihydroergotamine, steroids, Zofran	Yes	Yes
10013-10449/79	56/F	worsening migraine	180	3	17	Demerol, Dilaudid, IV fluids, steroids, Vistaril, Fioricet	Yes	No
10016-10204/79	20/F	status migraine without aura	155	1	49	dihydroergotamine	Yes	No
10032-11643/79	52/F	exacerbation of migraine	155	5	10	dihyroergotamine, Demerol, valproate, Phenergan	Yes	No
10039-10687/79	34/F	intractable migraine	155	4	6	Nubain, Vistaril, Demerol, dihydroergotamine, oxycodone, levetiracetam	Yes	No
10039-10731/79	51/F	worsening migraine	155	1	1	None	No	Yes

ID/ Protocol Number	Age/ Sex	SAE	BTA Dose	Cycle	Days post treatment	Treatment	Hosp.	DC from Study
10504-51615/80	51F	acute migraine	placebo	2	1	dihydroergotamine	Yes	No
11301-10960/79	43/F	severe worsening of migraine	placebo	1	56	None	No	Yes

Lack of Efficacy

During the review of line listings and CRFs for patients discontinued from the Phase 3 trials, it was noted that lack of efficacy appeared to be inconsistently reported and recorded in these documents. The sponsor was asked to conduct a search for all instances of drug ineffectiveness using the MedDRA SMQ for this outcome. A search of the discontinuation database was done for terms related to both lack of efficacy as well as migraine and headache as the latter were presumed to indicate a treatment failure consistent with a discontinuation for lack of efficacy. A total of 37 patients were included in the original tables as a discontinuation due to lack of efficacy. As a result of the expanded search for lack of efficacy an additional 39 patients were identified as having discontinued due to treatment ineffectiveness.

Table 25 summarizes the results of the expanded analysis of reasons for discontinuation. The results of this re-analysis for discontinuation are somewhat counterintuitive. During the double-blind phase of the study it would be expected that more patients in the placebo group would discontinue for "drug ineffectiveness"; however, the opposite is true in the pooled Phase 3 trials such that the result is statistically significant. During the open-label phase of the trial, the patients that received BTA during the double-blind phase are receiving their third treatment with BTA while the placebo treated patients are receiving their first treatment. The large number of patients discontinuing in the open label phase in the Placebo/BTA group compared to the continuing BTA treated patients in the BTA/BTA group is striking, in part because the patients are receiving active treatment for the first time and might be expected to have a more dramatic drug response after having received placebo for the first phase. While the discontinuation data for lack of efficacy is based on only about 5% of the overall pooled population, it is an adverse event that is the most common reason for discontinuing treatment in the Phase 3 trials.

Table 25: Pooled Phase 3 Trials: Reports of treatment ineffectiveness at discontinuation

	BTA/BTA N=687	Placebo/BTA N=692
Double-Blind Phase (2 treatment cycles)		
Drug Ineffective	12 (1.7%)	5 (0.7%)
Headache	1 (0.1%)	0
Migraine	3 (0.4%)	1 (0.1%)
TOTAL	16 (2.3%)*	6 (0.9%)
Open Label Phase (3 treatment cycles)		
Drug Ineffective	20 (2.9%)	32 (4.6%)
Headache	0	0
Migraine	0	2 (0.3%)
TOTAL	20 (2.9%)**	34 (4.9%)

*p=0.03; **p=0.055

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Pooled Phase 3 Trials; Double-Blind Placebo Controlled (DBPC) Exposure

The most frequently reported adverse events during the blinded portion (2 treatment cycles) of the pooled results of the Phase 3 trials are summarized in

Table 26. Individual adverse events reported in ≥ 1% of patients in either group are included in the table. Adverse events reported approximately 50% more frequently in the BTA group compared to placebo are **bolded** in the table. Vomiting, fatigue, injection site bruising, contusion, and anxiety were reported approximately 50% more frequently in the placebo group compared to the BTA group.

Table 26: Pooled Phase 3 Trials; DBPC Exposure; Number (%) of patients with adverse events reported by ≥1% of patients in either treatment group

System Organ Class Preferred Term	BTA (N = 687)	Placebo (N = 692)
OVERALL	**429 (62.4%)**	**358 (51.7%)**
Eye Disorders	38 (5.5%)	10 (1.4%)
Eyelid Ptosis	**25 (3.6%)**	**2 (0.3%)**
Gastrointestinal Disorders	49 (7.1%)	54 (7.8%)
Nausea	14 (2.0%)	17 (2.5%)
Vomiting	5 (0.7%)	10 (1.4%)
General Disorders & Administration Site Conditions	60 (8.7%)	57 (8.2%)
Injection site pain	**23 (3.3%)**	**14 (2.0%)**
Fatigue	3 (0.4%)	13 (1.9%)
Injection site bruising	3 (0.3%)	7 (1.0%)
Immune System Disorders	10 (1.5%)	8 (1.2%)
Seasonal allergy	5 (0.7%)	7 (1.0%)
Infections & Infestations	170 (24.7%)	167 (24.1%)
Nasopharyngitis	28 (4.1%)	30 (4.3%)
Sinusitis	28 (4.1%)	27 (3.9%)
Upper respiratory tract infection	27 (3.9%)	37 (5.3%)
Bronchitis	**17 (2.5%)**	**11 (1.6%)**
Influenza	11 (1.6%)	16 (2.3%)
Gastroenteritis viral	9 (1.3%)	13 (1.9%)
Urinary tract infection	6 (0.9%)	7 (1.0%)
Pharyngitis streptococcal	**8 (1.2%)**	**4 (0.6%)**
Injury, Poisoning and Procedural Complications	50 (7.3%)	54 (7.8%)
Procedural pain	8 (1.2%)	6 (0.9%)
Contusion	6 (0.9%)	9 (1.3%)

System Organ Class Preferred Term	BTA (N = 687)	Placebo (N = 692)
Musculoskeletal & Connective Tissue Disorders	169 (24.6%)	85 (12.3%)
Neck pain	**60 (8.7%)**	**19 (2.7%)**
Musculoskeletal stiffness	**25 (3.6%)**	**6 (0.9%)**
Muscular weakness	**24 (3.5%)**	**2 (0.3%)**
Myalgia	**21 (3.1%)**	**6 (0.9%)**
Musculoskeletal pain	**18 (2.6%)**	**10 (1.4%)**
Arthralgia	12 (1.7%)	9 (1.3%)
Muscle spasms	**13 (1.9%)**	**6 (0.9%)**
Back pain	8 I1.2%)	9 (1.3%)
Muscle tightness	**9 (1.3%)**	**3 (0.4%)**
Nervous System Disorders	117 (17.0%)	74 (10.7%)
Headache	**32 (4.7%)**	**22 (3.2%)**
Migraine	**26 (3.8%)**	**18 (2.6%)**
Facial paresis	**15 (2.2%)**	**0 (0.0%)**
Dizziness	11 (1.6%)	12 (1.7%)
Psychiatric System Disorders	26 (3.8%)	28 (4.0%)
Depression	8 (1.2%)	9 (1.3%)
Anxiety	5 (0.7%)	12 (1.7%)
Insomnia	8 (1.2%)	8 (1.2%)
Respiratory System Disorders	34 (4.9%)	36 (5.2%)
Cough	7 (1.0%)	10 (1.4%)
Pharyngolaryngeal pain	7 (1.0%)	9 (1.3%)
Skin Disorders	46 (6.7%)	33 (4.8%)
Rash	7 (1.0%)	6 (0.9%)
Pruritus	**7 (1.0%)**	**2 (0.3%)**
Vascular Disorders	13 (1.9%)	13 (1.9%)
Hypertension	**11 (1.6%)**	**7 (1.0%)**

BAL 103000/5215; Table 3.7.1

Other events that occurred more frequently (based on actual numbers) in patients in the BTA group versus placebo group at a frequency less than 1% and potentially BTA related include: **vertigo** (3 v 0); **dry eye** (3 v 0); **eyelid edema** (3 v 0); **dysphagia** (5 v 1); **cellulitis** (3 v 0); **eye infection** (3 v 0); and **jaw pain** (5 v 0).

The Musculoskeletal and Connective Tissue System in

Table 26 contains a number of individual adverse events that lack specificity with regard to the anatomic location of the event. This is concerning since the potential spread of BTA to other muscle groups could cause muscle weakness not attributable to local effect but reported in the general categories represented by the MedDRA Preferred Term (PT) . This concern, especially regarding muscle weakness, is also addressed in Section 7.3.5 (Regional and Distant Spread of Toxin).

The verbatim reports for the adverse events reports in the Musculoskeletal and Connective Tissue System were reviewed and the lower level term (LLT) in the MedDRA coding dictionary gave more specificity regarding anatomic location. In a requested amendment to the sBLA the sponsor provided an additional analysis of the adverse events in the pooled Phase 3 trials based on the LLT. Table 27 provides more specific information on the adverse events reported in the musculoskeletal system category using the LLT.

Table 27: Pooled Phase 3 Trials: DBPC Exposure: Musculoskeletal & Connective System Adverse Events; Preferred and Lower Level Terms

System Organ Class **Preferred Term** Lower Level Term	**BTA** **(N = 687)**	**Placebo** **(N = 692)**
Musculoskeletal & Connective Tissue Disorders	169 (24.6%)	85 (12.3%)
Neck pain	**60 (8.7%)**	**19 (2.7%)**
Musculoskeletal stiffness	**25 (3.6%)**	**6 (0.9%)**
Neck stiffness	16 (2.3%)	2 (0.7%)
Stiff neck	6 (0.9%)	5 (0.7%)
Muscular weakness	**24 (3.5%)**	**2 (0.3%)**
Myalgia	**21 (3.1%)**	**6 (0.9%)**
Musculoskeletal pain	**18 (2.6%)**	**10 (1.4%)**
Shoulder pain	13 (1.9%)	6 (0.9%)
Arthralgia	12 (1.7%)	9 (1.3%)
Muscle spasms	**13 (1.9%)**	**6 (0.9%)**
Cervical spasm	5 (0.7%)	3 (0.4%)
Back pain	8 I1.2%)	9 (1.3%)
Muscle tightness	**9 (1.3%)**	**3 (0.4%)**

BAL 103000/5215; Table 3.7.1

The analysis of the adverse events in the musculoskeletal system by the MedDRA LLT reveals that most of the reports of "musculoskeletal stiffness" were actually neck stiffness. Likewise the reports of "musculoskeletal pain" were primarily shoulder pain and the reports of "muscle spasm" were primarily cervical spasms. The review of the LLT for "muscular weakness," "myalgia," "arthralgia," and "muscle tightness" did not provide further specificity regarding the anatomical location of the adverse event; however, a review of the verbatim terms demonstrated a similar pattern of neck and shoulder distribution.

The adverse events reported more frequently in the BTA group compared to the placebo group were neck pain, headache, migraine, musculoskeletal (neck) stiffness, eyelid ptosis, muscular weakness, injection site pain, myalgia, musculoskeletal (shoulder) pain, bronchitis, facial paresis, muscle spasms (cervical), muscle tightness, hypertension, streptococcal pharyngitis, and pruritus. The emergence of migraine and

headache as more frequent in the BTA group is the subject of an analysis of serious adverse events reported as migraine in Section 7.3.5. The emergence of bronchitis and streptococcal pharyngitis as significantly more frequent in the BTA group compared to the placebo group is also surprising, although the approval of an indication for adult spasticity during the pendency of this sBLA included bronchitis as a serious adverse reaction noted in the Warnings and Precautions section of the PI.

Pooled Phase 3 Trials: Open Label Exposure

Protocols 079 and 080 had an open label extension whereby all enrollees in the DBPC portion of the trial were continued on open label BTA injections for an additional 3 treatment cycles. Of the initial randomized cohort of 1379 patients in the DBPC portion of the trial, 1205 (87%) continued into the open label extension. Table 28 compares the adverse events in the newly treated patients (Placebo/BTA) to the chronically treated patients (BTA/BTA). Adverse events with approximately a 50% increase in the number of events in the between group comparison, regardless of group are **bolded** in the table.

Table 28: Pooled Phase 3 trials; Open Label Exposure; Number (%) of patients with adverse events reported by ≥1% of patients in either treatment group

System Organ Class/ Preferred Term	BTA/BTA (N = 592)	Placebo/BTA (N = 613)
OVERALL	**329 (55.6%)**	**374 (61.0%)**
Eye Disorders	24 (4.1%)	35 (5.7%)
Eyelid ptosis	13 (2.2%)	17 (2.8%)
Gastrointestinal Disorders	41 (6.9%)	57 (9.3%)
Nausea	12 (2.0%)	10 (1.6%)
Vomiting	10 (1.7%)	7 (1.6%)
Diarrhea	6 (1.0%)	5 (0.8%)
Abdominal pain	**6 (1.0%)**	**2 (0.3%)**
General Disorders & Administration Site Conditions	46 (7.8%)	44 (7.2%)
Injection site pain	15 (2.5%)	11 (1.8%)
Influenza like illness	**4 (0.7%)**	**8 (1.3%)**
Fatigue	**8 (1.4%)**	**3 (0.5%)**
Non-cardiac chest pain	**7 (1.2%)**	**3 (0.5%)**

System Organ Class/ Preferred Term	BTA/BTA (N = 592)	Placebo/BTA (N = 613)
Infections & Infestations	144 (24.3%)	152 (24.8%)
Sinusitis	32 (5.4%)	29 (4.7%)
Nasopharyngitis (common cold)	26 (4.4%)	31 (5.1%)
Upper respiratory tract infection	24 (4.1%)	24 (3.9%)
Influenza	12 (2.0%)	13 (2.1%)
Urinary tract infection	12 (2.0%)	13 (2.1%)
Bronchitis	**8 (1.4%)**	**15 (2.4%)**
Gastroenteritis viral	6 (1.0%)	5 (0.8%)
Injury, Poisoning and Procedural Complications	51 (8.6%)	32 (5.2%)
Contusion	6 (1.0%)	4 (0.7%)
Fall	**8 (1.4%)**	**1 (0.2%)**
Investigations	23 (3.9%)	27 (4.4%)
Alanine aminotransferase increased	7 (1.2%)	10 (1.6%)
Aspartate aminotransferase increased	**3 (0.5%)**	**9 (1.5%)**
Musculoskeletal & Connective Tissue Disorders	89 (15.0%)	144 (23.5%)
Neck pain	27 (4.6%)	43 (7.0%)
Muscular weakness	**9 (1.5%)**	**27 (4.4%)**
Muscle tightness	**7 (1.2%)**	**22 (3.6%)**
Musculoskeletal stiffness (neck)	**5 (0.8%)**	**19 (3.1%)**
Musculoskeletal pain (shoulder)	**4 (0.7%)**	**21 (3.4%)**
Myalgia	**4 (0.7%)**	**16 (2.6%)**
Muscle spasms	10 (1.7%)	9 (1.5%)
Back pain	**11 (1.9%)**	**6 (1.0%)**
Arthralgia	7 (1.2%)	7 (1.1%)
Nervous System Disorders	71 (12.0%)	75 (12.2%)
Migraine	22 (3.7%)	17 (2.8%)
Headache	**12 (2.0%)**	**22 (3.6%)**
Dizziness	12 (2.0%)	9 (1.5%)
Facial paresis	**3 (0.5%)**	**12 (2.0%)**
Hypoesthesia	**6 (1.0%)**	**1 (0.2%)**
Psychiatric Disorders	19 (3.2%)	31 (5.1%)
Depression	**3 (0.5%)**	**13 (2.1%)**
Insomnia	**5 (0.8%)**	**10 (1.6%)**
Anxiety	**3 (0.5%)**	**8 (1.3%)**
Respiratory Disorders	23 (3.9%)	22 (3.6%)
Pharyngolaryngeal pain	6 (1.0%)	6 (1.0%)
Cough	4 (0.7%)	6 (1.0%)
Skin Disorders	23 (3.9%)	34 (5.5%)
Rash	**4 (0.7%)**	**10 (1.6%)**
Vascular Disorders	11 (1.9%)	11 (1.8%)
Hypertension	8 (1.4%)	8 (1.3%)

BAL 103000/5215; Table 3.7.2

In the group newly exposed to BTA, the frequency of musculoskeletal adverse events is much higher than in the chronically treated patient suggesting both a strong association with the use of BTA but also the development of tolerance to these effects over time. The same is true of facial paresis, headache and rash/pruritus. As with the analysis of the DBPC portion of the Phase 3 trials the emergence of bronchitis as more frequent in the newly treated group suggests that the reporting of this adverse event may indeed be associated with BTA use and an effect on respiratory function. Other events occurring more frequently in the newly exposed treatment group compared to the BTA/BTA group were influenza-like illness, AST increased, depression, insomnia and anxiety.

The imbalance between groups with more reports in the chronically BTA treated patients compared to the newly treated patients reveals a spectrum of adverse events not seen during the DBPC phase, but potentially reflecting adverse events associated with repeated exposure to BTA. These events include abdominal pain, fatigue, non-cardiac chest pain, fall, back pain, and hypoesthesia. (see Section 7.3.5 for further discussion of FALL).

Phase 3 Trials; Repeated Dosing, Chronic Use

There were 518 (75%) of the initial 687 patients randomized to the BTA group in the pooled Phase 3 trials that continued into the open label extension and received 5 cycles of BTA treatment (every 12 weeks). Adverse events occurring in ≥ 2% of patients in the 5 cycle group are summarized in Table 29.

The most frequently reported adverse events during five cycles of treatment were not different from the events reported after 2 cycles (see Table 26) of treatment with BTA. Those events that were reported 50% frequently compared to placebo during the DBPC portion of the Phase 3 trials are bolded in the table below. Compared to the DBPC reporting frequency, the five cycle frequency for eyelid ptosis was 4.8% v 3.6%; injection site pain 5.0% v 3.3%; bronchitis 3.5% v 2.5%; neck pain 11% v 8.7%; muscular weakness 4.1% v 3.5%; muscle tightness 2.1% v 1.3%; musculoskeletal stiffness 4.6% v 3.5%; musculoskeletal pain 3.3% v 2.6%; myalgia 3.5% v 3.1%; muscle spasms 2.9% v 1.9%; migraine 6.2% v 3.8%; headache 5.2% v 4.7%; facial paresis 2.1% v 2.2% and hypertension 3.1% v 1.6%. The proportional increase in these adverse events is consistent with the addition of three more treatment cycles. A more extensive discussion of adverse event reports by treatment cycle can be found in Section 7.5.2. and Table 38.

Table 29: Pooled Phase 3 Trials; Number (%) of adverse events occurring after 5 BTA treatment cycles in ≥ 2% of patients

System Organ Class/ Preferred Term	BTA/BTA (5 cycles) (N = 518)
OVERALL	**404 (78.0%)**
Eye Disorders	42 (8.1%)
Eyelid ptosis	**25 (4.8%)**
Gastrointestinal Disorders	65 (12.5%)
Nausea	19 (3.7%)
Vomiting	12 (2.3%)
General Disorders & Administration Site Conditions	74 (14.3%)
Injection site pain	**26 (5.0%)**
Immune System Disorder	13 (2.5%)
Infections & Infestations	213 (41.1%)
Sinusitis	49 (9.5%)
Nasopharyngitis	46 (8.9%)
Upper respiratory tract infection	39 (7.5%)
Influenza	19 (3.7%)
Urinary tract infection	14 (2.7%)
Bronchitis	**18 (3.5%)**
Gastroenteritis viral	12 (2.3%)
Injury, Poisoning and Procedural Complications	75 (14.5%)
Investigations	24 (4.6%)
Musculoskeletal & Connective Tissue Disorders	167 (32.2%)
Neck pain	**57 (11.0%)**
Muscular weakness	**21 (4.1%)**
Muscle tightness	**11 (2.1%)**
Musculoskeletal stiffness (neck)	**24 (4.6%)**
Musculoskeletal pain (shoulder)	**17 (3.3%)**
Myalgia	**18 (3.5%)**
Muscle spasms (cervical)	**15 (2.9%)**
Back pain	16 (3.1%)
Arthralgia	17 (3.3%)
Nervous System Disorders	117 (22.6%)
Migraine	**32 (6.2%)**
Headache	**27 (5.2%)**
Dizziness	14 (2.7%)
Facial paresis	**11 (2.1%)**
Psychiatric Disorders	32 (6.2%)
Respiratory Disorders	43 (8.3%)
Skin Disorders	54 (10.4%)
Vascular Disorders	20 (3.9%)
Hypertension	**16 (3.1%)**

Phase 2 Trials: Chronic Daily Headache

The Phase 3 trials were conducted primarily at a fixed dose and fixed injection scheme with a minimum dose of 155 units and a maximum dose of 195 units. The Phase 2 trials in chronic daily headache provide more information about the potential profile of adverse events if the injection scheme or dose is varied. Trial 038 was a flexible dose trial while Trial 039 was a fixed dose comparison trial. The adverse event results for Trial 039 are described in more detail below. A fuller description of Trial 039 is located In Section 7.3.3.and Table 19.

The most common adverse events during the first cycle of treatment in Trial 039 are summarized in Table 30. A disproportionality analysis was done comparing treatment groups. The data included in Table 30 reflects those adverse events for which a p value < 0.05 occurred. For these common adverse events, the majority show a clear dose response with only hypertonia and rhinitis demonstrating a disproportionality inconsistent with a dose response. Subsequent cycles of treatment showed less of a dose response; however, even by the third treatment cycle, muscular weakness and neck rigidity still demonstrated a dose reponse suggesting that these effects remain indicators of a dose related adverse event for which tolerance does not readily develop.

Table 30: Trial 39; Number (%) of patients with treatment emergent adverse events based on statistical significance during first active treatment cycle

Preferred Term	BTA 225	BTA 150	BTA 75	Placebo	p-value *
	N = 182	N = 168	N = 174	N = 178	
Muscular weakness	54 (29.7)	40 (23.8)	28 (16.1)	1 (0.6)	< 0.001
Neck pain	37 (20.3)	37 (22.0)	25 (14.4)	2 (1.1)	< 0.001
Neck rigidity	24 (13.2)	13 (7.7)	11 (6.3)	2 (1.1)	< 0.001
Blepharoptosis	11 (6.0)	6 (3.6)	4 (2.3)	1 (0.6)	0.024
Hypertonia	11 (6.0)	16 (9.5)	12 (6.9)	0 (0.0)	0.001
Dysphagia	10 (5.5)	5 (3.0)	2 (1.1)	2 (1.1)	0.042
Rhinitis	7 (3.8)	0 (0.0)	2 (1.1)	1 (0.6)	0.014

191622-039; Tables 12.2-3

* Pearson's chi-square test was performed to evaluate the equality of proportions among treatment groups. If 25% or more of the cells had expected counts of less than 5, Fisher's exact test was used.

A combined analysis of adverse events across all treatment cycles using the same disproportionality analysis retains the dose reponse relationship shown in Table 30, but adds some potentially additional BTA related events (**bolded**) including gastroenteritis and eyelid edema. (Table 31)

Table 31: Trial 39; Number (%) of patient with adverse events reported by > 5% of patients in any treatment group by COSTART term; all treatment cycles combined

Body System/ Preferred Term	BTA 225 (N=182)	BTA 150 (N=168)	BTA 75 (N=174)	Placebo (N=178)	p-value*
Any adverse event	146 (80.2%)	133 (79.2%)	142 (81.6%)	121 (68.0%)	0.008
Body as a Whole	**120 (65.9%)**	**91 (54.2%)**	**100 (57.5%)**	**78 (43.8%)**	**< 0.001**
Neck pain	**46 (25.3%)**	**42 (25.0%)**	**34 (19.5%)**	**4 (2.2%)**	**< 0.001**
Headache	24 (13.2%)	23 (13.7%)	18 (10.3%)	26 (14.6%)	0.666
Neck rigidity	**29 (15.9%)**	**14 (8.3%)**	**14 (8.0%)**	**2 (1.1%)**	**< 0.001**
Infection	18 (9.9%)	9 (5.4%)	13 (7.5%)	13 (7.3%)	0.457
Injection site pain	17 (9.3%)	10 (6.0%)	8 (4.6%)	10 (5.6%)	0.284
Arm (shoulder) pain	15 (8.2%)	15 (8.9%)	11 (6.3%)	5 (2.8%)	0.090
Accidental injury	15 (8.2%)	7 (4.2%)	10 (5.7%)	10 (5.6%)	0.441
Back pain	11 (6.0%)	11 (6.5%)	9 (5.2%)	7 (3.9%)	0.718
Asthenia	7 (3.8%)	9 (5.4%)	9 (5.2%)	1 (0.6%)	0.064
Abdominal pain	4 (2.2%)	9 (5.4%)	6 (3.4%)	10 (5.6%)	0.314
Cardiovascular	**18 (9.9%)**	**22 (13.1%)**	**16 (9.2%)**	**11 (6.2%)**	**0.184**
Migraine	7 (3.8%)	12 (7.1%)	8 (4.6%)	6 (3.4%)	0.356
Digestive System	**31 (17.0%)**	**36 (21.4%)**	**39 (22.4%)**	**26 (14.6%)**	**0.198**
Dysphagia	**11 (6.0%)**	**6 (3.6%)**	**3 (1.7%)**	**2 (1.1%)**	**0.034**
Nausea	7 (3.8%)	13 (7.7%)	12 (6.9%)	6 (3.4%)	0.184
Gastroenteritis	**3 (1.6%)**	**6 (3.6%)**	**9 (5.2%)**	**1 (0.6%)**	**0.036**
Metabolic and Nutritional	**9 (4.9%)**	**3 (1.8%)**	**3 (1.7%)**	**9 (5.1%)**	**0.133**
Hypercholesteremia	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	0.045
Musculoskeletal	**64 (35.2%)**	**54 (32.1%)**	**48 (27.6%)**	**12 (6.7%)**	**< 0.001**
Muscular weakness	**57 (31.3%)**	**47 (28.0%)**	**31 (17.8%)**	**2 (1.1%)**	**< 0.001**
Nervous System	**45 (24.7%)**	**45 (26.8%)**	**45 (25.9%)**	**29 (16.3%)**	**0.076**
Hypoesthesia	15 (8.2%)	12 (7.1%)	13 (7.5%)	4 (2.2%)	0.080
Hypertonia	**14 (7.7%)**	**16 (9.5%)**	**14 (8.0%)**	**2 (1.1%)**	**0.007**
Respiratory System	**39 (21.4%)**	**35 (20.8%)**	**46 (26.4%)**	**38 (21.3%)**	**0.558**
Infection	12 (6.6%)	12 (7.1%)	22 (12.6%)	18 (10.1%)	0.171
Sinus infection	8 (4.4%)	10 (6.0%)	11 (6.3%)	8 (4.5%)	0.793
Rhinitis	7 (3.8%)	3 (1.8%)	9 (5.2%)	3 (1.7%)	0.178
Bronchitis	6 (3.3%)	3 (1.8%)	10 (5.7%)	5 (2.8%)	0.219
Pharyngitis	5 (2.7%)	9 (5.4%)	8 (4.6%)	6 (3.4%)	0.593
Skin and Appendages	**18 (9.9%)**	**16 (9.5%)**	**19 (10.9%)**	**15 (8.4%)**	**0.887**
Rash	0 (0.0%)	3 (1.8%)	3 (1.7%)	8 (4.5%)	0.015
Special Senses	**27 (14.8%)**	**25 (14.9%)**	**19 (10.9%)**	**11 (6.2%)**	**0.033**
Blepharoptosis	12 (6.6%)	8 (4.8%)	6 (3.4%)	2 (1.1%)	0.059
Eyelid edema	**2 (1.1%)**	**4 (2.4%)**	**0 (0.0%)**	**0 (0.0%)**	**0.030**
Urogenital System	**7 (3.8%)**	**16 (9.5%)**	**14 (8.0%)**	**14 (7.9%)**	**0.197**

Source: 191622-039; Table 12.3-4

* Pearson's chi-square test was performed to evaluate the equality of proportions among treatment groups. If 25% or more of the cells had expected counts of less than 5, Fisher's exact test was used.

Trial 038 in chronic daily headache was a flexible dose (follow the pain) design utilizing doses from 105 to 260 units of BTA. Table 32 summarizes the adverse events where the difference between treatment groups approached statistical significance using a disproportionality analysis or where the event was reported in greater than 5% in either treatment group. Similar to the results in the pooled Phase 3 trials and Trial 039, the BTA related events (**bolded** in Table 32) were neck pain, shoulder pain, skin tightness and blepharoptosis (eyelid ptosis). However, because of the flexible dose design of this study the relationship between total dose and adverse events cannot be determined.

Table 32: Trial 38; Number (%) of patient with adverse events reported by > 5% of patients; all treatment cycles combined

Body System/ Preferred Term	BTA 105-260 (N=173)	Placebo (N=182)	P-Value*
Any adverse event	138 (79.8%)	119 (65.4%)	0.002
Body as a Whole	86 (49.7%)	67 (36.8%)	0.014
neck pain	23 (13.3%)	2 (1.1%)	< 0.001
infection	20 (11.6%)	21 (11.5%)	0.995
headache	19 (11.0%)	12 (6.6%)	0.143
arm (shoulder) pain	10 (5.8%)	2 (1.1%)	0.015
neck rigidity	9 (5.2%)	5 (2.7%)	0.235
pain	9 (5.2%)	5 (2.7%)	0.235
injection site hemorrhage	2 (1.2%)	9 (4.9%)	0.039
Musculoskeletal	48 (27.7%)	6 (3.3%)	< 0.001
muscular weakness	38 (22.0%)	0 (0.0%)	< 0.001
Nervous	32 (18.5%)	30 (16.5%)	0.617
hypertonia	10 (5.8%)	5 (2.7%)	0.156
hypoesthesia	10 (5.8%)	5 (2.7%)	0.156
Respiratory	48 (27.7%)	36 (19.8%)	0.078
infection	18 (10.4%)	17 (9.3%)	0.737
pharyngitis	10 (5.8%)	7 (3.8%)	0.394
infection sinus	10 (5.8%)	6 (3.3%)	0.260
bronchitis	9 (5.2%)	6 (3.3%)	0.372
Skin and Appendages	20 (11.6%)	16 (8.8%)	0.388
skin tightness	9 (5.2%)	0 (0.0%)	0.001
Special Senses	29 (16.8%)	10 (5.5%)	< 0.001
blepharoptosis	13 (7.5%)	1 (0.5%)	< 0.001

Source; 191622-038; Table 12.2-1

* Pearson's chi-square test was performed to evaluate the equality of proportions between treatment groups. If 25% or more of the cells had expected counts of less than 5, Fisher's exact test was used.

7.4.2 Laboratory Findings

Routine blood sampling for hematology and chemistry were only done at baseline and at trial exit. In some trials, a blood sample was taken prior to the next set of injections. However, in no trial were blood samples taken between BTA treatments.

No pooling of laboratory results across trials was done. A standard for identifying clinically significant laboratory values was applied to the results in each trial.

The results of the search for clinically significant laboratory findings produced no findings of concern. With few exceptions any significant laboratory findings were limited to a few individuals in a single study, balanced between BTA and placebo treated patients, and showing no reproducible pattern across the Phase 2 and Phase 3 trials. In the absence of any findings of interest from this search for clinically significant laboratory results, no further review was done.

7.4.3 Vital Signs

Vital signs, like clinical laboratories, were not routinely collected except at baseline and prior to the next dosing interval or at the end of the trial. Table 33 summarizes the change from baseline vital sign measurements done in the Phase 3 trials. As might be expected, there were no notable differences between treatment groups for vital sign changes.

Table 33: Trial 79 and 80; Change from baseline in vital signs

Trial #	SBP (mm Hg)		DBP (mm Hg)		Pulse Rate (beats/min)		Temperature (Celsius)	
080	BTA/BTA	PLC/BTA	BTA/BTA	PLC/BTA	BTA/BTA	PLC/BTA	BTA/BTA	PLC/BTA
Baseline	118.7 (N=347)	118.9 (N=358)	75.3 (N=347)	75.4 (N=358)	74.9 (N=347)	75.1 (N=358)	36.90 (N=347)	36.87 (N=357)
Week 24	-1.5 (N=308)	-0.6 (N=331)	-0.3 (N=308)	0.2 (N=331)	-0.1 (N=308)	-0.7 (N=331)	-0.01 (N=307)	-0.02 (N=329)
Week 56	-2.5 (N=261)	-1.2 (N=264)	-0.5 (N=261)	0.5 (N=264)	0.2 (N=261)	-0.2 (N=264)	0.01 (N=259)	0.00 (N=264)
079	BTA/BTA	PLC/BTA	BTA/BTA	PLC/BTA	BTA/BTA	PLC/BTA	BTA/BTA	PLC/BTA
Baseline	120.2 (N=340)	119.6 (N=334)	75.9 (N=340)	75.2 (N=334)	75.1 (N=340)	76.2 (N=334)	36.91 (N=340)	36.91 (N=334)
Week 24	0.1 (N=294)	-0.2 (N=285)	-0.4 (N=294)	0.2 (N=285)	0.7 (N=294)	-0.8 (N=285)	-0.01 (N=294)	-0.01 (N=285)
Week 56	0.1 (N=253)	-0.9 (N=232)	0.4 (N=253)	0.1 (N=232)	0.7 (N=253)	-0.1 (N=232)	-0.01 (N=252)	-0.03 (N=232)

ISS Table 6.1

7.4.4 Electrocardiograms (ECGs)

No routine electrocardiograms were included in any of the protocols included in this application.

7.4.5 Special Safety Studies/Clinical Trials

No specific safety studies of BTA were included in this submission.

7.4.6 Immunogenicity

BTA is a large protein with known immunogenic properties. In this submission the measurement of neutralizing antibodies was done in four clinical trials (37, 38, 39 and 509). The mouse protection assay was used to detect the presence of antibodies that neutralize the biological activity of BTA. Based on the lack of evidence for the presence of neutralizing antibodies in Trials 37, 38 and 39, the sponsor did not test the samples from 509 and subsequently destroyed the samples. There were 496 analyzable samples from BTA treated patients in these three trials. There were no clearly positive results for neutralizing antibodies and there was one inconclusive result in one patient. Table 34 summarizes the results of the mouse protection assay for neutralizing antibodies to BTA.

Table 34: Trials 037, 038, 039; Results of testing for neutralizing antibodies

	Trial 37	Trial 38	Trial 39
BTA Treated Patients	187	173	524
Placebo treated patients	182	182	178
Sample Collection (Days before or after treatment)	Day: -60, 180, 270	Day; -60, 90, 180, 270	Day; -60, 90, 180, 270
Day 270 samples BTA (completers) Placebo (completers)	 106 of 110 96 of 98	 67 of 70 67 of 71	 253 of 270 62 of 68
Total samples tested	251	159	424
Results No antibodies Inconclusive Insufficient serum to test	 239 1 11	 155 0 4	 401 0 23

While there were no distinctly positive results for neutralizing antibody, it is not clear who contributed the additional samples that were tested in these three trials since there is a discrepancy between the study reports and the results reported by the testing laboratory. Based on BTA treated patients completing the trial and contributing a sample, there were 426 samples for analysis with no positive outcomes. This result would suggest that neutralizing antibodies in a CM population under the conditions of use in these trials are probably an uncommon event.

Antibodies related to cross reactivity with other botulinum toxin products or producing hypersensitivity in BTA treated patients were not characterized in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The dose of onabotulinumtoxin A (BTA) recommended (b) (4)

(b) (4)

The dose and injection scheme used in the two Phase 3 BTA trials evolved over time based on the efficacy and dose-related safety results from previous trials using different dose and injection schemes. Chronologically, the first placebo controlled study reported in this sBLA was conducted in episodic migraine (EM) patients in 1998 (Protocol 005). It was a single treatment randomized controlled trial (RCT) comparing 0, 25 and 75 units of BTA injected at **11 sites in 4 muscles (frontal, temporal, corrugator, procerus) with a maximum per injection dose of 9 units**. There were no deaths or drug related serious adverse events. Dose related adverse events were blepharoptosis (0, 14.3%, and 17.5%) and injection site paralysis (2.4%, 9.5%, and 12.5%). Adverse events occurring only at the highest dose were diplopia, dizziness, epiphora (excessive

tearing), and photophobia. Adverse events that were not dose dependent but occurred more frequently in the BTA treated patients and in 4 (4.5%) or more patients in either group were skin tightness (2.4% v 11.0%), headache (4.9% v 8.5%), sinus infection (2.4% v 6.1%), migraine (0 v 4.9%) and eyelid edema (2.4% v 4.9%). Protocol 005 injected BTA only in facial and temporal muscles. The adverse event profile represents the expected eye muscle and facial muscle profile associated injection of these muscles.

After completion of Protocol 005 the sponsor conducted Protocol 009, a single treatment RCT comparing the effects of injecting a single muscle (**frontal, temporal, or glabellar**) to injecting all 3 muscles (FTG) to placebo. **Eleven (11) sites** were injected with either BTA or placebo with **a maximum injection dose of 3 units**. Adverse events that occurred in more than 2 patients (4%) and in at least twice as many BTA patients compared to placebo were flu syndrome (FTG, frontal and glabellar group), neck pain (FTG group only), muscle weakness (FTG group only), blepharoptosis (FTG group only), respiratory infection (FTG group only) and eyelid edema (FTG group only). The adverse events reported in this trial suggested that adverse events associated with the eye (blepharoptosis and eyelid edema) were the combined effect of injections in several muscles rather than an association with any single facial muscle. It is also worth noting that respiratory infection, a potential indicator of an effect on respiratory muscle function or the cough reflex, occurred more frequently in the combined group compared to placebo even though no neck muscles (trapezius and sternocleidomastoid) were injected.

One additional single treatment RCT was conducted using the same number and placement of injections as Protocols 005 and 009 but with a lower top dose. Protocol 024 compared 0, 7.5, 25 and 50 units of BTA injected at **11 sites across 3 muscles (glabellar, temporal, frontal) with a maximum injection dose of 6 units**. Two continuation protocols, 026 and 036, examined additional treatment cycles at the top two BTA doses of 25 and 50 units. Dose related adverse events included headache, dyspepsia, facial paralysis, skin tightness, blepharoptosis, and eyelid edema.

Protocol 027 is the first trial that included shoulder and neck muscles as a site for injection when treating a headache indication. The results of Protocol 027 were not (b) (4) The trial was a single treatment RCT conducted in patients with chronic tension-type headache (CTTH). It was conducted at 21 US sites and 7 non-US sites. It enrolled 300 patients who were randomized to either placebo or one of 5 BTA dose groups (50, 86sub, 100, 100sub or 150 units) at **10 injection sites evenly distributed across five muscle groups (frontal, temporal, sternocleidomastoid, trapezius, and splenius capitis) with a maximum injection dose of 20 units.** The 50, 100 and 150 unit BTA groups received active BTA in all 5 muscle groups while the 86sub group included BTA injections only in the frontal, sternocleidomastoid and trapezius muscles and the 100sub group injected BTA in the trapezius, splenius capitis, and temporal

muscles. The choice of these subsets of muscles was based on results of individual investigator trials that reported efficacy. Table 36 summarizes the adverse events reported for this trial. Adverse events probably associated with shoulder and neck muscle injections (sternocleidomastoid, trapezius and splenius capitis) and not reported in the previous trials in migraine include neck rigidity and dysphagia. In addition adverse events reported more frequently with any dose of BTA compared to placebo included muscular weakness, neck pain and myalgia.

Table 36: Trial 027; Adverse events reported in at least 3 subjects in a BTA group and greater than placebo

	150 units N=47	100 units N=51	sub* 100 units N=52	sub* 86 units N=51	50 units N=49	Placebo N=50
Any event	29 (61.7%)	33 (64.7%)	33 (63.5%)	28 (54.9%)	25 (51.0%)	26 (52.0%)
Infection	5 (10.6%)	3 (5.9%)	10 (19.2%)	5 (9.8%)	4 (8.2%)	5 (10.0%)
Muscular weakness	3 (6.4%)	10 (19.6%)	2 (3.8%)	4 (7.8%)	2 (4.1%)	2 (4.0%)
Neck Pain	3 (6.4%)	7 (13.7%)	3 (5.8%)	5 (9.8%)	5 (10.2%)	1 (2.0%)
Dizziness	2 (4.3%)	5 (9.8%)	2 (3.8%)	1 (2.0%)	1 (2.0%)	4 (8.0%)
Neck Rigidity	1 (2.1%)	5 (9.8%)	0	0	2 (4.1%)	0
Headache	1 (2.1%)	5 (9.8%)	3 (5.8%)	2 (3.9%)	2 (4.1%)	3 (6.0%)
Pain	1 (2.1%)	4 (7.8%)	4 (7.7%)	2 (3.9%)	0	3 (6.0%)
Myalgia	0	2 (3.9%)	2 (3.8%)	3 (5.9%)	4 (8.2%)	1 (2.0%)
Accidental injury	0	1 (2.0%)	1 (1.9%)	3 (5.9%)	0	0
Dysphagia	0	1 (2.0%)	0	3 (5.9%)	0	0
Paresthesia	0	0	1 (1.9%)	3 (5.9%)	0	1 (2.0%)

*Only subset of muscles injected; see text for explanation

Beginning with Protocol 037 and Protocol 509 initiated in 2001 in patients with episodic migraine (EM) the muscles injected and the total dose of BTA injected per treatment cycle escalated dramatically to doses greater than 200 units and included muscles of the back of the head (occipital), back of neck (splenius capitis, semispinalis capitis) and shoulder (trapezius). In addition the protocols were longer duration with multiple blinded treatment cycles.

Table 6 summarizes the dosing pattern for BTA that begin in 2001 with the initiation of Protocols 037 and 509 in EM and was repeated in Protocols 038 and 039 for chronic daily headache (CDH). Further adjustments in dosing scheme occurred in the Phase 3 Protocols, 079 and 080. Unlike the earlier trials at lower doses, the later trials no longer injected the glabellar area and added the occipital, trapezius and a combination of cervical/ paraspinal muscles as well as an option to inject the masseter muscle. The change in dosing scheme added a number of additional dose related adverse events compared to the earlier, primarily facial, adverse events. Protocol 039 is explored in detail with respect to dose related adverse events in the section on common adverse events. [See Section 7.4.1, Table 30, and Table 31]

Because of the variability in dose scheme between the Phase 3 trials and all the previous placebo controlled trials for a headache indication, there is no dose response information (b) (4) with regard to number of injections, site of injections, or amount of BTA per injection. The only potential dose response data is based on total dose with the minimum dose of 155 units used in Protocols 79 and 80 bridging to the fixed dose comparison studies, Protocols 39 and 509, where the middle dose was 150 units. Protocol 39 was a fixed dose comparison Phase 2 trial with a total dose of 150 units as the middle dose (compared to a low dose of 75 units and a high dose of 225 units) and included a population of patients most closely resembling the target population for the indication requested in this sBLA.

The end result of the Phase 2 dose finding trials was to define a dose and injection scheme for the Phase 3 trials that resulted in reducing the frequency of the most common adverse events. Table 37 summarizes the placebo and active treatment adverse event reporting frequencies for the Pooled Phase 3 trials compared to the top two doses in the fixed dose comparison study, Trial 039. The **bolded** adverse event terms are those where the reporting frequency was greater in the BTA group compared to placebo. The adverse events that were consistently reported in greater frequency in Protocols 039, 079 and 080 compared to placebo were: muscular weakness, neck pain, neck stiffness, myalgia, hypertonia, eyelid ptosis, dysphagia, and hypertension. When the placebo adverse event rate remained relatively constant across the three comparisons in Table 37 and the reporting rate in the BTA group was relatively high (e.g., muscular weakness, neck pain, hypertonia), the rate was substantially reduced using the dose and injection scheme in the Phase 3 trials compared to Protocol 039.

The evolution of the dose and injection scheme from Phase 2 into Phase 3 successfully reduced the overall rate of adverse event reporting as well as reducing the rate of common, but important, tolerability effects of BTA. While subject to all the limitations of cross study and cross population comparisons, it is also worth noting that the placebo rate of adverse events was also reduced from 51% in Protocol 039 to 37% in the Phase 3 trials. This suggests that the number of injections and the volume of the injections, even in the absence of active ingredient, are associated with significant tolerability effects. The high placebo adverse event rate in the BTA development program is discussed in Section 7.7.

Table 37: Pooled Phase 3 trials; DBPC; Comparison to Trial 039 BTA 225 & 150 unit dose; Common adverse events (>2%) occurring more frequently in BTA versus placebo group during first treatment cycle (compared to placebo)

		Table 14.6-5.1	ISS Table 4-8
Protocol Number	**39**	**39**	**79 & 80**
Dose	225 units in 20 injections	150 units in 20 injections	165 units (mean dose) in 31 or more injections
	N=182	N=168	N=687
Any adverse event	**72.0% (51.1%)**	**68.5% (51.1%)**	**48.9% (36.6%)**
Muscular weakness	**29.7% (0.6%)**	**23.8% (0.6%)**	**2.9% (0.1%)**
Neck pain	**20.3% (1.1%)**	**22.0% (1.1%)**	**6.7% (1.7%)**
Neck rigidity (stiffness)	**13.2% (1.1%)**	**7.7% (1.1%)**	**2.8% (0.4%)**
Injection site pain	**8.8% (4.5%)**	4.2% (4.5%)	**2.3% (1.6%)**
Headache	8.2% (11.8%)	10.1% (11.8%)	**3.5% (2.5%)**
Arm pain/myalgia	**6.6% (2.2%)**	**7.1% (2.2%)**	**2.3% (0.4%)**
Hypertonia/muscle stiffness	**6.0% (0.0%)**	**9.5% (0.0%)**	**2.8% (0.4%)**
Hypoesthesia	**6.0% (1.7%)**	**4.8% (1.7%)**	---
Eyelid ptosis	**6.0% (0.6%)**	**3.6% (0.6%)**	**3.3% (0.3%)**
Dysphagia	**5.5% (1.1%)**	**3.0% (1.1%)**	**0.6% (0.1%)**
Back pain	**5.5% (1.7%)**	**3.6% (1.7%)**	0.7% (0.6%)
Paresthesia	**2.2% (0.6%)**	0.6% (0.6%)	**0.6% (0.1%)**
Dizziness	**4.4% (2.2%)**	**3.6% (2.2%)**	0.9% (1.3%)
Rhinitis	**3.8% (0.6%)**	0.0% (0.6%)	0.3% (0.1%)
Nausea	**3.8% (2.2%)**	**4.8% (2.2%)**	1.6% (2.0%)
Pharyngitis	**2.7% (1.7%)**	1.8% (1.7%)	2.2% (2.2%)
Hypertension	**2.7% (0.6%)**	**1.8% (0.6%)**	**1.2% (0.4%)**
Pain	**2.7% (1.1%)**	1.8% (1.1%)	---
Migraine	2.2% (2.8%)	**5.4% (2.8%)**	**2.8% (1.4%)**
Tooth disorder	**2.2% (0.6%)**	0.6% (0.6%)	---
Eye dryness	1.6% (0.0%)	**2.4% (0.0%)**	0.3% (0.0%)
Injection site stinging	1.6% (1.1%)	3.0% (1.1%)	---
Gastroenteritis	1.1% (0.6%)	**3.0% (0.6%)**	---
Abdominal pain	1.1% (1.7%)	**3.6% (1.7%)**	0.1% (0.3%)
Facial paresis			**2.0% (0.0%)**

7.5.2 Time Dependency for Adverse Events

BTA is administered as a single set of intramuscular injections every 12 weeks. Reports of adverse events collected during the Phase 3 trials reflect any event occurring after one injection and before the next injection. Adverse events associated with tolerance to the injection procedure and the BTA would be expected to be reported less frequently with subsequent treatments and/or patients truly intolerant of the adverse effect would drop out of the study. Table 38 summarizes the frequency of adverse events reported in patients from the pooled Phase 3 trials who could have received 5 treatment cycles. Seventy-five percent of the patients eligible to receive 5 cycles of treatment actually received all 5 treatments. [Note; there was no table in the ISS that reported adverse events for treatment cycle 3 for the patients originally randomized to BTA in protocol 079 or 080, but the loss of information was minimal to the point being made by this table.]

Neck pain is the most frequently reported adverse event reported in the Phase 3 trials. It is dose related based on total dose administered to the neck muscles (See Section 7.4.1) and probably related to the total dose per injection (See Section 7.5.1). In the Phase 3 trials there was an option to give additional injections in the trapezius muscle and this option may have contributed to the continued reporting of neck pain as the investigator explored the best dose regimen for an individual patient. Most of the other muscle related adverse events appear to be tolerated after the first dose and do not appear in substantial numbers after the first dose. On the other hand, reports of migraine continue to occur throughout the study either as a result of lack of efficacy or potential exacerbation. (See discussion of Exacerbation of Migraine and Lack of Efficacy in Section 7.3.5). In addition, sinusitis and nasopharyngitis were reported in >1% of patients on BTA in every treatment cycle; however, during the DBPC portion of the Phase 3 trials, unlike reports of migraine, these adverse events reports never exceeded the placebo reporting rate.

Table 38: Pooled Phase 3 Trials: Number (%) of patients with adverse event reported by ≥ 1% of patients treated for 5 cycles

Adverse Event (Preferred Term)	First BTA Treatment (N = 687)	Second BTA Treatment (N=625)	Fourth BTA Treatment (N = 558)	Fifth BTA Treatment (N = 518)
OVERALL	336 (48.9%)	243 (38.9%)	151 (27.1%)	98 (18.9%)
Neck pain	46 (6.7%)	20 (3.2%)	12 (2.2%)	1 (0.2%)
Headache	24 (3.5%)	9 (1.4%)	4 (0.7%)	0
Eyelid ptosis	23 (3.3%)	4 (0.6%)	3 (0.5%)	2 (0.4%)
Muscular weakness	20 (2.9%)	7 (1.1%)	2 (0.4%)	2 (0.4%)
Migraine	19 (2.8%)	12 (1.9%)	7 (1.3%)	8 (1.5%)
Musculoskeletal stiffness	19 (2.8%)	10 (1.6%)	1 (0.2%)	0
Sinusitis	17 (2.5%)	12 (1.9%)	10 (1.8%)	6 (1.2%)
Upper respiratory infection	17 (2.5%)	11 (1.8%)	8 (1.4%)	4 (0.8%)
Myalgia	16 (2.3%)	8 (1.3%)	2 (0.4%)	2 (0.4%)
Injection site pain	16 (2.3%)	10 (1.6%)	7 (1.3%)	1 (0.2%)
Nasopharyngitis	15 (2.2%)	15 (2.4%)	10 (1.8%)	7 (1.4%)
Facial paresis	14 (2.0%)	2 (0.3%)	1 (0.2%)	0
Musculoskeletal pain	12 (1.7%)	6 (1.0%)	2 (0.4%)	0
Nausea	11 (1.6%)	3 (0.5%)	3 (0.5%)	1 (0.2%)
Bronchitis	9 (1.3%)	8 (1.3%)	4 (0.7%)	0
Muscles spasms	8 (1.2%)	5 (0.8%)	4 (0.7%)	1 (0.2%)
Hypertension	8 (1.2%)	3 (0.5%)	5 (0.9%)	1 (0.2%)
Procedural pain	1 (0.1%)	8 (1.3%)	2 (0.4%)	0
Arthralgia	5 (0.7%)	7 (1.1%)	2 (0.4%)	1 (0.2%)
Urinary tract infection	2 (0.3%)	6 (1.0%)	8 (1.4%)	3 (0.6%)

ISS Table 3-5.1 and ISS Table 3-5.

7.5.3 Drug-Demographic Interactions

The sponsor conducted analyses of common adverse events by gender and according to age less than or greater than 40 years old. As noted in Section 7.1.3 approximately 4% of the Phase 3 trial population was greater than 65 years old and no one in the Phase 2 population was in this age group; thus conducting an analysis based on this type of age split was not feasible. The 40 year old split represents the approximate median of the non-elderly (under 65) population.

Table 39 describes the most common adverse events according to gender. The adverse events **bolded** in the table indicate those occurring more frequently with BTA compared to placebo and possibly drug related. Musculoskeletal adverse events such as muscular weakness, pain/ myalgia and stiffness were infrequently reported by men. In women these same events were reported frequently and always at a greater rate with BTA than in placebo treated patients. The frequency of other BTA related events such as neck pain, headache, eyelid ptosis, migraine and injection site pain were not substantially different between genders and always more frequently reported with BTA than with placebo regardless of gender.

Table 39: Pooled Phase 3 Trials; DBPC Phase: Number (%) of Patients with adverse events reported by ≥ 3% in any group by gender

Adverse Event	Male		Female	
	BTA (N=84)	Placebo (N=103)	BTA (N=603)	Placebo (N=589)
Neck pain	**3 (3.6%)**	**2 (1.9%)**	**57 (9.5%)**	**17 (2.9%)**
Headache	**5 (6.0%)**	**3 (2.9%)**	**27 (4.5%)**	**19 (3.2%)**
Sinusitis	2 (2.4%)	2 (1.9%)	26 (4.3%)	25 (4.2%)
Nasopharyngitis	2 (2.4%)	4 (3.9%)	26 (4.3%)	26 (4.4%)
Muscular weakness	0	0	**24 (4.0%)**	**2 (0.3%)**
Musculoskeletal stiffness	**2 (2.4%)**	**0**	**23 (3.8%)**	**6 (1.0%)**
Eyelid ptosis	**3 (3.6%)**	**0**	**22 (3.6%)**	**2 (0.3%)**
Migraine	**4 (4.8%)**	**1 (1.0%)**	**22 (3.6%)**	**17 (2.9%)**
Upper respiratory infection	5 (6.0%)	5 (4.9%)	22 (3.6%)	32 (5.4%)
Injection site pain	**3 (3.6%)**	**0**	**20 (3.3%)**	**14 (2.4%)**
Myalgia	1 (1.2%)	1 (1.0%)	**20 (3.3%)**	**5 (0.8%)**
Musculoskeletal pain	0	2 (1.0%)	**18 (3.0%)**	**8 (1.4%)**

ISS Table 9-4

Table 40 describes the most common adverse events according to age group. The adverse events **bolded** in the table indicate those occurring more frequently with BTA compared to placebo and possibly drug related. The pattern and frequency of adverse events did not demonstrate any notable differences based on age compared to the combined analysis discussed in Section 7.4.1 although older patients appear to report more neck and musculoskeletal pain.

Table 40: Pooled Phase 3 Trials; DBPC Phase; Number (%) of patients with adverse events reported by ≥ 3% of patients in any group by age

Adverse Event	> 40 years		≤ 40 years	
	BTA (N=293)	**Placebo (N=287)**	**BTA (N=394)**	**Placebo (N=405)**
OVERALL	189 (64.5%)	151 (52.6%)	240 (60.9%)	207 (51.1%)
Neck pain	**30 (10.2%)**	**6 (2.1%)**	**30 (7.6%)**	**13 (3.2%)**
Headache	18 (6.1%)	8 (2.8%)	14 (3.6%)	14 (3.5%)
Sinusitis	16 (5.5%)	10 (3.5%)	12 (3.0%)	17 (4.2%)
Nasopharyngitis	14 (4.8%)	9 (3.1%)	14 (3.6%)	21 (5.2%)
Musculoskeletal stiffness	**13 (4.4%)**	**3 (1.0%)**	**12 (3.0%)**	**3 (0.7%)**
Musculoskeletal pain	**12 (4.1%)**	**4 (1.4%)**	**6 (1.5%)**	**6 (1.5%)**
Muscular weakness	**11 (3.8%)**	**0**	**13 (3.3%)**	**2 (0.5%)**
Upper respiratory infections	10 (3.4%)	24 (8.4%)	17 (4.3%)	13 (3.2%)
Injection site pain	**9 (3.1%)**	**7 (2.4%)**	**14 (3.6%)**	**7 (1.7%)**
Migraine	**9 (3.1%)**	**7 (2.4%)**	**17 (4.3%)**	**11 (2.7%)**
Mylagia	**8 (2.7%)**	**4 (1.4%)**	**13 (3.3%)**	**2 (0.5%)**
Eyelid ptosis	**8 (2.7%)**	**0**	**17 (4.3%)**	**2 (0.5%)**
Nausea	6 (2.0%)	10 (3.5%)	8 (2.0%)	7 (1.7%)
Fatigue	2 (0.7%)	1 (0.3%)	1 (0.3%)	12 (3.0%)

ISS Table 9-1

7.5.4 Drug-Disease Interactions

No analysis by disease was conducted in this sBLA other than the primary indication for BTA in CM. The current PI for BOTOX® contains a warning regarding close monitoring when using BOTOX in patients with pre-existing neuromuscular diseases including amyotrophic lateral sclerosis, myasthenia gravis, Lambert-Eaton syndrome and similar conditions affecting the neuromuscular junction.

7.5.5 Drug-Drug Interactions

No analysis for drug interactions was conducted in this sBLA. Since BTA is a locally administered and locally acting product, only systemically distributed drugs active at the

neuromuscular junction would be expected to have a potential interaction. The current PI for BOTOX® contains a precautionary statement about co-administration of BOTOX with aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies in animals have not been previously conducted with BTA and none were submitted in this sBLA.

In the aggregate safety data from all patients exposed to BTA in this sBLA, there were 17 reports of a neoplasm. Table 41 summarizes the type of neoplasms reported.

Table 41: All BTA exposures (N=3225); Serious adverse event reports of neoplasm

Neoplasms Benign, Malignant & Unspecified (Including Cysts & Polyps)	17* (0.5%)
Uterine leiomyoma	6 (0.2%)
Breast cancer	3 (0.1%)
Basal cell carcinoma	2 (0.1%)
Squamous cell carcinoma	2 (0.1%)
Benign colonic neoplasm	1 (<0.1%)
Brain neoplasm malignant	1 (<0.1%)
Malignant melanoma	1 (<0.1%)
Malignant melanoma in situ	1 (<0.1%)
Parathyroid tumor benign	1 (<0.1%)

*One patient had both basal cell and squamous cell carcinoma

Uterine leiomyoma, or fibroids, are common findings in this age group of women. They are not malignant and are usually associated with menstrual irregularities and pain. No further review of the cases of uterine leiomyoma was done.

The reports of breast cancer are described briefly below:

- A 60 year old Caucasian female with no reported history of malignancy received BTA 155 units on 25 April 2007 and 17 July 2007. On 03 August 2007 a routine mammogram was WNL. The patient felt a lump in her breast and on 02 October 2007 a breast biopsy was done which revealed invasive ductal carcinoma. BTA treatment was discontinued. The patient was lost to further follow up.
- A 57 year old Caucasian female with no reported history of malignancy received BTA 115 units on 30 March 2007. The patient had noted breast induration in November 2006 but mammogram and ultrasound were inconclusive. Breast

biopsy was done on 4 April 2007 with diagnosis of invasive lobular breast carcinoma. BTA treatment was discontinued. Patient received surgery and radiation treatment.

- A 55 year old Caucasian female with no reported history of malignancy received placebo on 9 February 2007 and 3 May 2007 followed by BTA 155 units on 27 July 2007. An abnormal mammogram was reported on 5 September 2007 with subsequent biopsy diagnosis of ductal carcinoma in situ. No further BTA injections were done.

According to American Cancer Society Cancer Statistics for 2009, the incidence rate of breast cancer for 1975-2005 among women in the US was approximately 100-150 per 100,000 (for all ages).[10] The reports of breast cancer in women receiving BTA do not constitute a safety signal at this time.

There was one case of melanoma in situ and one case of malignant melanoma. They are described briefly below.

- A 42 year old Caucasian female noticed a lesion on her right check approximately 2 months after receiving her second dose of BTA 155 units on (b) (6) She received BTA treatment #3 (155 units) and 15 days later was admitted to the hospital for diagnostic biopsy which showed a lentigo maligna. She was readmitted for complete excision on (b) (6). The patient subsequently discontinued from the study due to time commitment for the study and not due to any adverse event.
- A 65 year old Caucasian male was found to have a melanoma on his right check in December 2007, approximately 2 months following treatment #4 (165 units) with BTA. The patient received treatment #5 as scheduled in January 2008. The melanoma was excised approximately 2 months later (February 2008).

Both cases of squamous cell carcinoma were on the skin and were excised without sequellae. The same was true of the cases of basal cell carcinoma.

The single cases of brain neoplasm, colonic neoplasm and parathyroid tumor are described below.

- A 47 year old Caucasian female completed Protocol 080 after randomization to 2 cycles of placebo and three cycles of BTA (185 units). Sixteen days after the last dose of BTA she was hospitalized with a brain tumor for which she was receiving radiation and chemotherapy. She had a history of migraine of more than 25 years.
- The case of colonic neoplasm represents a miscoded serious adverse event of diverticulitis and not a colonic neoplasm occurring in a 27 year old Caucasian

[10] http://www.cancer.org/docroot/PRO/content/PRO_1_1_Cancer_Statistics_2009_presentation.asp

female who was hospitalized 33 days after her second treatment with BTA 155 units. She continued in the trial without recurrence of this event.

- A 55 year old Caucasian female enrolled and completed Protocol 038. She has a history of hyperparathyroidism and was hospitalized two days after her final BTA dose for an elective parathyroidectomy due to an enlarging parathyroid adenoma.

Based on the human safety data in this sBLA there is no suggestion of a cancer risk associated with BTA.

7.6.2 Human Reproduction and Pregnancy Data

There were no specific investigations of the effect of BTA on reproduction and pregnancy outcome included in this sBLA. The current PI for Botox® has a Pregnancy Category C precaution that includes results from reproductive studies in mice, rats and rabbits but contains no human data.

Women who were attempting to get pregnant were excluded from the Phase 3 trials. All women of child bearing potential had a urine pregnancy test prior to an injection of BTA. If the test was positive the woman was discontinued from the study. A total of 18 women became pregnant during the combined Phase 3 trials. One patient was dropped from the Phase 3 trials prior to randomization with 17 women actually receiving either BTA or placebo prior to the positive pregnancy test. Table 42 summarizes the information on the pregnancies that occurred during the Phase 3 trials. Eight of the pregnancies occurred during the double-blind placebo controlled portion of the trials, five in BTA treated patients and 3 in placebo treated patients [lightly shaded cases in Table 42]. All three placebo treated patients delivered healthy babies. Two of the patients in the BTA group were lost-to-follow before the outcome of the pregnancy was determined, one BTA patient delivered a healthy baby, one delivered a baby with metatarsus adductus and one experienced a spontaneous abortion. An additional 9 women became pregnant during the open label portion of the trial while receiving BTA treatment; seven delivered healthy babies, one had a miscarriage and one experienced a placenta abruptio at 25 weeks.

Eighty-eight percent of the patients enrolled in the Phase 3 trials were women and 43% of the enrollees were less than 40 years old. It is safe to assume that more than half of the patients in the Phase 3 trials were women of child-bearing potential and despite the requirements for contraception and the eligibility exclusions included in Protocols 79 and 80, at least 17 patients (1.6% of 1042 women) became pregnant during the trial. In the postmarketing setting it can be assumed that this proportion would be much higher.

Based on the known outcomes of pregnancies in women treated with BTA in the Phase 3 trials, 9 of the 12 pregnancies resulted in live births (75%). There is only one published survey study that assessed the outcome of pregnancies in women receiving

BTA [2] and it is too small and uncontrolled to provide any useful information. In 2004 in the United States, 64% of pregnancies resulted in a live birth, 17% in fetal loss and 19% in an induced abortion[11]. While the data from the Phase 3 trials appears to be crudely consistent with the US data, there were no induced abortions and the small numbers and lost-to-follow up cases could easily change the live birth proportion, especially if a larger cohort of pregnancies were studied.

Women of childbearing potential are a prime candidate for use of BTA in the treatment of migraine and the Phase 3 results reinforce the likelihood that women will become pregnant while taking BTA. While it can be argued that BTA is a locally active drug, there is sufficient evidence of regional and systemic side effects to raise concern about potential effects of BTA on pregnancy maintenance and outcome. As noted elsewhere in this review this is the first medical indication for BTA that did not involve an orphan designation; thus, this is the first indication for which a large number of women of childbearing potential are likely to be exposed to moderately high doses of BTA. A request was made to the Maternal Health Team of the Pediatric and Maternal Health Staff for advice on an appropriate response to the pregnancy data from the Phase 3 trials.

The response from the Maternal Health Team (MTA) concluded that based on available animal and human data, BTA is not detected in the maternal circulation when used at therapeutic doses.12 "...Case reports in pregnant and lactating women infected with Clostridium botulinum suggest that botulinum toxin A does not cross the placenta (or into human milk), most likely explained by its large molecular weight. Because of these findings, botulinum toxin A does not appear to have a direct effect on a developing fetus. However, it is possible that botulinum toxin A could have an indirect effect on the developing fetus through a possible placental effect...Botulinum toxin A binds to acceptor sites on motor sympathetic nerve terminals and inhibits the release of acetylcholine. Therefore, botulinum toxin A effects could potentially impact placental vasculature and placental perfusion if toxin spread systemically after a distal intramuscular injection..."

The MHT did not recommend either a pregnancy registry or a post-marketing study based on the available data. The MHT did recommend that the sponsor be asked to provide the results of any research that has been conducted on the potential effect of BTA on the function of the placenta. I agree with the recommendations of the MHT.

11 http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_15.pdf
12 Maternal Health Team Review by J.Best to DNP dated August 18, 2010

Table 42: Summary of pregnancies during Phase 3 trials

Patient Number	Estimated Date of Conception Based on Treatment Received	Treatment Received	Pregnancy Outcome
10024 - 50013	30 days following treatment #4	2 treatments with placebo and 2 treatments with BOTOX® 155 U to 195 U	Healthy baby
10012-50181	64 days following treatment #4	2 treatments with placebo and 3 treatments with BOTOX®	Healthy baby
10031 - 50484	36 days following treatment #1	1 treatment with BOTOX® 155 U to 195 U	Healthy baby
10047-50564	75 days following treatment #4	5 treatments with BOTOX® 155 U to 195 U	Healthy baby
10050 - 51498	54 days following treatment #1	1 treatment with placebo	Healthy baby
11301 50453	80 days following treatment #1	2 treatments with BOTOX® 155 U to 195 U	Spontaneous abortion considered unrelated to study treatment by investigator
10047-50581	30 days following treatment #4	4 treatments with BOTOX® 155 U to 195 U	Placenta abruption of 25-week pregnancy with fetal demise; considered unrelated to study treatment by investigator
10005-51486	Following treatment #4 EDC not determined	4 treatments with BOTOX® 155 U to 195 U	Miscarriage considered unrelated to study treatment by investigator
10031 - 50809	35 days following treatment #2	2 treatments with BOTOX® 155 U to 195 U	Lost to follow-up
10001-10550	77 days following treatment #3	2 treatments with placebo and 2 treatments with BOTOX® 155 U to 195 U	Healthy baby
10010 - 10576	59 days following treatment #2	2 treatments with placebo	Healthy baby
10029-10726	27 days following treatment #3	2 treatments with placebo and 1 treatment with BOTOX® 155 U to 195 U	Healthy baby
10018 - 10864	50 days following treatment #1	1 treatment with placebo	Healthy baby

Patient Number	Estimated Date of Conception Based on Treatment Received	Treatment Received	Pregnancy Outcome
10048 - 11441	79 days following treatment #4	2 treatments with placebo and 3 treatments with BOTOX® 155 U to195 U	Healthy baby
10005- 11539	32 days following treatment #5	5 treatments with BOTOX® 155 U to 195 U	Healthy baby
10041 – 11591	15 days prior to treatment #1	1 treatment with BOTOX® 155 U to 195 U	Metatarsus adductus (clubfoot) in the baby that was considered unrelated to study treatment by investigator
10021 - 10296	On the same day as treatment #1	1 treatment with BOTOX® 155 U to 195 U	Lost to follow-up
10001- 10413	During screening	None; patient was withdrawn from the study prior to being randomized	Lost to follow-up

Lightly shaded = occurring during DBPC phase

7.6.3 Pediatrics and Assessment of Effects on Growth

No data on the use of BTA in patients less than 18 years old was included in this sBLA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no specific reports of an overdose in the integrated safety database. However, the definition of overdose for BTA is a fine distinction between achieving the desired neuromuscular effects without producing unwanted muscular weakness and paralysis. The most extreme examples of an overdose would be evidence of systemic effects of a local injection. There were no such cases in the Phase 3 trials.

There were no trials investigating the potential for abuse; however, there is no pharmacological rational for suspecting potential abuse.

Withdrawal and rebound effects are part of the normal pharmacology for BTA, e.g. the pain of migraine will return in the absence of treatment. There were no specific trials looking at rebound with worse headaches; however, there were also no spontaneous reports of this effect.

7.7 Additional Submissions / Safety Issues

Placebo Response

A question not addressed by the CM development program is the effect of the injection of a placebo versus a sham or no injection group. If a considerable proportion of patients are responding to the injection of placebo then the incremental efficacy of adding BTA may add more risk than the incremental improvement with placebo alone. The placebo efficacy response in the controlled trials of BTA for prophylaxis of CM and EM were examined as a potential safety issue. It was compared to the known background placebo efficacy rate in previously conducted trials.

A meta-analysis of the placebo response in controlled trials of a putative active treatment for prophylaxis of migraine was recently published. [3] The common outcome across studies used to assess the placebo response was a 50% or greater reduction in migraine attacks. The pooled estimate of the placebo response was 21%. When the studies were categorized according to North America or Europe and trial design (parallel group versus crossover) there were statistically significant differences. The placebo response rate was 25.4% in North America compared to 16.8 % in Europe; the rate was 22% in parallel group studies compared to 10% in crossover studies. The adverse event rate in the placebo group was 30% overall, but considerably higher in North American trials compared to European trials, 63% versus 22%, respectively.

In the controlled trials of BTA, most of which were conducted in North America, the placebo response based on the same outcome measure of 50% or greater reduction from baseline in migraine frequency is summarized in Table 43. Regardless of the headache population studied in this development program, there is generally a higher placebo response rate than reported in previously published studies.

Of most interest with regard to the use of BTA in CM are the comparison of the placebo efficacy rates in the Phase 3 trials (shaded in the Table 43) to the history of such trials with other interventions. Despite all the limitations of such comparisons, the placebo efficacy rate in the Phase 3 trials of BTA (34-36%) are higher than the historical background rate (22%) providing some support to the hypothesis that injection of placebo according to the scheme used in the Phase 3 trials is potentially efficacious. However, the low frequency of adverse events with BTA (45-53%) compared to historical rates for placebo (63%) suggests that there is no elevated risk to patients, even if BTA is added to a background placebo injection. The latter is not necessarily true for many of the Phase 2 trials and may explain, at least in part, the difficulty with showing efficacy using the earlier dosing schemes.

Table 43: Studies of BTA for migraine; Placebo efficacy and adverse event rates

Protocol ID	Number of Placebo Exposures	Migraine Reduction from Baseline in Placebo Group (>50%)	Placebo Adverse Event Rate (First treatment cycle)	BTA Adverse Event Rate (First treatment cycle)
REFERENCE	**Meta-Analysis**	**22%**	**63%**	**----**
191622-080	358	34.4% (wk 24)	42.5%	53.0%
191622-079	338	36.0% (wk 24)	30.2%	44.7%
191622-039	178	23.7% (Day 90) 38.6% (Day 180)	51.1%	66.7 - 72.0%
191622-038	182	22.9% (Day 90) 25.3% (Day 180)	54.9%	68.8%
191622-037	182	51.5% (Day 90) 53.1% (Day 180)	45.6%	67.4%
191622-509	118	25.4% (Day 90) 41.2% (Day 180)	54.2%(overall)	77.2 – 77.6% (overall)
191622-024	106	31.7% (Day 90)	47.2%	46.5 – 56.6%
191622-009	45	40.9% (Day 90)	51.1%	40.0 – 55.1%
191622-005	41	34.1% (Day 90)	53.7%	53.7 – 64.3%

REMS

BOTOX has a REMS in place to manage the risk of distant spread of toxin. (b) (4)

As noted in the Safety Summary and specifically discussed in Safety Issue #1 and #2, the therapeutic window for demonstrating a drug effect of BTA for prophylaxis of chronic migraine is very small because of the close proximity of the dose response curve for safety to the efficacy effect. The Phase 3 trials effectively reduced the dose related adverse events through scrupulous adherence to a dosing and injection scheme different from all previously conducted headache trials. In order to maintain this margin of safety in the postmarketing environment it will be critically important that ALL healthcare providers administering BTA for migraine prophylaxis adhere to the dosing and injection scheme used in the Phase 3 trials. Therefore, it is recommended that the REMS be modified to include a requirement for training healthcare providers prior to administering BOTOX for the prophylaxis of migraine headaches.

8 Postmarket Experience

The most recent periodic safety update report (PSUR) for BOTOX® was submitted on February 27, 2009 and covers the 2008 calendar year. The PSUR notes the approval of BTA by regulatory authorities outside of the US for the treatment of migraine (tension-type headache) and includes Colombia, Guatemala, and El Salvador. Therefore, spontaneous reports of adverse events in patients treated for migraine are from patients being treated primarily outside the approved labeled indications and without labeled dosing recommendations.

Since its initial marketing in the US in 1989, Botox®, and its associated trademarked products, has been approved in 83 countries and is actively marketed in 70 countries. Over (b) (4) vials of medical Botox have been sold compared to over (b) (4) vials of the cosmetic product, although prior to approval of the cosmetic product it is likely that there was considerable use of the medical formulation for cosmetic purposes. In North America, up to the end of April 2009, approximately (b) (4) vials had been sold with about (b) (4) for cosmetic use and (b) (4) for medical use.

The sponsor queried their postmarketing database for cases reported between 01 January 1990 and 31 December 2008 in which Botox® was used for treatment of migraine and migraine prophylaxis, yielding 271 cases. A total of 237 of the 271 cases were spontaneous reports. The remaining cases were from literature reports, postmarketing studies, sponsored registries and regulatory authorities. There were 51 cases classified as serious by ICH criteria. No additional information on these 51 cases was included in the sBLA.

On January 26, 2010 the 120 day safety update was received from the sponsor in which postmarketing adverse event reports for the period between January 1, 2009 and October 31, 2009 for an indication of migraine were described. Approximately (b) (4) additional vials of Botox® were distributed in North America since the original sBLA submission (total of approximately (b) (4) vials since 1989 in North America). A total of 38 postmarketing cases were included. As noted by the sponsor "All of the cases were reported from countries that currently lack labeling guidance for the treatment or prevention of migraine headache." Seventy-one percent of the cases were from the US and 13% from Canada. Fifteen cases were considered serious by ICH criteria.

Table 44 summarizes the postmarketing case reports received in the original sBLA and the 120 day safety update. Unlike the postmarketing information included in the original sBLA, the 120 day safety update contains a specific summary of serious adverse events. Table 45 summarizes the available information on the serious adverse events. In addition to the cases described in the table there were five serious cases of local neck weakness after doses of 100 units in 3 cases and 300 units in 2 cases. There was

an additional case of generalized muscle weakness that lacked confirmatory information.

The postmarketing reports of adverse events summarized in Table 44 are similar in frequency and type of adverse events reported during the Phase 3 trials in CM. The cases summarized in Table 45 support the recent addition to the PI of precautionary wording regarding driving and using heavy machinery if a patient experiences any eye related adverse events with BTA.

Table 44: Postmarketing adverse event reports for BTA in patients treated for migraine for original sBLA and 120 day safety update

System Organ Class/ Preferred Term	1990-2008 ≥ 5 reports (N = 271)	1jan09-31oct09 ≥ 3 reports (N=38)
Total number of reported preferred terms	**368**	**131**
Eye Disorders	**32**	**7**
Eyelid ptosis	19	2
Lacrimation increased	5	0
Visual impairment	5	0
Gastrointestinal Disorders	**29**	**14**
Dysphagia	21	4
Dry mouth	5	1
Nausea		4
General Disorders & Administration Site Conditions	**39**	**24**
Injection site swelling	8	2
Injection site pain	7	4
Therapeutic response decreased	6	2
Immune System Disorders	**7**	**0**
Hypersensitivity	5	0
Musculoskeletal & Connective Tissue Disorders	**113**	**30**
Neck pain	35	5
Muscular weakness	33	12
Myalgia	13	1
Muscle spasms	13	3
Musculoskeletal stiffness	9	1
Muscle tightness	5	0
Nervous System Disorders	**52**	**18**
Migraine	22	3
Headache	10	2
Burning sensation	5	0
Respiratory, Thoracic & Mediastinal Disorders	45	9
Influenza and influenza-like illness	22	1
Dyspnea	9	4
Dysphonia	5	1
Skin & Subcutaneous Tissue Disorder	**41**	**12**
Pruritus	7	2
Alopecia	7	3
Urticaria	6	0
Swelling face	5	3

Table 10-2 and Table 2.7.4.10-2

Table 45: Postmarketing reports of serious adverse events; January - October 2009

ID Number	Age/ Sex	Adverse event	BTA dose/Timing	Comments
0902955US	unk	myocardial infarction	unk	rechallenge negative
0902133US	50/F	eye strain and ptosis	unk	unable to work
0901798US	46/F	reduced visual acuity	unk	attributed to Hx of Charcot-Marie-Tooth syndrome
0902571US	unk/F	blisters to vocal cord and esophagus (endoscopic finding), dysphagia, dyspnea, vocal cord dysfunction, throat tightness, muscle spasm, dysarthria	1 week after 400 units to neck, shoulders, forehead and temple	15 years of receiving injections of BTA every 3 months, experiencing deceased efficacy, positive antibodies for BTA; recovered after 4 months
0907716US	45/M	dysphagia, generalized weakness	2 weeks after 75 units (35 to forehead, 20 to splenius capitis, 20 to trapezius)	hospitalized with negative work up; recovered
091270US	58/F	dyspnea, dysphagia, neck weakness, chest numbness, head tingling	1 weeks after 200 units to head and neck and 100 units to lumbosacral paraspinalis;	Hs of myasthenia gravis and idiopathic dystonia;
0910167US	unk/F	dry mouth; no salivary gland function	unk	positive rechallenge
0911696US	59/F	myokymia (tics), painful injection, migraine and injection site swelling	unk; however previously treated with BTA for migraine	myokymia resulted in difficulty focusing eyes, double vision, blurred vision and nausea; unable to drive or work
0914679US	unk/F	head drooping	500 unites (75 units each gluteal, 75 units each trapezius, unk amount to right leg	
0906493US	51/F	dyspnea, generalized weakness; pneumothorax	300 units (neck shoulder and scalp)	hospitalized and discharged with dyspnea and weakness
0908742US	47/F	injection site pain, insomnia, head twisting, shoulder numbness; difficulty breathing	3 days after 300 units (head, neck, shoulder, upper back)	recovered 8 weeks after injection
0911022US	unk/F	vasculitis	5 days after 60-100units (forehead)	consumer report not confirmed by neurologist

9 Appendices

9.1 Literature Review/References

Reference List

(1) Burstein R, Jakubowski M, Levy D. Anti-migraine action of triptans is preceded by transient aggravation of headache caused by activation of meningeal nociceptors. *Pain* 2005;115:21-28.

(2) Morgan JC, Iyer SS, Moser ET, Singer C, Sethi KD. Botulinum toxin A during pregnancy: a survey of treating physicians. *Journal of Neurology Neurosurgery and Psychiatry* 2006;77:117-119.

(3) Macedo A, Banos JE, Farre M. Placebo response in the prophylaxis of migraine: A meta-analysis. *European Journal of Pain* 2008;12:68-75.

9.2 Labeling Recommendations

Safety Labeling Revisions Proposed by Sponsor Followed by Review Comments

The proposed changes from the Sponsor to the prescribing information (PI) for this new indication, besides the indication itself and the associated clinical trials and appropriate dosing and administration instructions, include:

- **Section 5.2; Spread of Toxin Effect; Revised last sentence of this section to read as follows:**
  - No definitive serious adverse events reports of distant spread of toxin effect associated with BOTOX® for blepharospasm at the recommended does (30 Units and below), ~~or for~~ strabismus, or chronic migraine at the labeled doses have been reported.

Reviewer Comment*: On the basis of the available data in this sBLA, I agree with the revised statement for Section 5.2.*

- **Section 6.1; Clinical Studies Experience; Addition of new subsection.**

  Chronic Migraine
  The most frequently reported adverse reactions following injection of BOTOX® for chronic migraine appear in Table(b)(4).

(b) (4)

2 Pages Immediately Follow Withheld - Draft Labeling b(4)

(b) (4)

[redacted]

9.3 Advisory Committee Meeting

Based on the review of safety there is no reason to recommend presentation at an advisory committee.

9.4 Narratives of Serious Migraine Headaches in BTA Treated Patients in Phase 3 Trials

Patient 10024-50090 (BOTOX® group), a 44-year-old Caucasian female in study 191622-080, reported **intractable migraine** (preferred term: migraine; Module 5.3.5.1, Report 191622-080, Table 14.3-1; Listing 16.2.7-3), which was the only serious adverse event reported during DBPC exposure that was considered to be treatment-related by the investigator (Module 5.3.5.3, ISS Table 3-1.1). She received the first treatment with 165 U BOTOX® on (b) (6) and symptoms began 7 days later. She was hospitalized on (b) (6) due to worsening severe headaches and her treatment included dihydroergotamine, a patient controlled analgesia pump, and high dose steroids. The following day, Valium® was also added for a recurrence of chronic trapezius muscle spasm. She was discontinued from the study due to the event, which resolved 4 days later without sequelae.

Patient 10018-51186 (BOTOX® group), a 40 year-old Caucasian female in study 191622-080, reported **worsening migraine** (preferred term: migraine; Module 5.3.5.1, Report 191622-080, Table 14.3-1; Listing 16.2.7-3). She received 190 U of BOTOX® at her second treatment ((b) (6) and was hospitalized (b) (6) (b) (6), 63 days later, with worsening of migraine. She was treated with IV fluids, morphine, and Phenergan®, recovered without sequelae, and was discharged from the hospital on (b) (6) and continued in the study.

Patient 10038-50607 (BOTOX® group), a 33-year-old Caucasian female in study 191622-080, reported an **intractable migraine** (preferred term: migraine; Module 5.3.5.1, Report 191622-080, Table 14.3-1; Listing 16.2.7-3). Three months prior to randomization, she was treated in an emergency department for migraine. She had not been admitted to the hospital. She received 155 U of BOTOX® at her second treatment on (b) (6). On (b) (6), 49 days later, a headache started, and she was hospitalized on (b) (6) and treated with dihydroergotamine. She recovered without sequelae and was discharged from the hospital on (b) (6) and continued in the study.

Patient 10005-11539 (BOTOX® group), a 30-year-old Caucasian female in study 191622-079, reported an **intractable migraine** (preferred term: migraine; Module 5.3.5.1, Report 191622-079, Table 14.3-1; Listing 16.2.7-3). She received the first treatment with 155 U of BOTOX® on 04 April 2007. On (b) (6) she awoke with a headache (after consuming chocolate and cheese the previous evening), and on (b) (6) she was admitted to the hospital and treated with dihydroergotamine, Dilaudid®, and Zofran®. She recovered without sequelae and was discharged on (b) (6) and continued in the study.

Patient 10016-10204 (BOTOX® group), a 20-year-old Caucasian female in study 191622-079, reported **status migraine without aura** (preferred term: migraine without

aura; Module 5.3.5.1, Report 191622-079, Table 14.3-1; Listing 16.2.7-3). She received the first treatment of 155 U of BOTOX® on (b) (6). She developed a headache on (b) (6), 49 days later, and was hospitalized on (b) (6) and treated with IV dihydroergotamine. She recovered without sequelae and was discharged from the hospital on (b) (6) and continued in the study.

Patient 10007-11324 (BOTOX® group), 31-year-old Caucasian female in study 191622-079, reported an **intractable headache** (preferred term: headache; Module 5.3.5.1, Report 191622-079, Table 14.3-1; Listing 16.2.7-3). She received her first of treatment of 160 U of BOTOX® on (b) (6) She was hospitalized 45 days later, on (b) (6) for a headache that had started 10 days prior to hospitalization. She was treated with Dilaudid®, followed by dihydroergotamine, steroids, and Zofran®. She recovered without sequelae and was discharged from the hospital on (b) (6) and continued in the study. She received her fourth treatment of 175 U of BOTOX® on (b) (6) Six days later, she experienced the onset of a migraine headache. She was hospitalized on (b) (6) and was treated with Zonegran®, followed by dihydroergotamine and steroids. She recovered without sequelae and was discharged from the hospital on (b) (6). She was discontinued from the study on 07 January 2008 due to lack of efficacy as determined by the investigator.

Patient 10041-50555 (BOTOX®/BOTOX® group), a 38-year-old Caucasian female in study 191622-080, reported **intractable migraine** (preferred term: migraine; Module 5.3.5.1, Report 191622-080, Table 14.3-2; Listing 16.2.7-3). She received 155 U of BOTOX® at her fifth and final treatment on 8 October 2007. She was hospitalized on (b) (6) and treated with IV dihydroergotamine, Reglan®, Benadryl®, and Compazine®. She recovered without sequelae and was discharged from the hospital on (b) (6) and continued in the study.

Patient 10032-11643 (BOTOX®/BOTOX® group), a 53-year-old Caucasian female with a history of multiple hospitalizations for migraine prior to her entry to study 191622-079, reported **exacerbation of migraine** (preferred term: migraine; Module 5.3.5.1, Report 191622-079, Table 14.3-2; Listing 16.2.7-3). She received her fifth treatment of 155 U of BOTOX® on (b) (6). Ten days later, she was hospitalized for exacerbation of migraine. She was treated with dihydroergotamine, Demerol®, Phenergan®, and valproic acid. She recovered without sequelae and was discharged from the hospital on (b) (6) and continued in the study.

Patient 10013-10449 (BOTOX®/BOTOX® group), a 56-year-old Caucasian female entered study 191622-079, reported **worsening migraine** (preferred term: migraine; Module 5.3.5.1, Report 191622-079, Table 14.3-2; Listing 16.2.7-3). She received her third dose of 180 U of BOTOX® on (b) (6). She developed a worsening of her migraine 17 days later and was hospitalized on (b) (6). She was treated with Demerol®, Dilaudid®, steroids, Vistaril®, and Fioricet®. Her condition improved, and she was discharged from the hospital on (b) (6) and continued in the study.

Worsening of migraine was reported for Patient 10039-10687 (BOTOX®/BOTOX® group), a 34-year-old Caucasian female with a pre-study history of multiple hospitalizations for migraine, who entered into study 191622-079 (Module 5.3.5.1, Report 191622-079, Listing 16.2.7-3). She received the fourth treatment of 155 U of BOTOX® on (b) (6). Her headache had started 9 days earlier on (b) (6). She was hospitalized due to worsening migraine on (b) (6), 6 days after receiving the fourth treatment with BOTOX®. She was treated with dihydroergotamine, OxyContin®, and Keppra®. The event resolved without sequelae, and she was discharged from the hospital on (b) (6).

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	103000/5215
Priority or Standard	Standard
Submit Date(s)	September 29, 2009
Received Date(s)	September 30, 2009
PDUFA Goal Date	October 29, 2010
Division / Office	DNP
Reviewer Name(s)	Suhail Kasim, MD MPH
Review Completion Date	August 30, 2010
Established Name	BOTOX OnabotulinumtoxinA
(Proposed) Trade Name	BOTOX
Therapeutic Class	Purified Neurotoxin Complex
Applicant	Allergan, Inc
Formulation(s)	Injection IM
Dosing Regimen	As needed
Indication(s)	Prophylaxis of Headache in Adults with Chronic Migraine
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval with labeling changes.

1.2 Risk Benefit Assessment

Not applicable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Pediatric studies should be required in patients with ≥15 headache days per month for prophylaxis of migraine headache who meet criteria for chronic migraine between the ages of 12 years and 16 years, 11 months (PREA). Since chronic migraine is not accurately diagnosed prior to age 11 years and there are not sufficient number of children in the age group who are also geographically dispersed, waiver for this age group is recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

BOTOX (OnabotulinumtoxinA) is sterile, vacuum-dried purified botulinum neurotoxin type A. It is produced from fermentation of Hall strain Clostridium botulinum type A, and purified to a complex of the neurotoxin and several accessory proteins.

BOTOX when reconstituted is a parenteral solution intended solely for administration by injection. The formulation used in the clinical trials in this submission is the currently approved and marketed BOTOX product.

2.2 Tables of Currently Available Treatments for Proposed Indication

Target Indication sought is - Prophylaxis of headaches in adults with chronic migraine.

There are FDA-approved treatments for the prevention of migraine headaches as listed in Table 1, however there are no drugs with regulatory approval for headache prevention or prophylaxis specifically in adults with chronic migraine defined as individuals with headache that occurs ≥15 days per month for longer than 3 months, and headache that lasts more than 4 hours per day[1].

Table 1: Drugs for Prevention of Migraine Headaches

DRUG CLASS	DRUG BRAND NAME	DRUG GENERIC NAME
β-adrenergic antagonists	Inderal tablets, (b) (4)	Propranolol hydrochloride
	Blocadren tablets	Timolol maleate
Anti-Epileptics	Topamax tablets, sprinkle, capsules	Topiramate
	Depakote ER tablets	Divalproex sodium

The classes of agents used for prophylaxis of chronic daily headache, of which chronic migraine is a subtype, include β-adrenergic antagonists, calcium-channel blockers, α2-adrenergic agonists, serotonin antagonists, antidepressants, nonsteroidal anti-inflammatory drugs, and antiepileptic drugs [2]. The US Headache Consortium published guidelines in 2000 on preventive pharmacological therapy for management of migraine headaches that listed several preventive agents that may be used in clinical practice (off-label) as shown in Table 2 [3].

Currently, there is also ongoing NINDS Clinical Research Collaboration chronic migraine treatment trial (NCT00772031) to determine if adding a second drug to topiramate treatment will further reduce the headache burden for people with chronic migraine. In the study, participants with chronic migraine are randomized to two groups - treatment with topiramate and propranolol or topiramate and placebo and followed for 6-months. Although topiramate and propranolol are not specifically approved for the treatment of chronic migraine, they are approved for prophylaxis of migraine in adults.

[1] Bigal ME, Lipton RB, Tepper SJ, et al. Primary chronic daily headache and its subtypes in adolescents and adults. *Neurology* 2004, 63:843–847.
[2] Mathew NT. Dynamic optimization of chronic migraine treatment: current and future options. *Neurology*. 2009 Feb 3;72(5 Suppl):S14-20.
[3] Ramadan NM, Silberstein SD, Freitag FG, et al. 2000. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. *Neurology*, http://www.aan.com/professionals/practice/pdfs/gl0090.pdf

Table 2: US Headache Consortium: Drugs for Prevention of Migraine Headaches

Group 1: *Medium to high efficacy, good strength of evidence, and a range of severity (mild to moderate) and frequency (infrequent to frequent) of side effects*	**Group 2:** *Lower efficacy than those listed in first column, or limited strength of evidence, and mild to moderate side effects*	**Group 3:** *Clinically efficacious based on consensus and clinical experience, but no scientific evidence of efficacy*	**Group 4:** *Medium to high efficacy, good strength of evidence, but with side effect concerns*	**Group 5:** *Evidence indicating no efficacy over placebo*
Amitriptyline Divalproex sodium Lisuride* Propranolol Timolol	Aspirin ‡‡ Atenolol Cyclandelate* Fenoprofen Feverfew Flurbiprofen Fluoxetine (racemic) Gabapentin Guanfacine Indobufen* Ketoprofen Lornoxicam* Magnesium Mefenamic acid Metoprolol Nadolol Naproxen Naproxen sodium Nimodipine Tolfenamic acid* Verapamil Vitamin B2	**a. mild-to moderate side effects** Cyproheptadine Bupropion Diltiazem Doxepin Fluvoxamine Ibuprofen Imipramine Mirtazepine Nortriptyline Paroxetine Protriptyline Sertraline Tiagabine Topiramate Trazodone Venlafaxine **b. (side effect concerns)** Methylergonovine Phenelzine	Methysergide Flunarizine* Pizotifen* TR-DHE*	Acebutolol Alprenolol* Carbamazepine Clomipramine, Clonazepam Clonidine DEK* Femoxetine* Flumedroxone* Indomethacin Iprazochrome* Lamotrigine Mianserin* Nabumetone Nicardipine Nifedipine Oxprenolol* Oxitriptan* Pindolol Tropisetron* Vigabatrin

2.3 Availability of Proposed Active Ingredient in the United States

BOTOX is approved for use since 29 December 1989 in the United States for the following indications: hyperhidrosis, cervical dystonia, strabismus, blepharospasm, and treatment of upper limb spasticity. On July 10th, 2010 BOTOX received regulatory approval in the United Kingdom for the prophylaxis of chronic migraine headache.

It is approved in 74 countries and marketed in 69 countries. Indications (world-wide) include cervical dystonia, blepharospasm, hemifacial spasm, focal dystonias, strabismus, equinus foot deformity due to spasticity in pediatric cerebral palsy patients, focal spasticity, upper limb spasticity associated with stroke, spasmodic dysphonia, achalasia, axillary hyperhidrosis, and cosmetic treatment of facial wrinkles. In a few

countries, BOTOX is approved for the treatment of essential tremor, anal fissure, migraine and/or tension type headache.

2.4 Important Safety Issues With Consideration to Related Drugs

Please refer to Dr. Cheryl Graham, MD safety review of sBLA 103000/5215.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Allergan filed IND 7480 to support BOTOX clinical development for "treatment of migraine headaches" in December 1997.

End of phase 2 meeting - December 2004

- (b) (4)

- During the discussion of the phase 3 chronic migraine development program it was agreed to evaluate BOTOX for 3-months with a fixed-schedule dose administration. Preliminary requirements were also discussed.

- FDA indicated that Allergan should evaluate "headache days" as the primary efficacy endpoint as opposed to "headache frequency/headache episodes" with the rationale that during frequent chronic headache, it is difficult to distinguish between two or three shorter headaches occurring back to back versus one headache that may be of several days duration. The FDA further stated that if the primary endpoint were "headache frequency" and indicated success but the "headache days" did not, then interpretation of the results would be difficult. However, Allergan and FDA agreed on the utility of evaluating both headache days and headache frequency. Allergan stated at the meeting that in their efficacy trials the primary endpoint would be "headache days" and the secondary endpoint would be "headache frequency."

Reviewer Comment
As shown in the discussion above summarized from the meeting minutes, and as it will be further discussed in section 6.1.4 of this review, Allergan chose to identify the primary endpoint as headache episodes in the initial phase 3 chronic migraine efficacy trial (191622-079) against FDA advice. FDA warned Allergan previously that this could

be problematic if the headache days and headache episodes endpoints gave inconsistent results. Subsequently the primary efficacy endpoint for the next efficacy trial (191622-080) was amended 2-weeks prior to data lock to identify headache days as the primary efficacy endpoint instead of the previously specified variable headache episodes.

- FDA informed that waiver of all pediatric studies would be problematic. Allergan stated that a plan to evaluate BOTOX in ages 12-18 year old pediatric population would be proposed.

Special Protocol Assessment - August 2005

- Allergan and the FDA reached agreement on the design and corresponding analysis plans for the two phase 3 protocols (191622-079 and 191622-080) in patients with chronic migraine with an understanding that an assessment of consistency of the study results across the primary and secondary endpoints would be important. Allergan proposed primary endpoint was "headache episodes." FDA once again recommended that Allergan should evaluate changes in frequency of "headache days" because it may be more informative than frequency of headache episodes.

pre-sBLA meeting - June 2009

- There was discussion of required datasets.
- *Allergan commented that BOTOX was not shown to be effective in patients with episodic migraine, so the label should state that although BOTOX (is) effective in chronic migraine it is not effective in episodic migraine.*
- Allergan stated that a priority review would be requested.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality and integrity was adequate and properly organized to perform a review consistent with GRMP expectations.

3.2 Compliance with Good Clinical Practices

Three domestic clinical investigators and one foreign investigator from the phase 3 trials (Study Protocols: 191622-079 and 191622-080) were inspected. These sites were targeted for inspection due to enrollment of a relatively large number of subjects and significant primary efficacy results pertinent to decision- making. DSI reported that the inspections of Site No: 10032, Site No: 10005, Site No: 10018 and Site No: 12506 revealed no significant problems that would adversely impact data acceptability. However, Dr. Riff (Site No: 10032) was issued FDA 483 (ORA policy requires issuance of the FDA 483 when objectionable conditions are noted during an inspection) because adverse events and use of concomitant medications were not reported on the CRFs. Dr. Riff acknowledged the inspection findings in a letter to the FDA. These findings appeared isolated and no similar deficiencies were identified at other sites inspected that may have affected data integrity, data analysis, or suggestive of monitoring inadequacies instituted by Allergan. Overall the data submitted from these sites are acceptable in support of the application.

3.3 Financial Disclosures

Financial disclosure and certification information was submitted in module 1.3.4. Information was collected for investigators and sub-investigators who participated in chronic migraine phase 3 studies: 191622-079, and 191622-080; supportive chronic daily headache studies: 191622-038, and 191622-039; and for clinical studies 191622-009, 191622-024, 191622-026, 191622-036, 191622-037, and 191622-509 conducted under Allergan's IND 7480.

The certification provided by Allergan had 3 components.

3.3.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests

Allergan provided a list of all such investigators and sub-investigators who were involved in the above mentioned studies in section 1.3.4.1 of the financial disclosure and certification section submitted in module 1.3.4.

- Allergan certified that they did not enter into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Allergan certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements

- Allergan certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

The certifications were provided on Form 3454.

3.3.2 Certification Pertinent To Investigators/Sub-Investigators From Whom Financial Information Could Not Be Obtained

Allergan listed investigators and sub-investigators involved in studies for whom financial information could not be obtained in section 1.3.4.2 of the financial disclosure and certification section submitted in module 1.3.4. Allergan stated they were unable to locate the financial disclosure information in the study files and that it was deemed unreasonable to go back to these sites to collect the information because these studies were completed. They addressed measures to minimize any potential bias in section 1.3.4.3 of the financial disclosure and certification section submitted in module 1.3.4.

The certification was provided on Form 3454.

3.3.3 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests

Allergan provided list of investigators who indicated the presence of financial interests or proprietary interest in this product, or a significant equity in the sponsor as defined in 21 CFR 54.2 (b), in addition to disclosures for the receipt of significant payments of other sorts as defined in 21 CFR 54.2 (f). Allergan stated that the following steps were taken to minimize the potential bias of clinical study results by any of the disclosed arrangement of interests:

- The study was randomized and double-blind
- Efficacy measures were variables derived from information electronically recorded by the patients during the study.
- Investigators were not aware of the randomization block size
- No efficacy or safety study results were released to any of the study investigators prior to locking the database. Baseline demographic data summaries for the 191622-079 and 191622-080 studies were released to D. Dodick and R. Lipton (participants on the 191622-080 study) and S. Silberstein (participant on the 191622-079 study) for use in chronic migraine epidemiology publications. These data summaries had no impact on measured study results.
- Majority of sites (296 out of 307) did not indicate the presence of financial interests or proprietary interest in this product, or a significant equity in the sponsor as defined in 21 CFR 54.2 (b). The 11 sites that did have some type of financial interest only enrolled 166 out of the 4536 patients across the studies that they participated on.

- Study payments were not made contingent upon study results.

Allergan made payments as grants to fund residency training and research, retainer for ongoing consultation, or honoraria. Only two investigators, one of whom was involved in the chronic migraine development program, were identified to have presence of financial interest for Allergan stock.

The certifications were provided on Form 3455.

Allergan informed the Division that study 191622-005 was concluded before the final rule enacted the requirement. Per both the "Amended final rule, [Federal Register: December 31, 1998 (Volume 63, Number 251)]," and the "20 March 2001 Guidance for Industry - Financial Disclosure by Clinical Investigators" the referenced documentation was required for "covered clinical studies that were ongoing on or after February 2, 1999."

Reviewer's comments
It appears unlikely that the financial arrangements disclosed above introduced significant bias in to the results of the phase 3 chronic migraine trials 191622-080 and 191622-079 conducted with BOTOX, and submitted with this sBLA application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Clinical Microbiology

Not Applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

Allergan stated that the chemical complexity of BOTOX, combined with its extreme potency and analytical sensitivity, limits the opportunity to study its pharmacokinetic profile in humans and hence no human pharmacokinetic studies were performed for migraine or any other indication. The clinical pharmacology of BOTOX has been reviewed in previous submissions. No new data was submitted.

4.4.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals and inhibiting the release of acetylcholine. Allergan also stated in their submission that BOTOX blocks the release of neurotransmitters associated with the genesis of pain. This information was detailed in section 2.5.3, module 2.5 of the sBLA submission. My limited review of the information submitted cannot verify the information and I recommend further input if necessary from other disciplines.

4.4.2 Pharmacodynamics

Not applicable.

4.4.3 Pharmacokinetics

Not applicable.

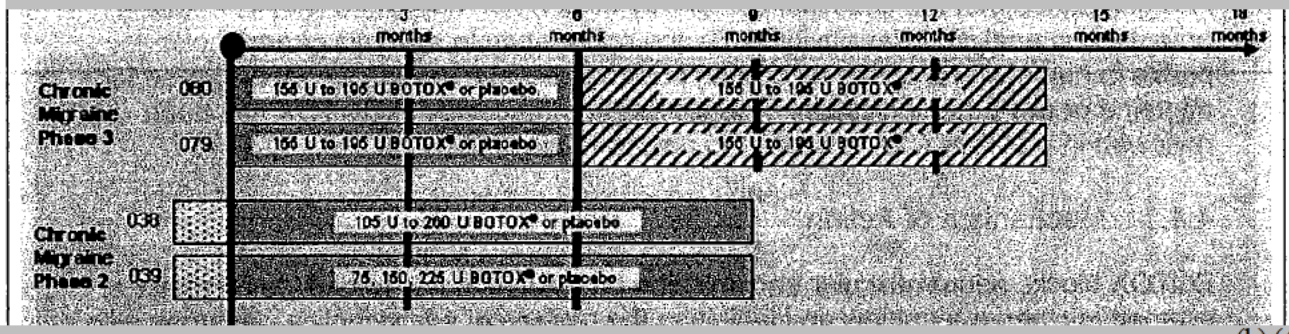
5 Sources of Clinical Data

In December 1997, Allergan initiated a clinical development program to evaluate the efficacy and safety of BOTOX as headache prophylaxis in adults with migraine.

(b) (4) The chronic migraine development program (≥15 headache days per month) consisted of two supportive studies in patients with chronic daily headache, 191622-038 and 191622-039, conducted between 2001 and 2003, and two studies in patients with chronic migraine, 191622-079 and 191622-080, conducted between 2006 and 2008. Figure 1 and Table 3 summarizes these programs.

Figure 1: BLA 103000/5215 BOTOX Migraine Clinical Development Program

(b) (4)



(b) (4)

(b) (4)

= double-blind, placebo-controlled

= treatment (tx)

= 30 day placebo run-in period

= open label

Ref: Module 2.5 Clinical Overview, Sponsor's Figure 2.5.1-1

5.1 Tables of Studies/Clinical Trials

Table 3: BLA 103000/5215 Overview of Migraine Clinical Efficacy Studies in Adults

Study ID ***Primary Endpoint***	**Design** **Total Enrolled/Goal**	**Target Population**	**Treatment Groups (Enrolled/Completed)**		**Muscles Injected (N)** **Type of Injection** (number of sites) *FixedDose/FixedSite,* ***FDFS*** *OR Follow-Pain,* ***FTP***	**No. of Treatment Cycles**
CHRONIC MIGRAINE - Double blind Placebo controlled Studies						
191622-080 *Frequency of HA days per 28-day period*	24-week DB, randomized, PC parallel group phase; 32-wk OL extension **705/650**	Migraineur's with ≥15 HA days/ 4-wk period. Each day ≥4 hours of continuous HA, ≥50% of baseline HA days being M/PM days, and ≥4 distinct HA episodes each lasting ≥4 hours	**BOTOX (155-195U)** DB=347/311 OL=347/259	**PLACEBO** DB=358/334 OL=358/257	N=7 **FDFS**=Frontalis(4), Corrugator(2), Procerus(1), Occipitalis(6), Temporalis(8), Trapezius(6), Cervical Paraspinal muscle group(4) **FTP**=*Optional* additional doses to Occipitalis(0-2), Temporalis(0-2), Trapezius(0-4)	DB = 2 OL = 3
191622-079 *Frequency of HA episodes per 28-day period*	24-week DB, randomized, PC parallel group phase; 32-wk OL extension **679/650**	Migraineur's with ≥15 HA days/ 4-wk period. Each day ≥4 hours of continuous HA, ≥50% of baseline HA days being M/PM days, and ≥4 distinct HA episodes each lasting ≥4 hours	**BOTOX (155-195U)** DB=341/296 OL=341/252	**PLACEBO** DB=338/295 OL=338/231	N=7 **FDFS**=Frontalis(4), Corrugator(2), Procerus(1), Occipitalis(6), Temporalis(8), Trapezius(6), Cervical Paraspinal muscle group(4) **FTP**=*Optional* additional doses to Occipitalis(0-2), Temporalis(0-2), Trapezius(0-4)	DB = 2 OL = 3
CHRONIC DAILY HEADACHE (Chronic Migraine Supportive Study) - Double blind Placebo controlled Studies						
191622-038 *Frequency of HA-free days per 30-day period*	DB, randomized, PC parallel group phase 2 study over 11 months **355/494**	Patients with **chronic daily HA** (≥16 HA days/month), including any combination of migraines, and/or episodic/ chronic TTH	**BOTOX (105-260U)** 173/133	**PLACEBO** 182/140	N=7 *The number of injection sites varied from 23-58* **FDFS**=Occipitalis(NS) **FTP**= Frontalis/Glabellar, Occipitalis, Temporalis, Splenius capitis, Trapezius, Semispinalis capitis *Optional* additional doses to Masseter	Placebo run-in period followed by DB = 3 treatment sessions

191622-039 *Frequency of HA-free days per 30-day period*	DB, randomized, PC parallel group phase 2 study over 11 months **702/790**	Patients with **chronic daily HA** (≥16 HA days/month), including any combination of migraines, and/or episodic/ chronic TTH	**BOTOX (75U, 150U or 225 U)** 524/393 **225U**= 182 **150U**=168 **75U**=174	**PLACEBO** 178/118	N=7 **FDFS**=Frontalis(4), Corrugator(2), Temporalis(4), Splenius capitis(2), Trapezius(4), Semispinalis capitis(2), Sub occipital region(2)	Placebo run-in period followed by DB = 3 treatment sessions

(b) (4)

(b) (4)

Ref: Modified (format only) Module 2.7.3 Migraine, Section 2.7.3.1.2.1, Sponsor's Table 2.7.3.1-2 and Table 2.7.3.6-1
DB=double-blind; **HA** = Headache; **IHS**=International headache Society; **M/PM** = Migraine/Probable migraine; **NS**=Not specified; **OL**=open-label; **PC**=placebo-controlled; **TTH**=Tension Type; **wk** = week

5.2 Review Strategy

Allergan submitted materials for review via eCTD submission. <\\cbsap58\M\eCTD_Submissions\STN103000\103000.enx> I reviewed four studies (191622-080, 191622-079, 191622-038, 191622-039) included in Table 3 for the clinical development of BOTOX for prophylaxis of *chronic migraine* headache.

The chronic migraine studies (191622-079 and 191622-080) are described after the (b) (4) review of chronic migraine supportive studies (191622-038, 191622-039) in patients with chronic daily headache (see patient population definition in section 5.3.2), of which a majority subset of patients met chronic migraine criteria.

The study reports submitted for BOTOX episodic migraine clinical development had limited review as they were negative trials and did not support Allergan's proposed claim in labeling for the product. I summarized the pertinent study design elements and literature findings in the individual studies summary section 5.3.1. The summary findings provide recommendations for inclusion of appropriate information in the Prescribing Information.

For sBLA103000/5215 I reviewed the efficacy section, Dr. Xiang Ling, PhD performed the statistical review, and Dr. Cheryl Graham, MD reviewed the safety of BOTOX for the indication.

5.3 Discussion of Individual Studies/Clinical Trials

The design, objectives, and target population of the chronic migraine clinical development program Study protocols 191622-079 and 191622-080 were similar. I described them together with the description of one clinical trial in detail and included comments on the differences in the chronic migraine phase 3 studies during the discussion of the primary endpoint in section 6.1.4. The study results for the chronic migraine phase 3 studies are discussed in Section 6. Results from a subgroup of subjects meeting chronic migraine studies criteria were included by Allergan as supportive efficacy data from two studies in patients with chronic daily headache (191622-038 and 191622-039).

(b) (4)

5 pages immediately following withheld - b(4)

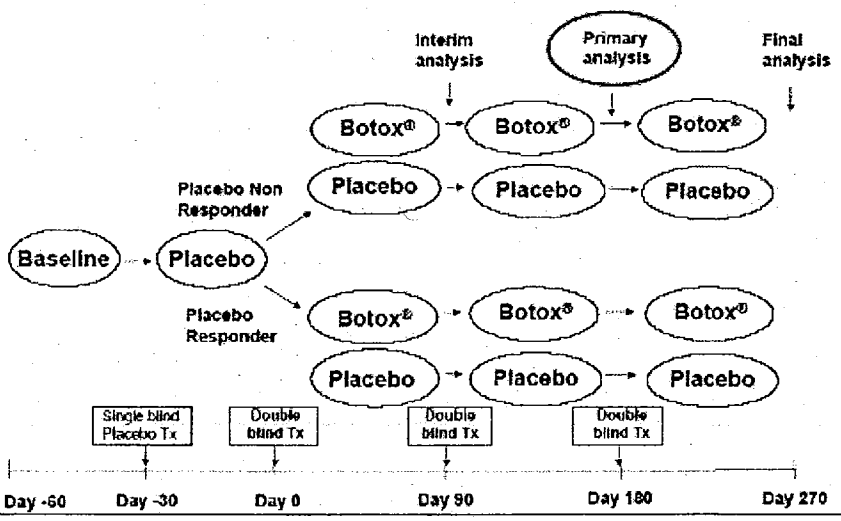
5.3.2 Chronic Daily Headache (Chronic Migraine Supportive Study) 191622-038

This exploratory multicenter, double-blind, randomized, placebo-controlled, parallel-group study of BOTOX for the prophylactic treatment of headaches in the chronic daily headache population included patients with primary headache disorder with ≥ 16 headache days per month. These headaches included

- Chronic migraine/transformed migraine,
- New daily persistent headache
- Hemicrania continua
- Migraine with/without aura
- probable migraine
- episodic migraine
- chronic TTH

Design and Dose: Following a 30-day placebo run-in period (due to high-placebo response seen in episodic migraine studies) *all patients* were stratified as placebo non-responder or placebo responder and randomized to BOTOX or placebo treatment. (placebo responder defined as <16 headache days or had a >30% decrease from baseline in the frequency of headache days).

Figure 2: BLA 103000/5215 Schematic of Supportive Phase 2 Chronic Migraine Study Design



Ref: Module 2.7.3 ISE, Sponsor's Figure 2.7.3.1-5

Patients were subjected to 4 treatment sessions over an 11-month period (30-day baseline period; Treatment 1 [placebo] with 30-day follow-up period; Treatments 2, 3, and 4 [BOTOX dose range: 105U to 260U or placebo], each with 90-day follow-up period).

BOTOX was injected intramuscularly at a dose range of ***105 U to 260 U*** *(0.1 mL or 5U per site) over 6 to 7 muscle areas including frontal/glabellar, occipitalis, temporalis, masseter (optional), trapezius, semispinalis, and splenius capitis. The number of injection sites varied from 23 to 58 injection sites.*

Investigators could select the dose of BOTOX to be injected in a minimum of 6 muscle areas (within the dose range specified in the protocol) based on the location and severity of pain experienced by the patient in a particular muscle area (**FOLLOW-THE-PAIN**), except for the occipitalis muscle where the dosage was fixed. The same dosing regimen (dose and volume) was to be used for **all 3 treatment cycles** (Day 0=treatment 2, Day 90=treatment 3, Day 180=treatment 4). Maximum total exposure could have been 780 U (based on 3 treatment cycles of up to 260 U each).

Table 8: BLA 103000/5215 Protocol 191622-038 Modified Follow-the-pain Injection Paradigm

Head/Neck Area	Number of units per muscle [a]	Bilateral Injection	TOTAL DOSE (U)
Frontalis/Glabellar	25-40	No	25-40
Occipitalis	10	Yes	20
Temporalis	10-25	Yes	20-50
Masseter (optional)	0-25	Yes	0-50
Trapezius	10-30	Yes	20-60
Semispinalis	5-10	Yes	10-20
Splenius Capitis	5-10	Yes	10-20
Total Dose Range			**105-260**

Modified format only: Module 5.3.5.1.1 (Study 191622-038), Section 9.1; Table 9.4-1
[a] 1 injection site = 0.1 mL = 5 U of BOTOX or 0 U of placebo

Dose selection rationale: chronic daily headache studies 191622-038 and 191622-039
Allergan stated that during the development of BOTOX for chronic migraine since several episodic migraine headache trials were done previously, subsequently a dose and injection paradigm was developed.

Episodic migraine trials: 191622-005, 191622-009, 191622-024, 191622-026, and 191622--036.
Chronic tension-type headache trial: 191622-027.

Table 9: BLA 103000/5215 Rationale for dose selection in study 191622-038 and 191622-039	
Episodic Migraine Phase 2 Trials (-005, (b) (4)	**Chronic Migraine Phase 2 Trials (-038 and -039)**
Fixed-site, fixed-dose treatment paradigm may not be the optimal treatment regimen	"Modified follow-the-pain" paradigm implemented (191622-038) as well as further evaluation of "fixed-site, fixed-dose" (191622-039)
Maximum dose of 150 U may not be high enough	Maximum dose increased to 225 U (in a single session) in the "fixed-site-fixed-dose" dose-ranging study (191622-039), and to 260 U in the "modified follow-the-pain" study (191622-038)
Number of injection sites (all frontal/temporal) may not have been enough to diffuse across the trigeminal nerve adequately	More injection sites added (up to 58 injection sites in 191622-038) including the posterior neck and head
Modified format only: Source: Study report 191622-038 page 110.	

STUDY RESULTS Chronic Daily Headache Study 191622-038

355 patients entered the placebo run-in period and were subsequently randomized to treatment. At the end of the run-in period (Day 0), 279 (78.6%) patients were classified as placebo non-responders and 76 (21.4%) patients as placebo responders. Within the placebo non-responder stratum, 134 patients received BOTOX and 145 patients received placebo. Within the placebo responder stratum, 39 patients received BOTOX and 37 patients received placebo. The 2 treatment groups were similar in demographic characteristics. *A total of 87% of patients had chronic migraine.*

Table 10: BLA 103000/5215 Study Protocol 191622-038 Summary of Subject Enrollment (Double-Blind Period)			
Disposition	**BOTOX N (%)**	**PLACEBO N (%)**	**TOTAL N (%)**
Enrolled	173	182	355
Completed (Day 120) 1-DB treatment cycle *Original pre-specified timepoint*	63 (36.4%)	69 (37.9%)	132 (37.2%)
Completed (Day 270) 3-DB treatment cycles	70 (40.5%)	71 (39.0%)	141 (39.7%)
Discontinued	40 (23.1%)	41 (22.5%)	81 (22.8%)
Lack of Efficacy	7 (4.0%)	11 (6.0%)	18 (5.1%)
Lost to Follow-up	3 (1.7%)	7 (3.8%)	10 (2.8%)
Personal reasons	4 (2.3%)	0 (0.0%)	4 (1.1%)
Protocol Violations	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	22 (12.7%)	21 (11.5%)	43 (12.1%)
Modified format only. Module 5.3.5.1.1; Source: Table 14.1-1.1			

The proportion of patients who received *doses of interest* (for efficacy studies in the chronic migraine development program) during 2 and 3-treatment cycles are shown below.

Table 11: BLA 103000/5215 Study Protocol 191622-038 Number of Subjects Exposed (%) and Total Dose by time period

Time Period	TOTAL DOSE (n, %)								
	BOTOX			PLACEBO			TOTAL		
	75 U	150 U	225 U	75 U	150 U	225 U	75 U	150 U	225 U
Day 0 Treatment2	0 (0.0%)	74 (42.8%)	99 (57.2%)	1 (0.5%)	72 (39.6%)	109 (59.9%)	1 (0.3%)	146 (41.1%)	208 (58.6%)
Day 90 Treatment3	1 (1.2%)	29 (35.8%)	51 (63.0%)	0 (0.0%)	36 (43.4%)	47 (56.6%)	1 (0.6%)	65 (39.6%)	98 (59.8%)
Day 180 Treatment4	0 (0.0%)	26 (36.1%)	46 (63.9%)	0 (0.0%)	34 (43.0%)	45 (57.0%)	0 (0.0%)	60 (39.7%)	91 (60.3%)

Modified format only. Module 5.3.5.1.1; Source: Table 14.1-7.3

PRIMARY EFFICACY ENDPOINT

The primary efficacy variable defined a priori was *the change from baseline in the frequency of headache-free days*. Initially the primary timepoint was the 30 days ending with day 120 compared to baseline. However, Allergan stated that more than 2 treatment cycles during the double-blind phase of the study was included to ensure sufficient drug exposure was obtained at the effective dose and treatment paradigm to adequately assess safety and to observe BOTOX expected clinical benefit. The protocol was amended to include a total of 3 treatment cycles (following the placebo run-in) and the primary timepoint was changed to Day 180 in the placebo non-responder stratum. By the time these amendments were put in place, a significant number of subjects had exited the original study at the planned Day 120 time point. Therefore, enrollment was extended to ensure that at least 90 placebo non-responder patients (45 per treatment group) were available for the Day 180 analysis.

There were no statistically significant differences between BOTOX and placebo at any time point, including Day 180 (the primary timepoint) for placebo non-responders which was the population of primary interest (Table 12 and Table 13) except for reduction in headache episodes. Allergan graphically presented (Figure 3) the frequency of headache days per 30-day period (*the complement of the prespecified primary timepoint: frequency of headache-free days per 30-day period for consistency with Chronic migraine phase 3 studies data presentation*).

Table 12: BLA 103000/5215 Study Protocol 191622-038 Primary Endpoint Analysis; LSMean Change From Baseline in the Frequency of Headache Days[b] per 30-Day Period (ANCOVA) for Placebo Non-responders and Placebo Responders

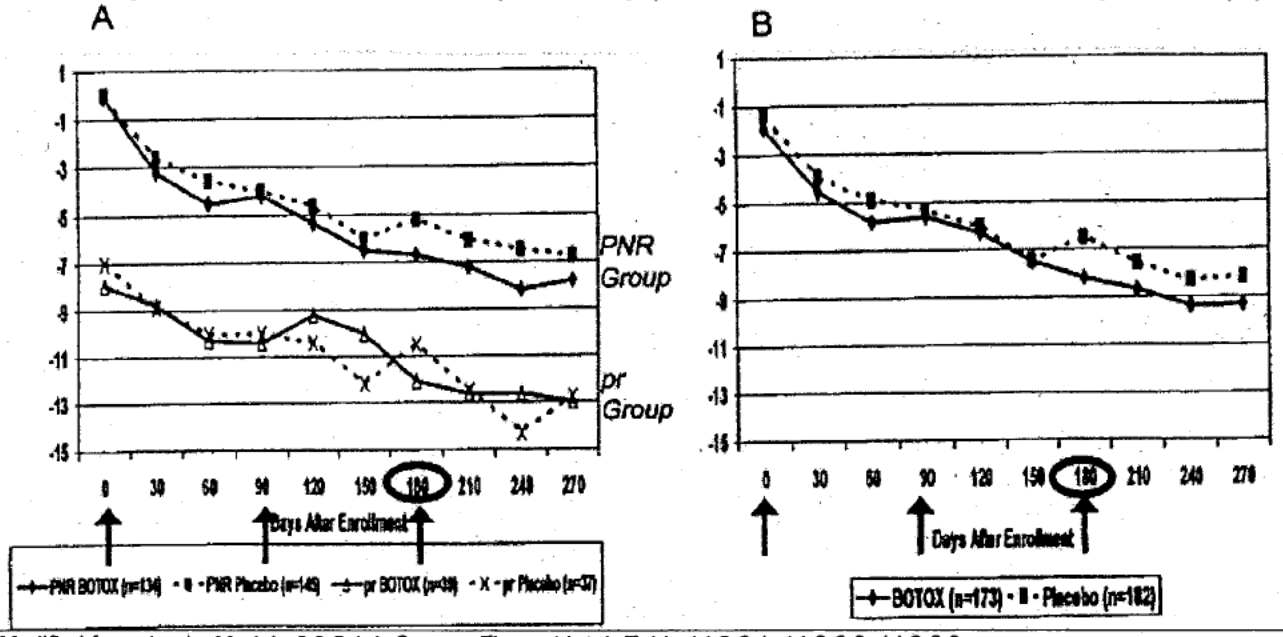
Time Period [a]	BOTOX N LSMean	PLACEBO N LSMean	p-value
Baseline	173 23.4	182 23.4	0.320
Run-In	173 -1.9	182 -1.4	0.320
Day 30	172 -4.4	182 -3.9	0.444
Day 60	164 -5.8	166 -4.9	0.237
Day 90	149 -5.6	157 -5.3	0.706
Day 120 **After 1-treatment cycle**	80 -6.3	82 -6.0	0.806
Day 150	75 -7.4	80 -7.6	0.916
Day 180 **After 2-treatment cycles**	72 -8.1	79 -6.6	0.200
Day 210	70 -8.6	77 -7.7	0.473
Day 240	70 -9.4	71 -8.4	0.478
Day 270	69 -9.3	69 -8.2	0.450

Modified format only. Module 5.3.5.1.1; Source: Figure 11.4-1; Table 14.2-2.6

[a] Statistics are for baseline and change from baseline. Baseline is the first 30 days of qualifying period preceding placebo run-in. Run-in is the first 30 days between placebo run-in injection and randomization injection.

[b] Prespecified endpoint was change from baseline in frequency of headache-free days. Headache days (the complement of headache-free days) were presented for consistency with chronic migraine phase 3 studies data presentation.

Figure 3: BLA 103000/5215 Study Protocol 191622-038 Primary Endpoint Analysis; Mean Change From Baseline in the Frequency of Headache Days per 30-Day Period for Placebo Non-responders and Placebo Responders (A) and for Both Strata Pooled Population (B)



Modified format only. Module 5.3.5.1.1; Source: Figure 11.4-1; Table 14.2-2.1, 14.2-2.2, 14.2-2.3
PNR = placebo non-responders, pr = placebo responders
Arrows indicate when dosing occurred (post placebo run-in). Day 180 (circled) was the primary time point.

There was approximately 15% treatment difference in proportion of patients with 50% reduction (responder rates) in headache days and headache episodes following 2-treatment cycles, however following 1-treatment cycle there was <5% treatment difference (Table 13).

Table 13: BLA 103000/5215 Study Protocol 191622-038 Mean change from Baseline at Day 180 (after 2-treatment cycles) Primary Timepoint for Key Efficacy Results [B]

Efficacy parameters (per 28 days)	BOTOX 105U-260U (N=173)	PLACEBO (N=182)	p-value [a]
Frequency of HA days	-8.1	-6.6	0.200
Frequency of HA Episodes	-7.1	-3.7	0.001
Frequency of M/PM days	-6.9	-6.0	0.387
Frequency of M/PM episodes	-5.8	-3.0	0.002
Frequency of acute HA pain medication intakes	-13.1	-11.2	0.237
Proportion of patients with 50% reduction in HA days (Day 120 - after 1 treatment cycles)	27.5%	22.0%	0.413
Proportion of patients with 50% reduction in HA days (Day 180 - after 2 treatment cycles)	40.3%	25.3%	0.050

Proportion of patients with 50% reduction in HA episodes	54.2%	38.0%	0.046

Modified format only. Module 2.7.3 ISE; Source: Table 2.7.3.2-3
[a] Among-group p-value is represented.
[B] ORIGINAL ANALYSIS: Methodology used no minimum time for HA days and episodes, observed data with no imputation for missing data, and summarized per 30-days

5.3.3 Chronic Daily Headache (Chronic Migraine Supportive Study) 191622-039

The study design, target population, and objectives were similar to chronic daily headache study protocol 191622-038.

Design and Dose: Following a placebo run-in period when all patients received *20 placebo injections in 7 muscle areas*, the patients were stratified on Day 0 (Treatment period 2) as placebo non-responder or placebo responder and randomized to 1 of the 3 fixed-dose active *treatment groups (75 U, 150 U or 225 U of BOTOX)* or placebo treatment within each of the 2 strata. Patients received the same dose and same number of injections in the same muscle areas during **all 3 treatment cycles** (Treatments 2, 3, and 4).

Table 14: BLA 103000/5215 Protocol 191622-039 Study Medication Fixed-Dose and Injection Sites

Muscle area		BOTOX 225 U	BOTOX 150 U	BOTOX 75 U	PLACEBO 0 U
Frontalis	**Per Site**	7.5 U/ 0.1 mL	5 U/ 0.1 mL	2.5 U/ 0.1 mL	0 U/ 0.1 mL
(4 sites)	**Per Muscle**	30 U/ 0.4 mL	20 U/ 0.4 mL	10 U/ 0.4 mL	0 U/ 0.4 mL
Corrugator	**Per Site**	7.5 U/ 0.1 mL	5 U/ 0.1 mL	2.5 U/ 0.1 mL	0 U/ 0.1 mL
(2 sites)	**Per Muscle**	15 U/ 0.2 mL	10 U/ 0.2 mL	5 U/ 0.2 mL	0 U/ 0.2 mL
Temporalis	**Per Site**	7.5 U/ 0.1 mL	5 U/ 0.1 mL	2.5 U/ 0.1 mL	0 U/ 0.1 mL
(4 sites)	**Per Muscle**	30 U/ 0.4 mL	20 U/ 0.4 mL	10 U/ 0.4 mL	0 U/ 0.4 mL
Splenius capitis	**Per Site**	15 U/ 0.2 mL	10 U/ 0.2 mL	5 U/ 0.2 mL	0 U/ 0.2 mL
(2 sites)	**Per Muscle**	30 U/ 0.4 mL	20 U/ 0.4 mL	10 U/ 0.4 mL	0 U/ 0.4 mL
Trapezius	**Per Site**	15 U/ 0.2 mL	10 U/ 0.2 mL	5 U/ 0.2 mL	0 U/ 0.2 mL
(4 sites)	**Per Muscle**	60 U/ 0.8 mL	40 U/ 0.8 mL	20 U/ 0.8 mL	0 U/ 0.8 mL
Semispinalis capitis	**Per Site**	15 U/ 0.2 mL	10 U/ 0.2 mL	5 U/ 0.2 mL	0 U/ 0.2 mL
(2 sites)	**Per Muscle**	30 U/ 0.4 mL	20 U/ 0.4 mL	10 U/ 0.4 mL	0 U/ 0.4 mL
Suboccipital region	**Per Site**	15 U/ 0.2 mL	10 U/ 0.2 mL	5 U/ 0.2 mL	0 U/ 0.2 mL
(2 sites)	**Per Muscle**	30 U/ 0.4 mL	20 U/ 0.4 mL	10 U/ 0.4 mL	0 U/ 0.4 mL
Total Injected per treatment	**20 sites**	**225 U/ 3.0 mL**	**150 U/ 3.0 mL**	**75 U/ 3.0 mL**	**0 U/ 3.0 mL**

Modified format only: Module 5.3.5.1.1; Section 9.4.1 Table 9.4-1

STUDY RESULTS Chronic Daily Headache Study 191622-039
702 patients entered the placebo run-in period and were subsequently randomized. At the end of the run-in period (Day 0), 538 (76.6%) patients were classified as placebo non-responders and 164 (23.4%) were classified as placebo responders. In each

stratum (placebo non-responders and placebo responders) patients were randomized to receive either BOTOX or placebo. A total of 182 patients received BOTOX 225 U, 168 received BOTOX 150 U, 174 received BOTOX 75 U, and 178 received placebo. Overall, 71.9% of the 538 placebo non-responders and 75.6% of the 164 placebo responders completed the study. For both placebo non-responders and placebo responders, discontinuation rates were higher in the placebo group (33.7%) compared with the BOTOX groups (23.2% to 26.4%), primarily due to lack of efficacy.

The treatment groups were similar in demographic characteristics, with no statistically significant differences among the groups. *A total of 84.6% of patients had chronic migraine.*

Table 15: BLA 103000/5215 Study Protocol 191622-039 Summary of Subject Enrollment (Double-Blind Period)

Disposition	BOTOX N (%)			PLACEBO N (%)	TOTAL N (%)
	225 U	150 U	75 U		
Enrolled	182	168	174	178	702
Completed (Day 120) 1-DB treatment cycle *Original pre-specified timepoint*	44 (24.2%)	46 (27.4%)	35 (20.1%)	50 (28.1%)	175 (24.9%)
Completed (Day 270) 3-DB treatment cycles	92 (50.5%)	83 (49.4%)	93 (53.4%)	68 (38.2%)	336 (47.9%)
Discontinued	46 (25.3%)	39 (23.2%)	46 (26.4%)	60 (33.7%)	191 (27.2%)
Lack of Efficacy	20 (11.0%)	9 (5.4%)	13 (7.5%)	32 (18.0%)	74 (10.5%)
Protocol Violations	1 (0.5%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	3 (0.4%)
Other	6 (3.3%)	5 (3.0%)	7 (4.0%)	12 (6.7%)	30 (4.3%)

Modified format only. Module 5.3.5.1.1 Source: Tables 14.1-1.1

No data tables regarding dose response relation was included in the submitted study report to identify the proportion of patients who received doses of interest (for efficacy studies in the chronic migraine development program) during 2 and 3-treatment cycles. However, Allergan stated in 191622-039 study report, section 11.4.4 of module 5.3.5.1.1, that no consistent dose-response relationships were observed.

PRIMARY EFFICACY ENDPOINT

The primary efficacy variable defined a priori was the change from baseline in the frequency of headache-free days. Initially the primary timepoint was the 30 days ending with day 120 compared to baseline.

There were no statistically significant differences between BOTOX and placebo at the primary timepoint Day 180 (Table 16 and Table 17). Allergan presented the frequency of headache days per 30-day period (*the complement of the prespecified primary timepoint: frequency of headache-free days per 30-day period for consistency with Chronic migraine phase 3 studies data presentation*).

Table 16: BLA 103000/5215 Study Protocol 191622-039 Primary Endpoint Analysis; LSMean Change From Baseline in the Frequency of Headache Days[b] per 30-Day Period (ANCOVA) for Placebo Non-responders and Placebo Responders

Time Period [a]	BOTOX N LSMean			PLACEBO N LSMean	p-value
	225 U	150 U	75 U		
Baseline	182 23.8	168 23.8	174 23.8	178 23.8	0.656
Run-In	182 -2.5	168 -1.4	174 -2.3	178 -2.1	0.181
Day 30	179 -5.4	167 -4.3	171 -6.0	177 -4.2	0.031
Day 60	173 -6.3	161 -5.9	164 -6.5	166 -5.0	0.239
Day 90	163 -7.0	154 -6.5	161 -6.8	156 -5.2	0.123
Day 120 After 1-treatment cycle	106 -7.0	98 -7.0	116 -8.1	98 -6.6	0.469
Day 150	104 -7.7	97 -7.9	112 -8.8	92 -6.9	0.388
Day 180 After 2-treatment cycles	99 -8.0	95 -8.6	107 -9.4	83 -8.6	0.646
Day 210	93 -8.5	86 -9.3	101 -9.6	69 -8.0	0.603
Day 240	91 -9.2	85 -10.3	97 -9.4	68 -7.8	0.370
Day 270	90 -9.0	81 -10.3	93 -9.6	67 -8.0	0.406

Modified format only. Module 5.3.5.1.1; Source: Figure 11.4-1; Table 14.2-2.6

[a] Statistics are for baseline and change from baseline. Baseline is the first 30 days of qualifying period preceding placebo run-in. Run-in is the first 30 days between placebo run-in injection and randomization injection.

[b] Prespecified endpoint was change from baseline in frequency of headache-free days. Headache days (the complement of headache-free days) were presented for consistency with chronic migraine phase 3 studies data presentation.

Table 17: BLA 103000/5215 Study Protocol 191622-039 Mean change from Baseline at Day 180 (after 2-treatment cycles) Primary Timepoint for Key Efficacy Results [B]

Efficacy parameters (per 28 days)	BOTOX			PLACEBO (N=178)	p-value [a]
	225 U (N=182)	150 U (N=168)	75 U (N=174)		
Frequency of HA days	-8.0	-8.6	-9.4	-8.7	0.646
Frequency of HA Episodes	-7.2	-6.2	-7.6	-7.9	0.683
Frequency of M/PM days	-6.6	-7.6	-8.4	-6.5	0.402
Frequency of M/PM episodes	-5.5	-4.6	-6.1	-5.2	0.224
Frequency of acute HA pain medication intakes	-15.0	-10.7	-12.7	-13.0	0.632
Proportion of patients with 50% reduction in HA days (Day 120 - after 1 treatment cycle)	30.2%	30.6%	35.3%	24.5%	0.397
Proportion of patients with 50% reduction in HA days (Day 180 - after 2 treatment cycles)	34.3%	42.1%	39.3%	38.6%	0.737
Proportion of patients with 50% reduction in HA episodes	45.5%	52.6%	53.3%	50.6%	0.680

Modified format only. Module 2.7.3 ISE; Source: Table 2.7.3.2-3
[a] Among-group p-value is represented.
[B] ORIGINAL ANALYSIS: Methodology used no minimum time for HA days and episodes, observed data with no imputation for missing data, and summarized per 30-days

5.3.4 Phase 3 Chronic Migraine Study Protocols 191622-079 and 191622-080

Both Phase 3 study protocols were discussed with the FDA in August 2005 during Special Protocol Assessment.

Study design: A multicenter study evaluating the efficacy and safety of BOTOX as headache prophylaxis in migraine patients with 15 or more headache days per 4-week period during a 24-week, double-blind, randomized, placebo-controlled, parallel-group phase followed by a 32-week open- label extension phase.

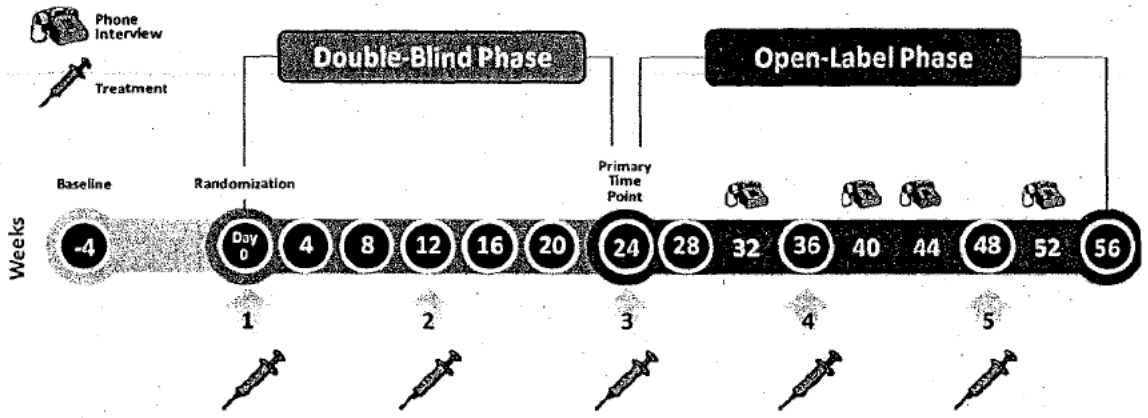
Duration: 60 weeks (included a 4-week baseline phase, followed by a 24-week, double-blind treatment phase prior to patients entering a 32-week, open-label extension phase).

Dose:
The total minimum *required fixed-dose* = 155 U with 31 head/neck injections.
The total maximum dose = 195 U with 39 head/neck injections.

Study Treatments: *2 treatment sessions* with BOTOX or 2 treatments with placebo during the double-blind phase (day 0 and week 12) after patients were stratified based on medication overuse (yes/no) during the 4-week baseline phase.

During the 32-week open-label phase, all patients were to receive 3 treatments of BOTOX (weeks 24, 36, and 48).

Figure 4: BLA 103000/5215 Study Protocols 191622-080 and 191622-079 Study Design Schematic and Treatment Schedules



* In-office visits were conducted every 4 weeks, except when noted by telephone.

Ref: Module 2.7.3 Summary of Clinical Efficacy; Source: Figure 2.7.3.1-3

BASELINE PHASE
- Visit 1: Week -4 (Screening)

DOUBLE-BLIND PHASE
- Visit 2: Day 0 (Randomization and ***Treatment 1***)
- Visit 3: Week 4
- Visit 4: Week 8
- Visit 5: Week 12 (***Treatment 2***)
- Visit 6: Week 16
- Visit 7: Week 20
- Visit 8: Week 24 (**Primary timepoint**)

OPEN-LABEL EXTENSION PHASE
- Visit 8: Week 24 (***Treatment 3***) All patients will receive OL treatment with BOTOX.
- Visit 9: Week 28
- Visit 10: Week 32 (Telephone Visit)
- Visit 11: Week 36 (***Treatment 4***)
- Visit 12: Week 40 (Telephone Visit)
- Visit 13: Week 44 (Telephone Visit)
- Visit 14: Week 48 (***Treatment 5***)
- Visit 15: Week 52 (Telephone Visit)
- Visit 16: Week 56 (Exit)

Rationale for two treatment cycles during double-blind phase
Allergan stated that a total of 2 treatment cycles during the double-blind phase of the study and 3 treatment cycles during the open-label phase were included to ensure sufficient drug exposure was obtained at the effective dose and treatment paradigm to adequately assess safety. These were learned from clinical experts and Allergan cited literature report (Allergan Reference: Troost, 2004).

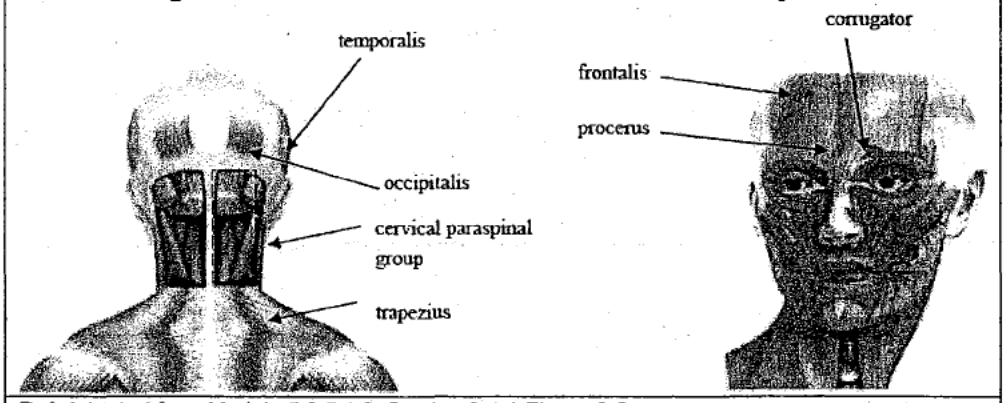
REQUIRED **FIXED DOSE**: In the double-blind phase, all patients received a minimum fixed dose of 155 U BOTOX or placebo administered as 31 fixed-site, fixed-dose injections across seven (7) specific head/neck muscle areas. For specific Injection details please refer to Appendix 9.4 Training Materials for Injection Procedure Used in Phase 3 Chronic Migraine Studies. Dosing and number of possible injection sites are shown in Table 18 and Figure 5.

Table 18: BLA 103000/5215 Protocol 191622-079 and 191622-080 Required Fixed-Site, Fixed-Dose Injection Paradigm

Head/Neck Area	LEFT Number of units per muscle (number of injection sites [a])	RIGHT Number of units per muscle (number of injection sites [a])	TOTAL Number of units per muscle (number of injection sites [a])
Frontalis	10 (2 sites)	10 (2 sites)	20 (4 sites)
Corrugator	5 (1 site)	5 (1 site)	10 (2 sites)
Procerus	-	-	5 (1 site)
Occipitalis	15 (3 sites)	15 (3 sites)	30 (6 sites)
Temporalis	20 (4 sites)	20 (4 sites)	40 (8 sites)
Trapezius	15 (3 sites)	15 (3 sites)	30 (6 sites)
Cervical Paraspinal Muscle Group	10 (2 sites)	10 (2 sites)	20 (4 sites)
Minimum Total	-	-	**155 U (31 sites)**

Ref: Modified format only: Module 5.3.5.1.4, Section 7.1.2; Table 7.1.2-1
[a] 1 injection site = 0.1 mL = 5 U of BOTOX or 0 U of placebo

Figure 5: BLA 103000/5215 Muscles To be Injected



Ref: Adapted from Module 5.3.5.1.3, Section 9.4.1 Figure 9-2

OPTIONAL ADDITIONAL DOSE, **FOLLOW-THE PAIN**: In addition, at the investigator's discretion, additional injections of BOTOX or placebo could be administered unilaterally or bilaterally using a follow-the-pain paradigm of up to 8 injection sites in up to 3 specific head/neck muscle areas (temporalis, occipitalis, and/or trapezius). These *optional* additional injections need not be consistent across treatment visits, with respect to dose or number of injection sites, but must still not exceed the maximum dose allowed (195U). The dose injected was fixed for a muscle injection site but the total optional dose injected could vary because of the decision criteria used by Allergan. For example, if tenderness persisted in the Occipitalis muscle, after injecting the required fixed-dose per protocol, then either 5 units in one site or 10 units at two sites could be additionally injected.

The decision on how many additional units to inject took into account the following criteria using Table 19 below as a guide:

- Patient-reported usual location of predominant pain
- While palpating the muscle prior to injection, severity of the muscle tenderness
- Clinician's best judgment on the potential benefit of additional doses in the specified muscles (eg, large muscle size)

Table 19: BLA 103000/5215 Protocol 191622-079 and 191622-080 Optional Additional Dosing: FOLLOW-THE-PAIN Injection Paradigm

Head/Neck Area	Number of units per muscle (number of injection sites [a])		Location of Usual Pain or Tenderness on Palpation	TOTAL
	LEFT	RIGHT		Number of units per muscle (number of injection sites [a])
Occipitalis [b]	5 U/site (up to 2 sites)	0	Left side	0, 5 or 10 U (0,1 or 2 sites)
	0	5 U/site (up to 2 sites)	Right side	
	5 U (1 site)	5 U (1 site)	Both sides	
Temporalis [b]	5 U/site (up to 2 sites)	0	Left side	0, 5 or 10 U (0,1 or 2 sites)
	0	5 U/site (up to 2 sites)	Right side	
	5 U (1 site)	5 U (1 site)	Both sides	
Trapezius	5 U/site (up to 4 sites)	0	Left side	0, 5, 10, 15 or 20 U (0,1, 2, 3 or 4 sites)
	5 U/site (up to 3 sites)	5 U (1 site)		
	0	5 U/site (up to 4 sites)	Right side	
	5 U (1 site)	5 U/site (up to 3 sites)		
	5 U/site (up to 2 sites)	5 U/site (up to 2 sites)	Both sides	

Maximum Additional	-	-	-	**40 U (8 sites)**
Maximum Total	-	-	-	**195 U (39 sites)**

Modified format only: Module 5.3.5.1.4, Section 7.1.2; Table 7.1.2-2
[a] 1 injection site = 0.1 mL = 5 U of BOTOX or 0 U
[b] Max additional dose per muscle distributed unilaterally or bilaterally: Occipitalis=10 U, Temporalis=10 U, Trapezius=20 U

Reviewer comment
Evidence of efficacy was evaluated including up to BOTOX 195 U dose. However, there was no standardized approach as shown above whereby a determination could be made about which patients required >155 U. The decision on amount of optional additional units to inject was determined by patient-reported usual location of predominant pain, severity of muscle tenderness by muscle palpation prior to injection, and using the clinician's best judgment. The study was not designed to determine the clinical benefit of treatment with a dose higher than 155 U.

Drug Reconstitution: Each vial of BOTOX or placebo was reconstituted with 2.0 ml of preservative free saline per vial for a concentration of 50 U/ml and filled in tuberculin syringes. Reconstituted study medication was inspected for color and clarity (i.e., it should be clear and colorless) and should have been administered within 4 hours of reconstitution. Syringes filled with study medication should not be stored in the refrigerator.

Maintaining study blinding to treatment: During the double-blind treatment phase an independent individual was assigned to reconstitute the study medication with preservative-free normal saline to each vial and draw the medication into syringes to be injected. The investigator, injector, nor site personnel involved in evaluating the patient were to prepare the study medication and remained blinded to treatment. The evaluators were blinded to efficacy parameters since they were electronically reported by patients via IVRS.

Key Inclusion criteria
- Male or female, 18 to 65 years old
- History of migraine headache disorder meeting any of the diagnostic criteria listed in ICHD-II (2004) Section 1, Migraine, with the exception of migraine disorders as listed in the exclusion criteria of "complicated migraine"
- ≥4 distinct headache episodes during the 4-week baseline phase each with a duration of at least 4 hours
- ≥15 headache days during the 4-week baseline phase, with each day consisting of 4 or more hours of continuous headache
- At least 50% of baseline headache days were migraine or probable migraine days (ICHD-II 2004 Sections 1.1 [migraine without aura], 1.2 [migraine with aura], and 1.6 [probable migraine])

- Routine non-headache medications of stable dose and regimen for at least 1 month prior to week -4 and during the baseline phase

Key Exclusion criteria

- Use of any headache prophylactic medication within 28 days prior to week -4
- The patient was not in the baseline phase (week -4 to day 0) for at least 28 days or did not record a minimum of 20 days worth of diary data
- Unremitting headache lasting continuously throughout the 4-week baseline period
- Any medical condition that may have put the patient at increased risk with exposure to BOTOX, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other significant disease that may have interfered with neuromuscular function
- Patients who had been diagnosed with the following headache disorders, as listed in ICHD-II (2004) Section 1: complicated migraine (eg, hemiplegic migraine [1.2.4, 1.2.5], basilar migraine [1.2.6], ophthalmoplegic migraine [13.17], or migrainous infarction [1.5.4])
  Note: Patients with only a diagnosis of retinal migraine [1.4], persistent aura without infarction [1.5.3], or migraine-triggered seizure [1.5.5] were not to be enrolled (e.g., a patient with migraine without aura [1.1] and retinal migraine [1.4] may have been enrolled in the study).
- Headache diagnosis of chronic tension-type headache (ICHD-II 2.3), hypnic headache (ICHD-II 4.5), hemicrania continua (ICHD-II 4.7), or new daily persistent headache (ICHDII 4.8)
- Headache attributed to another disorder (eg, cervical dystonia, craniotomy, head/neck trauma)
- Patients with a known or suspected temporomandibular disorder (TMD), including pain in or around the temporomandibular joint (TMJ)
- Patients with a concurrent diagnosis of fibromyalgia
- Beck Depression Inventory score > 24 at week -4
- Previous treatment with botulinum toxin therapy of any serotype for any reason, or immunization to any botulinum toxin serotype
- Acupuncture, TENS (transcutaneous electrical nerve stimulation), cranial traction, nociceptive trigeminal inhibition or occipital nerve block treatments, or injection of anesthetics or steroids into the study target muscles within 4 weeks prior to week -4 or on or after week -4

Rational for evaluating BOTOX in selected population

During the initial studies in patients with chronic daily headache (chronic migraine supportive studies 191622-038 and 191622-039) the vast majority of patients enrolled were those with chronic migraine (85%) defined by Silberstein and Lipton, 2001 (Allergan reference). Even though the primary endpoints were not met in these studies, exploratory analyses of the chronic daily headache study 191622-038 suggested that the BOTOX-responsive population included those patients who suffered headaches on 15 or more days each month, had a high burden of long-lasting (≥ 4 hours) headaches

with at least 50% of their headache days being migraine or probable migraine as determined by the International Classification of Headache Disorders (ICHD-II) types 1.1, 1.2, or 1.6, and not taking concurrent headache prophylaxis treatments.

Patients meeting the selection criteria following a 4-week baseline period on day 0 were stratified based on acute medication overuse (yes/no), as determined by the frequency of use of acute headache pain medications during the baseline phase and then assigned to study treatment in 1:1 ratio.

Withdrawal criteria: Patients could have been discontinued prematurely from the study for adverse events, lack of efficacy, pregnancy, protocol violation, personal reasons, lost to follow-up, or other reasons. In addition, patients could have voluntarily withdrawn from the study at any time. All withdrawals were to be noted in the CRF.

Concomitant medications/therapy: Patients were to take acute headache medications as prescribed and record this use on their daily diary. Routine non-headache medications were to be maintained on a stable dose and regimen for at least 1 month prior to the week -4 visit. Any concurrent chronic therapies were to be maintained at a stable dose and dose regimen during the study.

In Allergan's Medication List Reference Guide for Investigators, (Allergan reference linked from section 9.4.7.2 to Appendix 16.1.13 in the study report for study 191622-079) headache prophylaxis medication use was characterized by daily, ongoing scheduled use of a medication. Acute medication use was characterized by taking a medication when needed. Intermittent use of muscle relaxants, or intermittent use of combination analgesics, NSAIDs and opioid medications was considered acute use and was not prohibited. If, however, these medications were taken on an ongoing, daily schedule, their use was considered prohibited headache prophylaxis.

Since some medications used for headache prevention may overlap with medications used for acute headache treatment, *Investigators were instructed to reinforce information that prophylactic medications were not to be taken even for other medical conditions.*

The drug classes comprising this list of prohibited headache prophylaxis medications are included in Table 20: BLA 103000/5215 Prohibited Headache Prophylaxis Medications. For details please see sponsors submission, Appendix 16.1.13 Medication List Reference Guide.

Table 20: BLA 103000/5215 Prohibited Headache Prophylaxis Medications

Anticonvulsants	Combination pain medication, e.g., combinations of two or three medications which may include medications from the analgesic, non-steroidal anti-inflammatory, opioid, caffeine, and/or barbiturate drug classes

Antidepressants of various types including monamine oxidase inhibitors, serotonin selective reuptake inhibitors, tricyclic antidepressants and an "other classification	Dietary supplements including those which are vitamin, or vitamin-like, herbs, minerals, hormonal, or combinations
Antihistamine and Serotonin Antagonists	Ergot alkaloids
Antihypertensives	Muscle relaxants
Antipsychotics	NSAIDS
Beta-blockers	Opioids
Calcium channel blockers	

Rationale for Exclusion of patients on headache prophylaxis treatment
Allergan stated that the evaluation of concurrent headache prophylaxis at baseline was considered an important confounding variable based on results of the supportive chronic daily headache study 191622-038, which demonstrated that the frequency of headache-free days in patients without concurrent headache prophylaxis was significantly increased following BOTOX treatment compared with placebo (headache-free days was the a priori primary variable for this study, published data Allergan reference: Dodick et al, 2005). Therefore, patients who were using concurrent headache prophylaxis were excluded from the phase 3 studies to avoid confounding the efficacy assessments.

Additionally, Allergan referred to guidelines for chronic migraine prophylaxis trials recommend that monotherapy, rather than adjunctive (add-on) prophylaxis therapy, be evaluated (Allergan reference: Silberstein et al, 2008).

Reviewer comment
The criteria described above may have excluded patients with co-morbid illnesses with chronic migraine since they were on therapy also used as prophylactic headache treatment which was listed as prohibited study medications. The exclusion of such subgroups of patients may have to be reflected in the Prescribing Information as limitations for use, if these populations were known or have been shown to be impacted by the existing disease co-morbidity with chronic migraine or of drug-drug interactions with BOTOX. Since this issue has potential impact in labeling further discussion with Allergan is recommended. Please see additional comments in section 6.1.2 of this review.

General Discussion of Endpoints used for Efficacy Measurements
Electronic Diary was used by patients for recording all the headache characteristics and use of acute headache medications. In addition it was also used to classify patients with regard to medication overuse (yes/no). Each patient was required to enter data daily into an electronic diary. Patients were asked to make their daily call within a pre-specified window of time towards the end of each day and were allowed to enter data

for up to three consecutive calendar days preceding the call-in date; however they were only able to report data that was subsequent to their most recent call.

Headache Episode: defined as patient reported headache pain with a start and stop time that indicates that the pain lasted at least 4 continuous hours per patient diary.

Headache Day: defined as a day (00:00 to 23:59) with 4 or more continuous hours of headache per patient diary.

Migraine Day: defined as a day (00:00 to 23:59) with 4 or more continuous hours of migraine headache (ICHD-II criteria 1.1 Migraine without aura or 1.2 Migraine with aura) per patient diary.

Probable Migraine Day: defined as a day (00:00 to 23:59) with 4 or more continuous hours of probable migraine headache (ICHD-II criteria 1.6 Probable migraine) per patient diary.

Acute Headache Pain Medication Intakes: defined as a time at which a patient reports taking acute headache pain medication, regardless of the dose or number of types of medication taken at the same time. It is essentially the number of times a patient seeks such medication. There can be multiple intakes within a given day. "Acute" headache medications are those reported in the patient diary as being taken for headache. Acute headache "pain" medications are defined as including (1) ergotamines, (2) triptans, (3) simple analgesics, (4) opioids and (5) combination analgesics.

Migraine Episode: defined as patient reported headache pain with a start and stop time that indicates that the pain lasted at least 4 continuous hours and meets ICHD-II 1.1 Migraine without aura or 1.2 Migraine with aura criteria per patient diary.

Probable Migraine Episode: defined as patient reported headache pain with a start and stop time that indicates that the pain lasted at least 4 continuous hours and meets ICHD-II 1.6 Probable Migraine criteria per patient diary.

This table (adapted from module 2.7.3 ISE) show the differences in definitions of terms used in the chronic migraine phase 3 and phase 2 programs.

Term	Definition for Phase 3 Chronic Migraine Studies	Definition for Phase 2 Chronic Migraine Studies
acute headache pain medication day	a day where acute headache pain medication was taken during any period of time in the 24-hour period from midnight (12:00 AM) at the start of the day to the end of the day (11:59 PM)	a day where acute headache pain medication was taken during any period of time in the 24-hour period from midnight (12:00 AM) at the start of the day to the end of the day (11:59 PM)
acute headache pain medication intake/use	a patient-reported intake of medication(s) to treat headache pain per the patient diary	a patient-reported intake of any acute medication(s) to treat headache per the patient diary
overuse of acute headache pain medications	intake of medication at least twice per week in any week with at least 5 diary days and at least 10-15 days per 28-day period (varying with medication category)	Not applicable
BOTOX®/BOTOX® group	patients who received BOTOX® in both the double-blind and open-label phases of the phase 3 studies	Not applicable
chronic daily headache	headache on ≥ 15 days per month, headache duration of ≥ 4 hours, and at least 1 of the following 4 underlying causes: chronic migraine (previously referred to as "transformed migraine"), chronic tension-type headache, new daily persistent headache, and hemicrania continua, as defined by Silberstein and Lipton, 1996	
chronic migraine	migraine diagnosis and headache on ≥ 15 days per month	
episodic migraine	migraine diagnosis and headache on < 15 days per month	
headache day	a day (time from 00:00 to 23:59) when a patient reported 4 or more continuous hours of headache in the electronic diary	a day (from time 00:00 to 23:59) when a patient reported headache for any period of time in the electronic diary
headache episode	patient-reported headache pain with a start and/or stop time recorded in the electronic diary indicating that the pain lasted at least 4 continuous hours. All contiguously adjacent and/or overlapping headaches were merged into one headache episode.	patient-reported headache pain with a start and/or stop time recorded in the electronic diary indicating pain of any duration. All contiguously adjacent and/or overlapping headaches were merged into one headache episode.

Term	Definition for Phase 3 Chronic Migraine Studies	Definition for Phase 2 Chronic Migraine Studies
fixed-site, fixed-dose injection paradigm	The number of injection sites and minimum dose injected is fixed for each muscle area.	
follow-the-pain injection paradigm	Optional additional maximum dosing in the occipitalis, temporalis and/or trapezius muscles that could have been given at the discretion of the injector. Flexibility was permitted for dosing in these muscle groups to reflect the individual needs of each patient with respect to the severity and location of their headache pain.	Optional additional maximum dosing in the frontal/glabellar, temporalis, massetar, semisplinalis, splenius capitis and/or trapezius muscles that could have been given at the discretion of the injector. Flexibility was permitted for dosing in these muscle groups to reflect the individual needs of each patient with respect to the severity and location of their headache pain.
migraine day	a day (from time 00:00 to 23:59) when a patient reported 4 or more continuous hours of migraine headache (ICHD-II criteria 1.1 or 1.2)	a day (from time 00:00 to 23:59) when a patient reported migraine headache (ICHD-II criteria 1.1 or 1.2) of any duration
migraine/probable migraine day	a day (from time 00:00 to 23:59) when a patient reported 4 or more continuous hours of migraine headache (ICHD-II criteria 1.1 or 1.2) or probable migraine headache (ICHD-II criteria 1.6)	a day (from time 00:00 to 23:59) when a patient reported migraine headache (ICHD-II criteria 1.1 or 1.2) or probable migraine headache (ICHD-II criteria 1.6) of any duration
migraine/probable migraine episode	patient-reported headache pain with a start and stop time that indicated that the pain lasted at least 4 continuous hours and met ICHD-II criteria 1.1 Migraine without aura, 1.2 Migraine with aura, or 1.6 Probable Migraine per patient diary	patient-reported headache pain with a start and stop time that indicated pain of any duration and met ICHD-II criteria 1.1 Migraine without aura, 1.2 Migraine with aura, or 1.6 Probable Migraine per patient diary
moderate/severe headache day	a day (time from 00:00 to 23:59) when a patient reported 4 or more continuous hours of headache and reported a maximum severity of moderate or severe for at least one headache episode that occurred on that day.	Not applicable

Term	Definition for Phase 3 Chronic Migraine Studies	Definition for Phase 2 Chronic Migraine Studies
Phase 2 subgroup	Not applicable	subgroup of patients from the phase 2 chronic migraine studies who met key phase 3 study inclusion/exclusion criteria
Placebo/BOTOX® group	patients who received placebo in the double-blind phase and BOTOX® in the open-label phase of the phase 3 studies	Not applicable
prestudy headache prophylactic medications	any medication prescribed for headache prophylaxis or any medication listed in the headache prophylaxis medication guide taken by the patient prior to the 28 days ending at week -4	Not applicable

PROTOCOL 191622-079 EFFICACY MEASUREMENTS and ANALYSIS PLAN

Primary Efficacy Endpoint

In study **191622-079**, the primary efficacy variable pre-specified was the *frequency of headache episodes* per 28-day period with the primary endpoint being the 28-day period ending with week 24 following 2 treatment cycles.

Allergan chose to identify the primary endpoint as headache episodes in study 191622-079 against FDA advice. Please see section 2.5 of this review summarizing end of phase 2 meeting discussion held December 2004.

Secondary Efficacy Endpoint

There were no prior agreements on analysis plans for secondary endpoints that were pre-specified for study protocol 191622-079. Several patient-reported outcomes and secondary endpoints were evaluated. Statistical methods to control the type I error rate for the secondary endpoints were not pre-specified. Allergan stated that *post hoc* conservative Bonferroni multiple comparison adjustment was applied to compare p-values to a critical level of 0.01, which adjusted the type I error rate of 0.05 for all 5 variables that were prespecified as primary or secondary in study 191622-080.

PROTOCOL 191622-080 EFFICACY MEASUREMENTS and ANALYSIS PLAN

Primary Efficacy Endpoint

For study protocol 191622-080, following an amendment to the statistical analysis plan on 05 August 2008, about 2-weeks prior to the primary database lock and treatment unblinding (20 August, 2008), *the initial pre-specified primary endpoint was changed from frequency of headache episodes to change in frequency of headache days, and multiple secondary variables were identified.* The change was primarily based on results from study 191622-079 which did not demonstrate statistical significance for the prespecified primary endpoint.

There were 2 amendments to the original 191622-080 protocol. The first amendment incorporated minor administrative changes, and the second amendment incorporated changes to the statistical analyses. The original protocol was approved on 16 September 2005 and Amendment 02 was approved on 05 August 2008. The amendment included changes to the primary and secondary endpoints, as well as removal of investigator center from ANCOVA models since the majority of investigator centers enrolled a small number of patients.

Secondary Efficacy Endpoint(s)

The following secondary efficacy variables were identified

1. Frequency of migraine/probable migraine days
2. Frequency of moderate/severe headache days
3. Total cumulative hours of headache occurring on headache days
4. Proportion of patients with severe headache impact test (HIT-6) category scores
5. Frequency of headache episodes

To control the type 1 error rate for multiple secondary endpoints, a fixed-sequence gate keeping approach was used for the 5 ranked secondary variables at the week 24 primary visit. If the p-value of a secondary endpoint was not ≤ 0.05, the tests of any lower-ranked secondary endpoints were not considered statistically significant, regardless of p-value.

6 Review of Efficacy

Efficacy Summary

Table 21 provides an overview of the specific efficacy end-point that was measured in each of the primary efficacy studies, and Table 22 is the summary table of efficacy results in the chronic migraine phase 3 studies.

Table 21: BLA 103000/5215 Chronic Migraine Key Primary Efficacy Endpoints

Study	Primary	
	Headache Days	Headache Episodes
191622-079	No [a]	Yes
191622-080	Yes	No [a]
191622-038	Yes [b]	No [a]
191622-039	Yes [b]	No [a]

Yes- means measured; No- means not measured
[a] Measured secondary variable
[b] HA-free days was the pre-specified endpoint. HA days is the complement of HA-free days.

Table 22: BLA 103000/5215 SUMMARY TABLE Chronic Migraine PHASE 3 STUDIES (191622-079 & 191622-080) Primary and Secondary Efficacy Measurements at Primary timepoint (24 Weeks) LSMean Change from Baseline

Efficacy variable (per 28 days)	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=341)	PLACEBO (N=338)	p-value
Frequency of HA Days[A]	-7.8	-6.4	0.006	-9.2	-6.9	<0.001
Frequency of HA Episodes[B]	-5.4	-5.0	0.344	-5.6	-4.6	0.003
Frequency of M/PM HA days[C]	-7.6	-6.0	0.002	-8.8	-6.5	<0.001
Frequency of moderate/severe HA days[C]	-7.2	-5.8	0.004	-8.4	-6.0	<0.001
Frequency of M/PM HA Episodes	-5.0	-4.5	0.206	-5.1	-4.2	0.003
Total cumulative hours of headache on HA days[C]	-106.70	-70.40	0.003	-134.15	-94.54	<0.001
Proportion of patients with 50% reduction in HA days	43.5%	36.0%	0.082	50.5%	34.4%	<0.001
Proportion of patients with 50% reduction in HA episodes	46.9%	47.5%	0.905	50.2%	39.1%	0.008

Frequency of acute HA pain medication intake	-10.1	-9.8	0.795	-9.7	-8.1	0.132

Source references from this review: Table 28 - Table 34
[A] Primary End-point 191622-080
[B] Primary End-point 191622-079
[C] Pre-specified Secondary Endpoint 191622-080

The focus of the clinical efficacy evaluations rested in the data from two 24-week phase 3, double-blind, randomized, placebo-controlled studies of BOTOX (191622-079 and 191622-080). These studies were completed in the United States and Europe involving 1384 patients with chronic migraine, 688 of whom were treated with BOTOX at doses of 155 U to 195 U (2-treatment cycles of BOTOX/PLACEBO during the double-blind phase).

The efficacy data was also reviewed by the FDA Statistician, Dr. Xiang Ling. Dr. Ling re-analyzed the efficacy data. These re-analyses, according to Dr. Ling, included protocol specified statistical analysis plans and it was found that the statistical findings for the primary efficacy endpoints were consistent with that of Allergan's reported efficacy findings. Dr. Ling further noted that in each study, although a few patients dropped out from the study before the protocol defined endpoint week 24, the missing data had no impact on the efficacy conclusions of the studies.

The mean time since onset of frequent migraine was 18 years (approximately 40% of patients had > 20 years since onset), and the mean age of onset of frequent migraine was 22.4 years. The mean number of headache days for the overall study population at baseline was 19.8 days, composed predominantly of migraine/probable migraine headache days (mean 18.9 days). The majority of patients (approximately 65.0%) had received 1 or more headache preventative treatments prior to enrolling into this study.

Overall, patients were 18 to 65 years of age (mean, 41.3 years), 58.0% (803/1384) were ≥ 40 years of age, and 90.1% (1247/1384) were Caucasian. As expected in this patient population, the majority of patients were female (86.4% [1196/1384]).

Patients who were on other prophylactic migraine therapy were excluded from the study. The selected patients were stratified at baseline based on acute headache pain medication use (yes/no). A total of 88.2% (607/688) of patients treated with BOTOX and 90.4% (629/696) of patients treated with placebo completed the double-blind phase. 10.7% (148/1384) of all patients in the phase 3 studies discontinued the study prior to the open-label phase. 1.3% (9/688) of patients treated with BOTOX and 0.1% (5/696) of patient's treated with placebo discontinued the double-blind phase due to lack of efficacy. At baseline, in both studies patients suffered frequent, long, painfully intense headache episodes that lasted over several days.

For the primary endpoint *headache episodes* (Table 28), no statistically significant between-group differences were observed in the frequency of headache episodes at any timepoint during the double-blind phase of study 191622-079. In study 191622-080 (secondary endpoint *headache episodes*), there was statistically significant mean between-group difference favoring BOTOX (-5.6 ± 5.12) over placebo (-4.6 ± 4.84; p = 0.003) at the primary timepoint. Patients treated with BOTOX reported an average of 11-12 headache episodes at baseline, with a mean reduction of 6 headache episodes at week 24 compared to a mean reduction of 5 episodes in the placebo group.

For the primary endpoint *headache days* (Table 29) there was statistically significant mean between-group difference favoring BOTOX (-9.2 ± 6.54) over placebo (-6.9 ± 6.67; p < 0.001) at the primary timepoint in Study 191622-080. In study 191622-079 BOTOX treated group had statistically significant reduction in frequency of headache days (-7.8 ± 6.57) than patients treated with placebo (-6.4 ± 6.69, p = 0.006) at most timepoints during the double-blind phase of the study except during week 16. BOTOX treated patients reported approximately 19-20 headache days at baseline, with a mean reduction of 8-9 headache days at week 24 compared to 6-7 days reduction if given placebo injections.

There were no prior agreements on analysis plans for secondary endpoints that were pre-specified for study protocol 191622-079 except for the key secondary endpoint change in frequency of headache days that had an analysis plan similar to the primary variable. Study protocol 191622-080 had five secondary variables with prespecified analysis plans.

As summarized in section 6.1.5 of this review multiple secondary endpoint measures were evaluated. The prespecified secondary endpoints in study 191622-080 showed statistically significant between-group differences favoring BOTOX over placebo. The quality of life or disability measures have not been validated by FDA and were not prespecified for testing for statistical significance after adjusting for multiplicity. Treatment with BOTOX resulted in significant reductions in the frequency of moderate/severe headaches days and significantly fewer total cumulative hours of headache occurring on headache days compared to those treated with placebo in study 191622-080. Similarly nominal p values were under 0.05 for both variables in study 191622-079 but there was no adjustment for multiple comparisons. In study 191622-080 there was a statistically significant mean reduction of 40 hours of headache experienced. That difference represents a full work week, which is probably clinically meaningful to the migraineurs.

There may be a possibility that regardless of blinding techniques both the subject and observer may have been unblinded to study treatments due to the reduction of facial lines and any muscle weakness associated with BOTOX treatment. One would expect the placebo response to be lower than the active treatment arm in that case. However, treatments were administered once in 3-months and efficacy outcome measures were

reported by the study subjects through electronic diary reporting during the study period. Additionally, episodic migraine prophylaxis treatments are generally shown to have up to 50% reduction in headache episodes or days in at least 50% of the patients. Recent guidelines issued by the International Headache Society suggest that "in [the] chronic migraine population, a > 30% responder rate can be clinically meaningful" (Allergan reference: Silberstein et al, 2008). At the primary timepoint in study 191622-079, the 50% responder rates for BOTOX compared to placebo group for headache episodes was 46.9% vs. 47.5%, and headache days was 43.5% vs. 36%. And in study 191622-080, the 50% responder rates for BOTOX compared to placebo group for headache episodes was 50.2% vs. 39.1%, and headache days was 50.5% vs. 34.4%.

Further, as the efficacy outcome measures suggested, the two phase 3 trials were associated with high placebo response rates. 'Placebo analgesia' refers to reduction or abolition of pain following a therapeutic intervention that is not believed to have an independent exogenous effect on pain [6]. Allergan provided the following rationale that placebo response rates observed were significantly higher in parallel group studies compared with crossover trials (Allergan reference: Macedo et al, 2008) and that studies of prophylactic treatment of migraine demonstrated a higher variability in the rate of the placebo response than acute migraine treatment studies (Allergan reference: Macedo et al, 2008) because of the different primary endpoints used as well as the inherent variability in response measured over a period of months compared with one measured over a period of hours (Allergan reference: Diener et al, 2008). Allergan stated that since the perception of pain was a highly subjective experience influenced by cognitive factors such as expectation, attention, anxiety, and previous experiences placebo analgesia was one of the most striking examples of the cognitive modulation of pain perception (Allergan reference: Diener et al, 2008). Even though almost all patients in both treatment groups used acute headache pain medications at baseline, and the majority of patients were overusing their acute pain medications, it is possible that concomitant use of acute headache pain medications could have further contributed to the high placebo response observed. However during the study there was no increase from baseline for acute headache pain medication use observed. I think the high placebo response may have been observed because of a combination of above factors including the use of parenteral therapy as in these phase 3 studies where there were a high number of injections in both groups and probably because of patient selection whereby subjects qualified for study entry only at the severe clinical state of migraine. Possibly patients may have begun to show improvement on their own regressing to the mean.

There were no statistically significant between-group differences in acute headache pain medication intake at any timepoint during the double-blind phase of the studies except during weeks 4, 8, and 20 during the double blind phase of study 191622-080.

[6] Schwedt TJ, Hentz JG, Dodick DW. Factors associated with the prophylactic effect of placebo injections in subjects enrolled in a study of botulinum toxin for migraine. *Cephalalgia*. 2007 Jun;27(6):528-34.

Please see further discussion in section 6.1.6 of this review. Similar observations were noted during evaluation of topiramate for prophylaxis of chronic migraine in 59 subjects where there was no significant reduction in the mean number of days of acute medication intake when compared with the effect of placebo during trials[7].

As discussed in section 6.1.8 of this review although the current dosing regimen resulted in two positive trials demonstrating clinical efficacy, a dose-response relationship was not evaluated. However, that said, several negative BOTOX trials had already evaluated different treatment paradigms involving other muscle groups and doses. This is a substantial limitation to the application which demonstrated efficacy within a strictly regimented treatment paradigm and in a select group of migraineurs. I believe that if the BOTOX chronic migraine injections are not adhered to as demonstrated in studies 191622-079 and 191622-080, this may possibly result in loss of efficacy. As I discussed previously in section 5.3.4 evidence of efficacy was evaluated including up to BOTOX 195 U dose. However, there was no standardized approach whereby a determination could be made about which patients required >155 U. The decision on optional additional units to inject were determined by patient-reported usual location of predominant pain, severity of muscle tenderness by muscle palpation prior to injection, and using the clinicians best judgment. There were no objective criteria to identify candidates for an additional dose, and more importantly the study was not designed to determine the clinical benefit of treatment with a dose higher than 155 U. Post hoc subgroup analysis was performed as shown in section 6.1.8 (Table 42 and Table 43) of this review to verify that efficacy was preserved in the group that received fixed doses of 155 U.

Allergan's application for prophylaxis of headache in adults with chronic migraine included additional supportive efficacy data. A subgroup of patients were identified from the supportive chronic daily headache studies (191622-038 and 191622-039) who met key phase 3 study criteria (referred to as the 'chronic migraine subgroup') that most closely aligned with the patient population and dose/treatment paradigm in the phase 3 studies. However, this supportive 'chronic migraine subgroup' efficacy data should not be included for evaluation of overall supportive efficacy. The chronic daily headache studies were different in study design from the phase 3 studies and the target population defined a broader population. Additionally, patients in these supportive studies were not stratified by acute medication overuse and prohibited prophylactic migraine therapy users were not excluded as the phase 3 evaluation.

Even though in study 191622-080 the study statistical analysis plan and primary endpoint was changed 2-weeks prior to data lock and the primary endpoint was different from study 191622-079, essentially both studies were identical in study design. There

[7] Diener HC, et al; TOPMAT-MIG-201(TOP-CHROME) Study Group. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2007 Jul;27(7):814-23. Epub 2007 Apr 18

were highly statistically significant primary and secondary efficacy outcomes after correction for multiplicity across multiple headache symptom measures with independently substantive results across study subsets in study 191622-080. Statistically significant reduction in secondary efficacy measure headache days was observed in study 191622-079, and there were results favoring BOTOX group in other secondary efficacy outcomes where nominal p values were under 0.5 although these measures were not pre-specified with statistical methods to control for the type I error. Allergan's application included clinical studies for evaluation of efficacy from adequately designed and well-controlled studies of sufficient study duration. The data provide a reasonable assessment of benefit supporting effectiveness for the proposed indication with reference to 21 CFR 601.25 (d)(2) and 21 CFR 314.126.

Table 23: BLA 103000/5215 SUMMARY TABLE Chronic Migraine Supportive Phase 2 Studies - PHASE 2 SUBGROUP (191622-038 & 191622-039) Primary and Secondary Efficacy Measurements at Primary timepoint (24 Weeks) Mean Change from Baseline

Efficacy variable (per 28 days)	191622-038 PHASE 2 SUBGROUP			191622-039 PHASE 2 SUBGROUP			Pooled 191622-038+191622-039		
	BOTOX N=76	PLACEBO N=78	p-value	BOTOX N=105	PLACEBO N=63	p-value	BOTOX N=181	PLACEBO N=141	p-value
Frequency of HA Days	-9.9	-7.7	0.026	-9.7	-8.1	0.138	-9.8	-7.9	0.008
Frequency of HA Episodes	-5.0	-3.2	0.012	-5.6	-6.4	0.538	-5.4	-4.6	0.090
Frequency of M/PM HA days	-9.1	-7.3	0.095	-8.9	-7.4	0.189	-8.9	-7.3	0.027
Frequency of M/PM HA Episodes	-4.4	-2.7	0.036	-5.1	-5.4	0.858	-4.8	-3.9	0.062
Total cumulative hours of headache on HA days	-134.08	-142.29	0.637	-123.13	-102.48	0.206	-127.73	-124.50	0.294
Proportion of patients with 50% reduction in HA days	48%	23.1%	0.063	50.9%	48.4%	0.821	50%	36.8%	0.129
Proportion of patients with 50% reduction in HA episodes	56%	38.5%	0.210	52.8%	61.3%	0.451	53.8%	50.9%	0.733
Frequency of acute HA pain medication intake	-14.9	-11.0	0.152	-12.1	-10.4	0.482	-13.2	-10.7	0.178

Ref: pre-BLA Meeting package BB IND 7480/Serial No. 118
HA=Headache; HIT-6=Headache Impact Test; M/PM=migraine/probable migraine; NA=not collected and therefore not applicable; SD=standard deviation

6.1 Indication

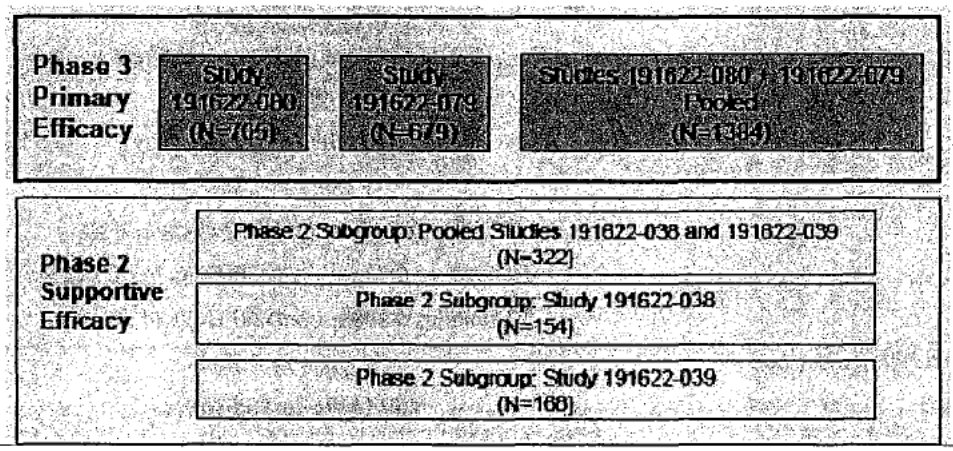
Target Indication sought is - Prophylaxis of headaches in adults with chronic migraine.

6.1.1 Methods

As discussed in Table 3 and Section 5.3, Allergan's clinical development program to support the approval of BOTOX for "prophylaxis of headaches in adults with chronic migraine" included two phase 3 studies (191622-079 and 191622-080) and data from a subgroup of patients (Figure 6) from the two chronic daily headache supportive studies (191622-038 and 191622-039) who met key phase 3 study criteria (discussed below). Allergan identified a subgroup of patients from the supportive chronic daily headache studies who met key phase 3 study criteria (*referred to as the 'chronic migraine subgroup'*) that most closely aligned with the patient population and dose/treatment paradigm in the phase 3 studies which provided the supportive data for Allergan's application for prophylaxis of chronic migraine.

Study results from 191622-038 and 191622-039 were discussed in sections 5.3.2 and 5.3.3 of this review. A summary of supportive data from the subgroup of patients referred to as the 'chronic migraine subgroup' who met key phase 3 study criteria (191622-038 and 191622-039) is shown in Table 23.

Figure 6: BLA 103000/5215 BOTOX Chronic Migraine Efficacy Data Sources



Ref: Module 2.7.3 Summary Clinical Efficacy, Sponsor's Figure 2.7.3.1-1

The following excerpt (italicized) is from the draft label (submitted April 2010) that incorporated changes into the currently approved BOTOX label. The sections with the major changes were: indications and usage, dosage and administration, adverse reactions, (b) (4) and use in specific populations.

(b) (4)

(b) (4)

6.1.2 Demographics

Phase 3 Studies

There were no statistically significant differences between the treatment groups with respect to their baseline demographic characteristics, Table 25. Overall, patients were 18 to 65 years of age (mean, 41.3 years), 58.0% (803/1384) were ≥ 40 years of age, and 90.1% (1247/1384) were Caucasian with the majority of patients being female (86.4% [1196/1384]). It appears efficacy was not evaluated in subgroup of patients who may have had comorbid illnesses with migraine disorder meeting chronic migraine definition requiring patients to be concomitantly treated with anticonvulsants, antidepressants or antihypertensives for adjunct treatment. Please see additional comments in section 5.3.4 under Concomitant medications/therapy of this review.

Chronic migraine SUBGROUP

Baseline demographic characteristics for the chronic migraine subgroup were similar to the phase 3 studies, Table 25. The ages ranged from 18 to 65 years (mean, 43.4 years) and the majority of patients were female (87.0%; 280/322) and Caucasian (89.8%; 289/322). (Allergan reference Module 5.3.5.3, ISE Table 1-5).

Table 25: BLA 103000/5215 Demographics and Baseline Characteristics Phase 3 Studies 191622-079, 191622-080, and Chronic Migraine Subgroup 191622-038, and 191622-039

DEMOGRAPHIC CHARACTERISTICS	Study 191622-079		Study 191622-080		Study 191622-038		Study 191622-039	
	BOTOX (N=341)	PLACEBO (N=338)	BOTOX (N=347)	PLACEBO (N=358)	BOTOX (N=76)	PLACEBO (N=78)	BOTOX (N=105)	PLACEBO (N=63)
Age (years), Mean ± SD	41.2±10.49	42.1±10.46	41.0±10.39	40.9±10.82	42.6±10.53	43.6±11.20	43.0±9.96	44.9±10.59
Age, n (%)								
<40 years	144 (42.2%)	128 (37.9%)	149 (42.9%)	160 (44.7%)	27 (35.5%)	32 (41.0%)	36 (34.3%)	15 (23.8%)
≥40 years	197 (57.8%)	210 (62.1%)	198 (57.1%)	198 (55.3%)	49 (64.5%)	46 (59.0%)	69 (65.7%)	48 (76.2%)
Gender, n (%)								
Male	37 (10.9%)	48 (14.2%)	48 (13.8%)	55 (15.4%)	4 (5.3%)	15 (19.2%)	11 (10.5%)	12 (19.0%)
Female	304 (89.1%)	290 (85.8%)	299 (86.2%)	303 (84.6%)	72 (94.7%)	63 (80.8%)	94 (89.5%)	51 (81.0%)
Race, n (%)								
Caucasian	305 (89.4%)	309 (91.4%)	312 (89.9%)	321 (89.7%)	68 (89.5%)	66 (84.6%)	94 (89.5%)	61 (96.8%)
Non-Caucasian	36 (10.6%)	29 (8.6%)	35 (10.1%)	37 (10.3%)	8 (10.5%)	12 (15.4%)	11 (10.5%)	2 (3.2%)
Baseline acute HA med use, n (%)	335 (98.2%)	327 (96.7%)	337 (97.1%)	351 (98.0%)	71 (93.4%)	72 (92.3%)	102(97.1%)	62 (98.4%)
Simple analgesics	239 (70.1%)	220 (65.1%)	231 (66.6%)	238 (66.5%)				
Ergotamines	16 (4.7%)	12 (3.6%)	10 (2.9%)	2 (0.6%)				
Triptans	221 (64.8%)	209 (61.8%)	220 (63.4%)	226 (63.1%)				
Opioids	36 (10.6%)	35 (10.4%)	21 (6.1%)	23 (6.4%)				
Combination analgesics	199 (58.4%)	211 (62.4%)	169 (48.7%)	189 (52.8%)				
Combined categories	215 (63.0%)	207 (61.2%)	187 (53.9%)	196 (54.7%)				

Baseline acute HA meds OVERUSE,n(%)	226 (66.3%)	236 (69.8%)	220 (63.4%)	224 (62.6%)	50 (65.8%)	41 (52.6%)	62 (59.0%)	35 (55.6%)
Simple analgesics	43 (12.6%)	51 (15.1%)	52 (15.0%)	36 (10.1%)				
Ergotamines	2 (0.6%)	1 (0.3%)	2 (0.6%)	1 (0.3%)				
Triptans	78(22.9%)	81 (24.0%)	83 (23.9%)	85 (23.7%)				
Opioids	7 (2.1%)	10 (3.0%)	3 (0.9%)	4 (1.1%)				
Combination analgesics	87 (25.5%)	98 (29.0%)	55 (15.9%)	69 (19.3%)				
Combined categories	165 (48.4%)	174 (51.5%)	143 (41.2%)	150 (41.9%)				
Prestudy HA prophylactic meds, n(%)	203 (59.5%)	217 (64.2%)	222 (64.0%)	237 (66.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Beta blockers	94 (27.6%)	95 (28.1%)	108 (31.1%)	123 (34.4%)				
Calcium blockers	46 (13.5%)	45 (13.3%)	56 (16.1%)	50 (14.0%)				
Anticonvulsants	149 (43.7%)	163 (48.2%)	162 (46.7%)	178 (49.7%)				
Antidepressants	120 (35.2%)	110 (32.5%)	129 (37.2%)	139 (38.8%)				
Other	79 (23.2%)	72 (21.3%)	99 (28.5%)	101 (28.2%)				

Ref: Phase 3 studies Module 5.3.5.1.3, Section 10.4 (191622-079), Section 10.3 (191622-080), Sponsor's Table 10-2, Source Tables: 14.1-8, 14.1-9, 14.1-14, and 14.1-15
Ref: Phase 2 Subgroup Module 2.7.3 Summary Clinical Efficacy, ISE Table 1-5
Note: The BOTOX group excludes subjects receiving <150U at the day-0 injection. Summary statistics are for subjects who met the phase-3 constraints (e.g. (1) headaches and headache days≥4 hours, (2) ≥4 headaches during baseline, (3)≥15 headache days during baseline, with at least half being MPM days, and (4) no headache prophylactic medication use during baseline). Baseline is the first 28 days of the qualifying period preceding placebo run-in.

BASELINE DISEASE CHARACTERISTICS

Phase 3 Studies

I concur with Allergan's findings that in study 191622-079 at baseline there were fewer headache episodes in the BOTOX treated group than in the placebo group ($p \leq 0.023$), fewer migraine/probable migraine headache episodes with BOTOX than with placebo, and more total cumulative hours of headache occurring on headache days with BOTOX than with placebo ($p \leq 0.022$). However, the mean number of headache days at baseline was similar with predominantly moderate/severe and migraine/probable migraine days. Other baseline disease characteristics were similar between study groups as shown in Table 26. The mean time to onset of frequent migraine was 20 years and the mean age of onset was 20.6 years.

In study 191622-080 there was no difference in the mean number of headache days or headache episodes at baseline with predominantly moderate/severe and migraine/probable migraine days. The baseline disease characteristics were similar between study groups as shown in Table 26. The mean time to onset of frequent migraine was 18 years and the mean age of onset was 22.4 years.

Chronic migraine SUBGROUP

Baseline disease characteristics for the chronic migraine subgroup were very similar to those observed in the phase 3 studies as shown in Table 26.

Table 26: BLA 103000/5215 Baseline Disease Characteristics Phase 3 Studies 191622-079, 191622-080, and Chronic Migraine Subgroup 191622-038, and 191622-039

DISEASE CHARACTERISTICS	Study 191622-079		Study 191622-080		Study 191622-038		Study 191622-039	
	BOTOX (N=341)	PLACEBO (N=338)	BOTOX (N=347)	PLACEBO (N=358)	BOTOX (N=76)	PLACEBO (N=78)	BOTOX (N=105)	PLACEBO (N=63)
Baseline HA Days, mean ± SD	20.0±3.73	19.8±3.71	19.9±3.63	19.7±3.65	21.1±3.78	21.1±3.97	20.9±3.80	20.7±4.08
Baseline M/PM HA Days, mean±SD	19.1±4.04	19.1±4.05	19.2±3.94	18.7±4.05	19.6±4.40	19.4±4.32	18.0±4.99	17.8±4.93
Baseline moderate/severe HA Days, mean±SD	18.1±4.22	18.3±4.23	18.1±4.03	17.7±4.26	17.8±5.32	17.9±4.89	17.5±4.73	16.6±5.28
Total cumulative hours of HA on HA days, mean±SD	295.66± 116.81[a]	274.88± 110.90	296.18± 121.04	287.20± 118.09	263.08± 135.93	290.76± 134.82	249.13± 142.57	256.39± 139.44
Baseline HA episodes, mean±SD	12.3±5.23[b]	13.4±5.71	12.0±5.27	12.7±5.29	10.9±4.54	11.0±5.44	11.7±4.93	12.4±5.08
Baseline M/PM HA episodes, mean±SD	11.5±5.06[b]	12.7±5.72	11.3±4.99	11.7±5.08	10.1±4.15	9.9±5.22	9.9±4.41	10.1±4.25
Baseline acute HA pain medication intakes, mean±SD	29.1±19.27	30.4±22.29	24.7±18.76	25.4±18.87	27.0±16.52	24.1±15.24	25.4±18.51	24.6±13.88

Ref: Module 2.7.3, Section 2.7.3.3.4, Sponsor's Table 2.7.3.3-3, Source: ISE Tables 2-1, 2-3, 2-5, 2-7, 2-9, 2-13, 2-15, 2-17, 2-20, 2-22, 2-24, 2-26, 2-28, 2-32, 2-34
HA=Headache; HIT-6=Headache Impact Test; M/PM=migraine/probable migraine; NA=not collected and therefore not applicable; SD=standard deviation
[a] $p \leq 0.022$
[b] $p \leq 0.023$

6.1.3 Subject Disposition

Table 27: BLA 103000/5215 Patient Disposition at Primary Timepoint/ Week24 Chronic Migraine Primary Efficacy Studies

Study	Number Treated	Completed			Discontinued Due to Lack of Efficacy		
		Total N (%)	BOTOX	PLACEBO	BOTOX N	PLACEBO N	TOTAL (%)
191622-079	679	591 (87.0%)	296 (341 exposed)	295 (338 exposed)	5	4	1.3%
191622-080	705	645 (91.5%)	311 (347 exposed)	334 (358 exposed)	4	1	0.7%
Phase 3 Total	1384	1236 (89.3%)	607 (688 exposed)	629 (696 exposed)			
191622-038 CM Subgroup	154	112 (72.7%)	55 (76 exposed)	57 (78 exposed)	4	7	7.1%
191622-039 CM Subgroup	168	118 (70.2%)	73 (105 exposed)	45 (63 exposed)	9	10	11.3%
CM SUBGROUP Total	322	230 (71.4%)	128 (181 exposed)	102 (141 exposed)			
Total	**1706**	**1466 (85.9%)**	**735 (869exposed)**	**731 (837 exposed)**			

Ref: Module 2.7.3, Section 2.7.3.3.3, Sponsor's Table 2.7.3.3-2, Source: ISE Table 1-1, 1-4
CM=Chronic Migraine
Note: The BOTOX subgroup excludes subjects receiving <150U at the day-0 injection. Summary statistics are for subjects who met the phase-3 constraints (e.g. (1) headaches and headache days≥4 hours, (2) ≥4 headaches during baseline, (3)≥15 headache days during baseline, with at least half being MPM days, and (4) no headache prophylactic medication use during baseline). Baseline is the first 28 days of the qualifying period preceding placebo run-in.

Phase 3 Studies

In study 191622-079, 1713 patients were screened over the week -4 to day 0 baseline. 679 patients (BOTOX=341 and placebo=338 patients) were randomized to the double-blind phase. These patients were stratified based on frequency of use of acute headache pain medications (yes/no). The reasons stated for screening failures were primarily for not meeting study selection criteria. 771 (75%) screened subjects did not meet inclusion criteria and 129 (13%) did not meet exclusion criteria.

Some of the reasons stated for study withdrawal were listed as "other", N=24. Allergan submitted response up on request when asked to conduct a search for reasons of drug ineffectiveness and for those patients identified in the submission as "other" reasons for study withdrawal. I identified a total of 9 patients (BOTOX=5, Placebo=4) with reason "discontinued due to lack of efficacy" as opposed to just 1 patient identified initially.

In study 191622-080, out of a total of 1621 patients screened over week -4 to day 0 (baseline) 705 patients were enrolled into the double-blind phase and stratified based on frequency of use of acute headache pain medications (yes/no). No other patients were identified who discontinued due to lack of efficacy. The reasons stated for screening failures were primarily for not meeting study selection criteria. 697 (76%) screened subjects did not meet inclusion criteria and 147 (16%) did not meet exclusion criteria.

In the phase 3 clinical studies, a combined total of 1384 patients were enrolled and randomized to receive study treatment: 688 patients (341 in study 191622-079 and 347 in study 191622-080) were randomized to receive BOTOX and 696 patients (338 in study 191622-079 and 358 in study 191622-080) were randomized to receive placebo in the double-blind phase (Table 27). The majority of patients (65.5% [906/1384]) were stratified to the group that was overusing acute headache pain medications at baseline (Allergan reference: Module 5.3.5.3, ISE Table 1-3). In study 191622-079, a total of 87.0% (591/679) of patients completed the double-blind phase (86.8% [296/341] BOTOX and 87.3% [295/338] placebo), while 71.1% (483/679) of all patients completed the open-label phase. In study 191622-080, a total of 91.5% (645/705) of patients completed the double-blind phase (89.6% [311/347] BOTOX and 93.3% [334/358] placebo). 74.0% (522/705) of all patients completed the open-label phase.

A total of 88.2% (607/688) of patients treated with BOTOX and 90.4% (629/696) of patients treated with placebo completed the double-blind phase. 10.7% (148/1384) of all patients in the phase 3 studies discontinued the study prior to the open-label phase. 1.3% (9/688) of patients treated with BOTOX and 0.1% (5/696) of patient's treated with placebo discontinued the double-blind phase due to lack of efficacy.

Chronic Daily Headache Studies (191622-038 and 191622-039)
In study 191622-038, a total of 355 patients were enrolled, of whom 37.2% (132/355) completed only 1 double-blind treatment cycle as per the original protocol and 39.7% (141/355) completed 3 double-blind treatment cycles. In study 191622-039, a total of 702 patients were enrolled, of whom 24.9% (175/702) patients completed only 1 double-blind treatment cycle as per the original protocol, and 47.9% (336/702) completed 3 double-blind treatment cycles.

Chronic migraine SUBGROUP (*used for supportive efficacy data*)
The chronic daily headache supportive studies 191622-038 and 191622-039, enrolled a combined total of 1057 patients (Allergan reference: Module 2.7.3 ISE, Table 2.7.3.1–2). *Of these, 322 patients (N = 181 BOTOX, N = 141 placebo) were analyzed in the pooled efficacy analyses of the subgroup of patients who met key phase 3 criteria.* A total of 70.7% (128/181) of these patients treated with BOTOX and 72.3% (102/141) of these patients treated with placebo completed the studies, including those who completed only 1 treatment cycle per the original protocol (Allergan reference: Module

2.7.3 ISE, ISE Table 1-4). 7.2% (13/181) of patients treated with BOTOX and 12.1% (17/141) patients treated with placebo discontinued the study due to lack of efficacy.

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Endpoint

- In study **191622-079**, the a priori primary efficacy variable was the *frequency of headache episodes* per 28-day period with the primary endpoint being the 28-day period ending with week 24 following 2 treatment cycles.

  The primary efficacy analysis was on the change from baseline in the frequency of headache episodes per 4 weeks and the primary visit was Week 24. *The primary analysis database for 191622-079 (i.e., week 24 data) was locked on 08 February 2008 and the treatment code unblinded on 11 February 2008.*

- In study **191622-080**, the primary efficacy variable was the *frequency of headache days* per 28-day period with the primary endpoint being the 28-day period ending with week 24 following 2 treatment cycles. *About 2-weeks prior to primary database lock and treatment unblinding (August 20, 2008) it was changed from frequency of headache episodes, which was the initial pre-specified primary endpoint. Amendments were made to the statistical analysis plan and study protocol.*

  The primary efficacy analysis was on the change from baseline in the frequency of headache days per 4 weeks and the primary visit was Week 24. Please see additional information in section 5.3.4, Efficacy and Analysis Plan.

The intent-to-treat (ITT) population (all randomized patients) was used for efficacy data analyses. In efficacy data analyses, the patients were analyzed according to the randomization assignment, regardless of actual treatment received.

Allergan Rationale for Endpoint Changes: Chronic migraine definition evolution and relevance to endpoint changes

In 2005, when the phase 3 trials were designed, Allergan stated that the largest well-controlled studies evaluating headache prophylaxis in the chronic migraine patient population were the BOTOX supportive chronic daily headache studies, 191622-038 and 191622-039 (Allergan ref: Dodick et al, 2005; Mathew et al, 2005; Silberstein et al, 2005). In the supportive chronic daily headache study 191622-038, there was no statistically significant improvements favoring BOTOX for headache-free days however statistically significant improvements in the change from baseline for the frequency of *headache episodes* were observed (Table 13). It should be noted that headache episodes was not the primary efficacy endpoint measured and the secondary endpoints measured were not adjusted for multiplicity.

Since there was not a universally accepted, primary efficacy endpoint for the evaluation of new therapies in the treatment of chronic migraine, the BOTOX supportive chronic daily headache studies were used for selection of the primary endpoint for the phase 3 program. Allergan found these models supported significant improvements from baseline for both headache episodes and headache days. Allergan discussions with various global regulatory agencies regarding their preference for the primary endpoint were mixed. The change from baseline at week 24 for the frequency of headache episodes was designated as the primary efficacy measure for both phase 3 studies and frequency of headache days was called out in the protocol and analysis plans as the most important secondary efficacy measure by virtue that all sensitivity analyses that were pre-specified for headache episodes were also pre-specified for headache days, but not for any other secondary efficacy variable.

Since the initiation of the phase 3 studies, controlled studies evaluating topiramate as headache prophylaxis in patients with chronic migraine were published in 2007. In these studies the primary endpoints were met, which were an evaluation of migraine headache days (Allergan reference: Diener et al, 2007) and migraine/migrainous headache days (Allergan reference: Silberstein et al, 2007). In addition, the IHS published guidelines for the controlled studies of headache prophylaxis treatments in patients with chronic migraine (Allergan reference: Silberstein et al, 2008) suggesting that moderate/severe headache days, migraine/probable migraine days or migraine/probable migraine episodes (in that order) may be appropriate primary efficacy measures for chronic migraine studies.

When Allergan performed the primary efficacy analysis for study 191622-079 there was no statistically significant change for the primary endpoint (frequency of headache episodes) even though there was a large mean improvement from baseline. However, highly significant improvements from baseline were observed for both headache days and migraine/probable migraine days. With all this new information, Allergan concluded that 'headache days' was likely a more sensitive endpoint for evaluating headache prophylaxis treatment in patients with chronic migraine.

Reviewer comment
The FDA previously communicated information to Allergan that *headache days* would be the preferred endpoint during their clinical development phase. Please see additional discussion comments in section 2.5 of this review. Briefly, FDA informed Allergan that the primary endpoint should be evaluation of reduction in headache days and the reduction in frequency of headache episodes would be a secondary endpoint. However, Allergan chose to evaluate headache episodes as the primary efficacy variable in initial phase 3 study 191622-079. In the later study (191622-080) the primary endpoint was changed to headache days. I concur with Allergan rationale for later choosing headache days. Migraine treatment may reduce the hours of headache, and thereby reduce the number of headache days and the headache-associated burden, resulting in a change in the frequency of headache days, but not necessarily

the frequency of headache episodes. If only headache episodes were evaluated, clinically meaningful improvements may be obscured. For these reasons, in the context of a clinical study to evaluate headache prophylaxis treatment in patients with chronic migraine, 'headache days' is a more clinically meaningful endpoint than 'headache episodes'. Both endpoints, however, are clinically relevant and are evaluated in the phase 3 studies.

Primary Endpoint - Headache Episodes (191622-079)

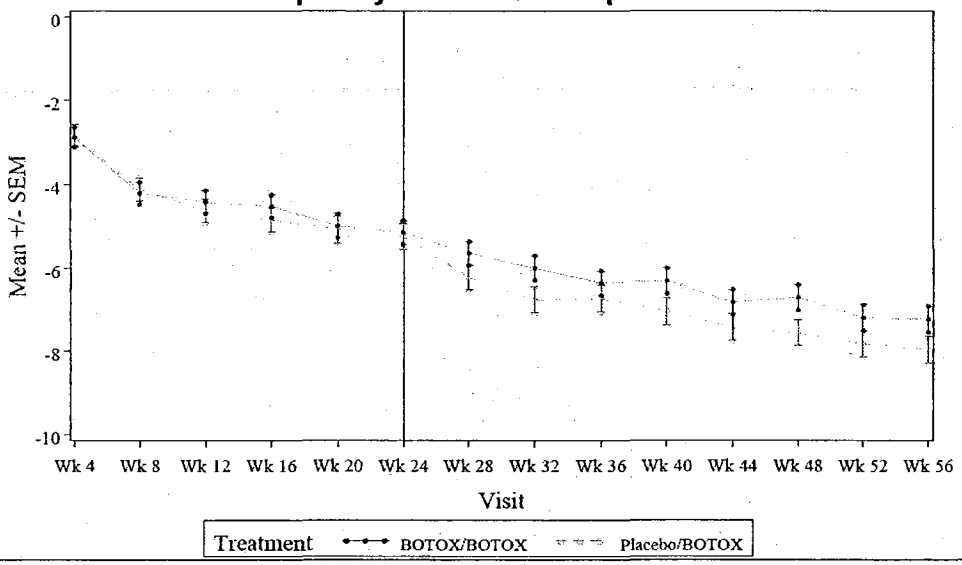
There were no statistically significant between-group differences in the frequency of headache episodes at any timepoint during the double-blind phase of the study. Allergan stated that this may have been caused by baseline imbalance when patients randomized to BOTOX in the double-blind phase had a significantly lower frequency of headache episodes (11.9 ± 5.23) than those randomized to receive placebo (12.8 ± 5.71; p = 0.023) (Table 28; Figure 7). Please see additional information section 6.1.2.

Table 28: BLA 103000/5215 Study Protocol 191622-079 and 191622-080 LSMean (SD) Change From Baseline in the Frequency of HEADACHE EPISODES per 28-Day Period (ANCOVA)

Time Period [a]	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=347)	PLACEBO (N=358)	p-value
Baseline	11.9 (5.23)	12.8 (5.71)	0.023	11.7 (5.27)	12.4 (5.29)	0.067
Week 4	-3.1 (4.35)	-2.7 (4.73)	0.203	-3.2 (4.99)	-2.4 (4.13)	0.010
Week 8	-4.5 (4.91)	-4.0 (5.15)	0.140	-4.5 (5.03)	-3.4 (4.25)	<0.001
Week 12 After 1-treatment cycle	-4.7 (5.12)	-4.5 (5.36)	0.566	-4.7 (4.96)	-3.8 (4.75)	0.009
Week 16	-4.7 (5.03)	-4.6 (5.49)	0.720	-5.2 (5.07)	-4.2 (4.78)	0.001
Week 20	-5.3 (5.23)	-4.9 (5.94)	0.343	-5.7 (5.18)	-4.3 (4.69)	<0.001
(Primary TimePoint) Week 24 After 2-treatment cycles	-5.4 (5.27)	-5.0 (5.85)	0.344	-5.6 (5.12)	-4.6 (4.84)	0.003

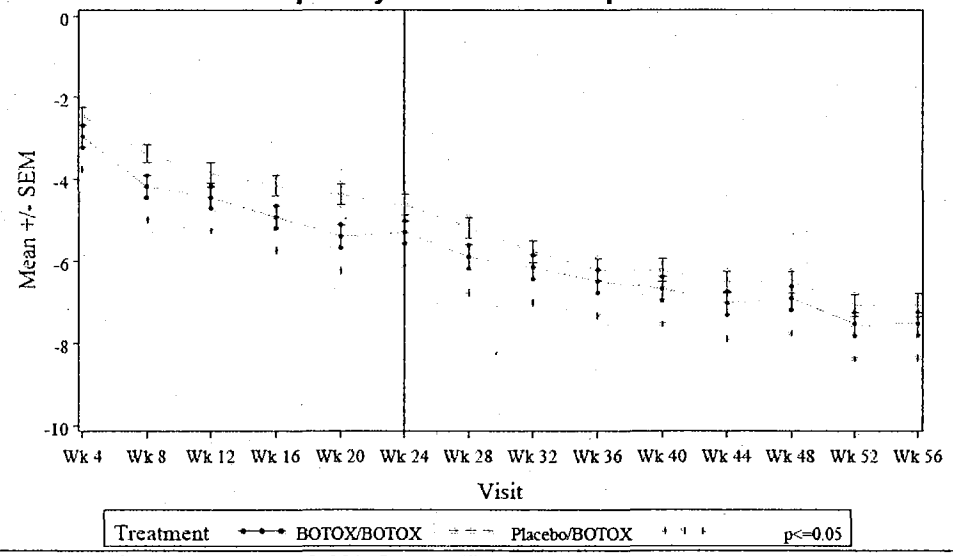
Modified format only. Module 5.3.5.1.1 Study report 191622-079 and 191622-080; Table 14.2-1
[a] After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Figure 7: BLA 103000/5215 Study 191622-079 Mean Change from Baseline in Frequency of Headache Episodes



Ref: Module 5.3.5.1.1 Study report 191622-079; Source: Figure 14.2-1.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Figure 8: BLA 103000/5215 Study 191622-080 Mean Change from Baseline in Frequency of Headache Episodes



Ref: Module 5.3.5.1.1 Study report 191622-080; Source: Figure 14.2-1.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Primary Endpoint - Headache Days (191622-080)

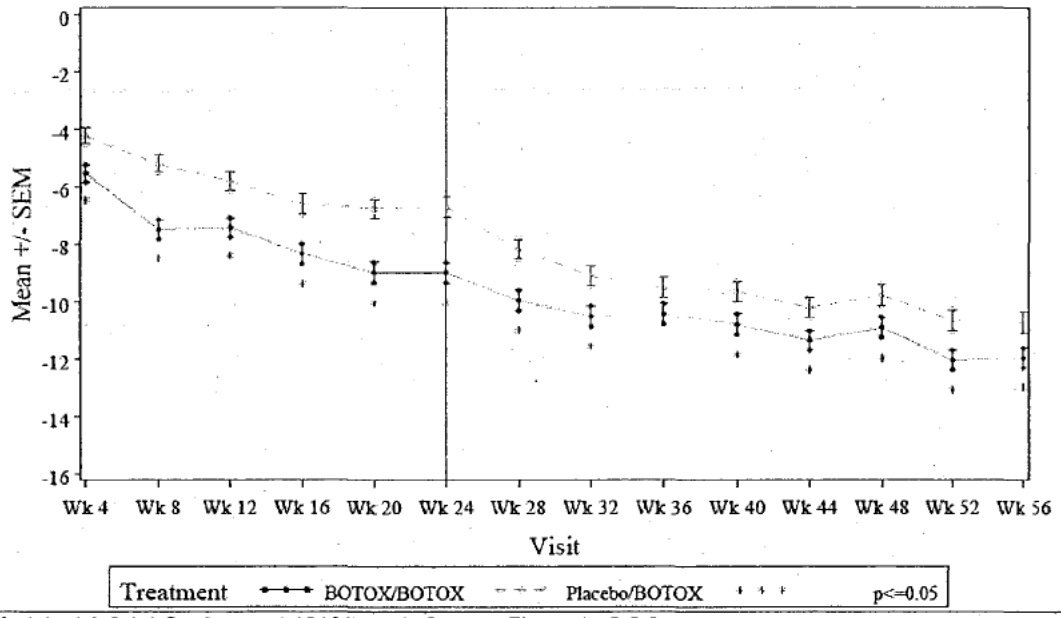
There was statistically significant mean between-group difference favoring BOTOX (-9.2 ± 6.54) over placebo (-6.9 ± 6.67; $p < 0.001$) beginning at week 4 through 24 weeks the primary timepoint (Table 29; Figure 9) during the controlled portion of the study.

Table 29: BLA 103000/5215 Study Protocol 191622-079 and 191622-080 LSMean (SD) Change From Baseline in the Frequency of HEADACHE DAYS per 28-Day Period (ANCOVA using mLOCF)

Time Period [a]	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=347)	PLACEBO (N=358)	p-value
Baseline	19.9 (3.73)	19.7 (3.71)	0.571	19.8 (3.63)	19.7 (3.65)	0.682
Week 4	-5.0 (5.26)	-4.0 (5.25)	0.012	-5.6 (5.78)	-4.3 (5.37)	0.002
Week 8	-6.8 (5.85)	-5.8 (5.56)	0.022	-7.6 (6.24)	-5.4 (5.68)	<0.001
Week 12 After 1-treatment cycle	-7.1 (6.39)	-6.2 (6.01)	0.044	-7.6 (6.14)	-6.0 (6.14)	<0.001
Week 16	-7.1 (6.39)	-6.2 (6.03)	0.080	-8.5 (6.42)	-6.8 (6.35)	<0.001
Week 20	-8.1 (6.48)	-6.6 (6.46)	0.003	-9.1 (6.64)	-6.9 (6.11)	<0.001
(Primary TimePoint) Week 24 After 2-treatment cycles	-7.8 (6.57)	-6.4 (6.69)	0.006	-9.2 (6.54)	-6.9 (6.67)	<0.001

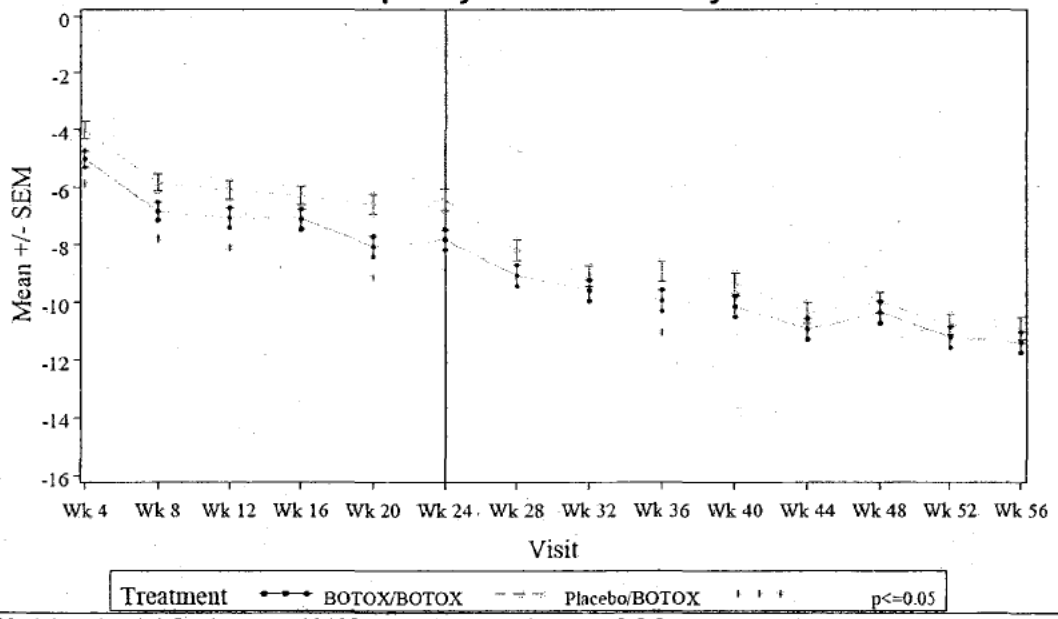
Modified format only. Module 5.3.5.1.1 Study report 191622-079 and 191622-080; Table 14.2-6
[a] After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Figure 9: BLA 103000/5215 Study 191622-080 Mean Change from Baseline in Frequency of Headache Days



Ref: Module 5.3.5.1.1 Study report 191622-080; Source: Figure 14.2-2.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Figure 10: BLA 103000/5215 Study 191622-079 Mean Change from Baseline in Frequency of Headache Days



Ref: Module 5.3.5.1.1 Study report 191622-079; Source: Figure 14.2-2.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

6.1.5 Analysis of Secondary Endpoints(s)

Study 191622-079

There were no prior agreements on analysis plans for secondary endpoints that were pre-specified for study protocol 191622-079. However several patient-reported outcomes and secondary endpoints were evaluated. Allergan stated that *post hoc* conservative Bonferroni multiple comparison adjustment was applied to compare p-values to a critical level of 0.01, which adjusted the type I error rate of 0.05 for all 5 variables that were prespecified as primary or secondary in study 191622-080. Please see additional information regarding analysis of secondary endpoints in phase 3 studies in section 5.3.4, Efficacy and Analysis Plan.

The study results for secondary endpoints are included without a priori statistical methods applied to control for multiplicity. The results should be interpreted in the context that it was evaluated post hoc without being pre-specified in the protocol statistical analysis plan and analyzed without statistical methods to control for type I error.

Headache Days

BOTOX treated group had statistically significant mean decrease from baseline in the reduction in frequency of headache days (-7.8 ± 6.57) than patients treated with placebo (-6.4 ± 6.69, p = 0.006) at primary timepoint and at most timepoints during the double-blind phase of the study except during week 16 (Table 29; Figure 10).

Frequency of migraine/Probable migraine Headache Days

The nominal p-values during the post hoc analysis were <0.05 during the time periods in the double blind phase of study 191622-079 (Table 30).

Frequency of moderate/severe Headache Days

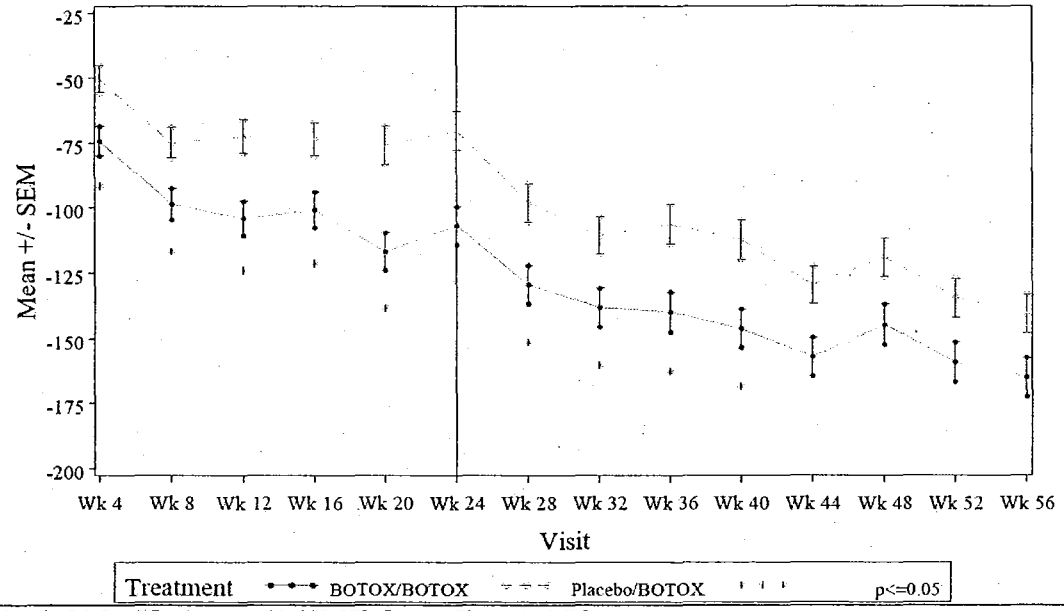
The nominal p-values during the post hoc analysis were <0.05 during the time periods in the double blind phase of study 191622-079 except week 16 (Table 31).

Total cumulative hours of headache occurring on headache days

In study 191622-079, at baseline (Table 26), the BOTOX treated group had statistically significant higher mean total cumulative hours of headache on headache days (295.66 ± 116.8) than the placebo group (274.88 ± 110.9; p = 0.022). At primary timepoint week 24 mean total cumulative hours of headache occurring on headache days for BOTOX was -106.7 ± 134.0 and Placebo group was -70.4 ± 136.8 (p = 0.003). During the

double-blind phase (2-treatment cycles) the nominal p-values during the post hoc analysis were <0.05 and the BOTOX group maintained fewer mean numbers of total cumulative hours of headache that occurred on headache days compared with the placebo group (Figure 11).

Figure 11: BLA 103000/5215 Study 191622-079 Mean Change from Baseline in Total cumulative hours of headache occurring on headache days



Ref: Module 5.3.5.1.1 Study report 191622-079; Source: Figure 14.2-7.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Study 191622-080

For study protocol 191622-080, following an amendment to the statistical analysis plan 2-weeks prior to database lock the following secondary efficacy variables analyses were prespecified: frequency of migraine/probable migraine days; frequency of moderate/severe headache days; total cumulative hours of headache occurring on headache days; proportion of patients with severe headache impact test (HIT-6) category scores; and frequency of headache episodes. To control the type 1 error rate for multiple secondary endpoints, a fixed-sequence gate keeping approach was used for the 5 ranked secondary variables at the week 24 primary visit. If the p-value of a secondary endpoint was not ≤ 0.05, the tests of any lower-ranked secondary endpoints were not considered statistically significant, regardless of p-value.

Headache Episodes
After adjusting for multiplicity, there was statistically significant mean between-group difference favoring BOTOX (-5.6 ± 5.12) over placebo (-4.6 ± 4.84; p = 0.003) at the primary timepoint and at other time periods during the double blind phase where there was reduction in the frequency of headache episodes (Table 28; Figure 8).

Frequency of migraine/Probable migraine Headache Days
There was statistically significant mean between-group difference favoring BOTOX (191622-080= -8.8 ± 6.64) over placebo (191622-080= -6.5 ± 6.71) at the primary timepoint and at other time periods during the double blind phase after adjusting for multiplicity, where there was reduction in the frequency of migraine/probable migraine headache days.

Table 30: BLA 103000/5215 Study Protocol 191622-079 and 191622-080 Secondary Endpoint Analysis; LSMean (SD) Change From Baseline in the Frequency of Migraine/Probable Migraine Days per 28-Day Period (ANCOVA)

Time Period [a]	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=347)	PLACEBO (N=358)	p-value
Baseline	19.0 (4.04)	19.0 (4.05)	0.978	19.1 (3.94)	18.7 (4.05)	0.156
Week 4	-5.1 (5.32)	-4.0 (5.40)	0.004	-5.8 (5.97)	-4.3 (5.46)	<0.001
Week 8	-6.7 (5.64)	-5.6 (5.60)	0.007	-7.4 (6.33)	-5.2 (5.73)	<0.001
Week 12 After 1-treatment cycle	-7.0 (6.24)	-5.9 (6.05)	0.021	-7.3 (6.20)	-5.6 (6.10)	<0.001
Week 16	-7.0 (6.34)	-5.9 (6.09)	0.026	-8.1 (6.61)	-6.5 (6.21)	<0.001
Week 20	-7.9 (6.50)	-6.2 (6.66)	0.001	-8.8 (6.71)	-6.6 (6.20)	<0.001
(Primary TimePoint) Week 24 After 2-treatment cycles	-7.6 (6.51)	-6.0 (6.78)	0.002	-8.8 (6.64)	-6.5 (6.71)	<0.001

Modified format only. Module 5.3.5.1.1 Study report 191622-079 and 191622-080; Table 14.2-14
[a] After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Frequency of moderate/severe Headache Days
There was statistically significant mean between-group difference favoring BOTOX (191622-080= -8.4 ± 6.37) over placebo (191622-080= -6.0 ± 6.59) after adjusting for multiplicity at the primary timepoint and at other time periods during the double blind phase where there was reduction in the frequency of moderate/severe migraine headache days (Table 31).

Table 31: BLA 103000/5215 Study Protocol 191622-079 and 191622-080 Secondary Endpoint Analysis; LSMean (SD) Change From Baseline in the Frequency of Moderate/Severe Headache Days per 28-Day Period (ANCOVA)

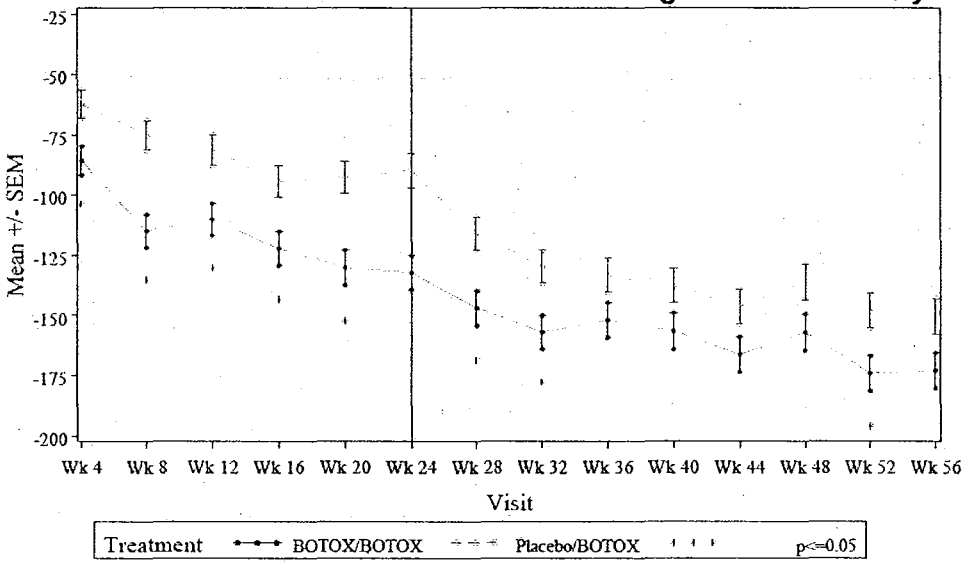
Time Period [a]	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=347)	PLACEBO (N=358)	p-value
Baseline	17.9 (4.22)	18.0 (4.23)	0.674	18.0 (4.03)	17.6 (4.26)	0.333
Week 4	-5.0 (5.36)	-3.8 (5.26)	0.005	-5.8 (5.75)	-4.2 (5.48)	<0.001
Week 8	-6.2 (5.71)	-5.3 (5.59)	0.045	-7.3 (5.88)	-5.0 (5.67)	<0.001
Week 12 After 1-treatment cycle	-6.4 (6.05)	-5.5 (5.90)	0.040	-7.1 (5.81)	-5.3 (6.07)	<0.001
Week 16	-6.5 (6.34)	-5.7 (5.92)	0.089	-7.9 (6.17)	-5.9 (6.24)	<0.001
Week 20	-7.4 (6.32)	-5.9 (6.41)	0.002	-8.4 (6.30)	-6.1 (6.22)	<0.001
(Primary TimePoint) Week 24 After 2-treatment cycles	-7.1 (6.32)	-5.6 (6.63)	0.004	-8.4 (6.37)	-6.0 (6.59)	<0.001

Modified format only. Module 5.3.5.1.1 Study report 191622-079 and 191622-080; Table 14.2-70
[a] After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Total cumulative hours of headache occurring on headache days

In study 191622-080, there were statistically significant differences in the mean number of total cumulative hours of headache that occurred on headache days between BOTOX treatment (-134.15 ± 130.2) and placebo (-94.54 ± 133.7; p<0.001) at week 24 and at other timepoints during the double-blind phase (Figure 12).

Figure 12: BLA 103000/5215 Study 191622-080 Mean Change from Baseline in Total cumulative hours of headache occurring on headache days



Ref: Module 5.3.5.1.1 Study report 191622-080; Source: Figure 14.2-7.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

6.1.6 Other Endpoints

Frequency of Acute Headache Pain Medication Intake

This was not a pre-specified endpoint for analysis in study 1916220-079 and study 191622-080 with a priori statistical methods applied to control for multiplicity. However one would expect that by using therapy for managing a chronic condition there would be a change in frequency of use of medication for managing intermittent episodes. There were no statistically significant between-group differences in the frequency of acute headache pain medication intake at the primary timepoint in study 191622-079 (Table 32; Figure 13) and in study 191622-080 (Table 32; Figure 14).

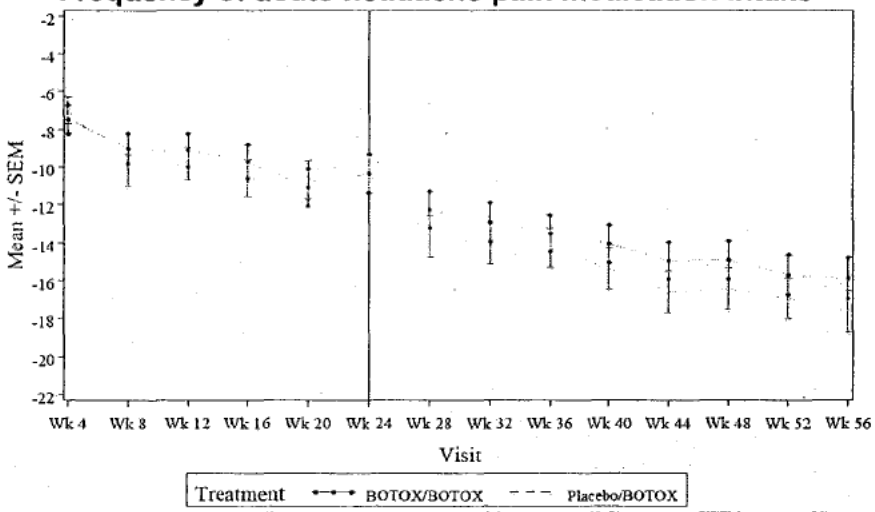
Table 32: BLA 103000/5215 Study Protocol 191622-079 and 191622-080 Secondary Endpoint Analysis; LSMean (SD) Change From Baseline in the Frequency of acute headache pain medication intake per 28-Day Period (ANCOVA)

Time Period [a]	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=347)	PLACEBO (N=358)	p-value
Baseline	25.2 (19.27)	25.7 (22.29)	0.709	21.9 (18.76)	22.8 (18.87)	0.458
Week 4	-7.5 (14.04)	-6.8 (13.27)	0.465	-7.2 (12.02)	-5.5 (11.86)	0.050

Week 8	-9.0 (14.87)	-9.8 (15.21)	0.453	-9.6 (14.15)	-6.8 (13.21)	0.003
Week 12 After 1-treatment cycle	-9.0 (16.36)	-9.4 (16.16)	0.760	-8.8 (13.60)	-7.0 (13.62)	0.063
Week 16	-9.8 (16.58)	-10.3 (17.80)	0.713	-9.5 (14.80)	-7.9 (14.03)	0.112
Week 20	-11.1 (18.09)	-10.3 (18.91)	0.514	-10.6 (15.51)	-8.6 (14.97)	0.050
(Primary TimePoint) Week 24 After 2-treatment cycles	-10.1 (18.67)	-9.8 (18.54)	0.795	-9.7 (15.53)	-8.1 (14.92)	0.132

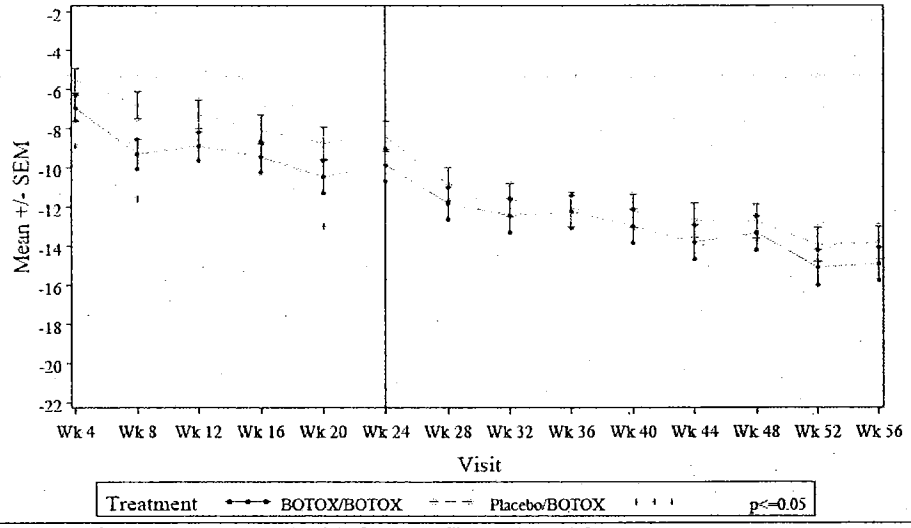
Modified format only. Module 5.3.5.1.1 Study report 191622-079 and 191622-080; Table 14.2-15
[a] After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Figure 13: BLA 103000/5215 Study 191622-079 Mean Change from Baseline in Frequency of acute headache pain medication intake



Ref: Module 5.3.5.1.1 Study report 191622-079; Source: Figure 14.2-5.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

Figure 14: BLA 103000/5215 Study 191622-080 Mean Change from Baseline in Frequency of acute headache pain medication intake



Ref: Module 5.3.5.1.1 Study report 191622-080; Source: Figure 14.2-5.2
After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

50% Responder Rates - Headache Episodes (Decreases from baseline)
It is defined as the percentage of subjects with 50% or greater reduction in headache *episodes* receiving study medication compared with the baseline period.

This was not a pre-specified endpoint for analysis in study 1916220-079 and study 191622-080 with a priori statistical methods applied to control for multiplicity. In study 191622-079, there were no statistically significant between-group differences for the 50% responder rates at the primary timepoint during the double-blind phase of the study. However, there was a high placebo response rate overall and almost 50% patients experienced 50% or greater reduction in headache episodes in both groups at the primary timepoint.

In study 191622-080, at the primary timepoint the nominal p-value = 0.008, and there was an 11% treatment difference compared to placebo. All results should be interpreted in the context that the results are from post hoc analysis without adjusting for multiplicity.

Table 33: BLA 103000/5215 Study Protocol 191622-079 and 191622-080 Responder Rate - Headache Episodes; Decrease from Baseline of 50% or More of Headaches per 28-Day Period

Time Period [a]	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=347)	PLACEBO (N=358)	p-value
Week 4	21.6%	17.2%	0.146	19.7%	17.5%	0.465
Week 8	38.5%	30.6%	0.032	37.0%	28.2%	0.018
Week 12 After 1-treatment cycle	39.9%	37.6%	0.469	42.0%	35.8%	0.114
Week 16	36.9%	39.9%	0.523	45.8%	37.1%	0.031
Week 20	41.6%	45.6%	0.402	50.9%	40.0%	0.008
(Primary TimePoint) Week 24 After 2-treatment cycles	46.9%	47.5%	0.905	50.2%	39.1%	0.008

Modified format only. Module 5.3.5.1.1 Study report 191622-079 and 191622-080; Table 14.2-17
[a] After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

50% Responder Rates - Headache Days (Decreases from baseline)
It is defined as the percentage of subjects with 50% or greater reduction in headache days receiving study medication compared with the baseline period.

This was not a pre-specified endpoint for analysis in study 1916220-079 and study 191622-080 with a priori statistical methods applied to control for multiplicity. In study 191622-079, the nominal p-value = 0.082 at the primary timepoint for the 50% responder rates as noted in Table 34. Even though the difference was not statistically significant there was a 7% treatment difference compared to placebo group at the primary timepoint.

In study 191622-080, the nominal p-value < 0.001 and at the primary timepoint there was a 16% treatment difference compared to placebo group. All results should be interpreted in the context that the results are from post hoc analysis without adjusting for multiplicity.

Table 34: BLA 103000/5215 Study Protocol 191622-079 and 191622-080 Responder Rate - Headache Days; Decrease from Baseline of 50% or More of Headache Days per 28-Day Period

Time Period [a]	191622-079			191622-080		
	BOTOX (N=341)	PLACEBO (N=338)	p-value	BOTOX (N=347)	PLACEBO (N=358)	p-value
Week 4	20.3%	16.6%	0.229	25.2%	19.0%	0.050

Week 8	34.2%	26.9%	0.052	38.6%	25.1%	<0.001
Week 12 After 1-treatment cycle	38.1%	27.6%	0.007	43.3%	27.8%	<0.001
Week 16	36.1%	31.3%	0.229	44.8%	33.2%	0.004
Week 20	44.6%	31.5%	0.002	49.8%	34.8%	<0.001
(Primary TimePoint) Week 24 After 2-treatment cycles	43.5%	36.0%	0.082	50.5%	34.4%	<0.001

Modified format only. Module 5.3.5.1.1 Study report 191622-079 and 191622-080; Table 14.2-21
[a] After week 24, all patients continuing in each group were treated with BOTOX (open-label phase).

6.1.7 Subpopulations

As noted in Dr. Ling's review section 4, subgroup analyses performed for the primary efficacy measures headache episodes and headache days by gender, race, and age showed consistency across the subgroups in the pooled phase 3 populations.

In the subgroup of patients from both phase 3 studies with a history of prophylactic headache medication use prior to study entry [they were to have discontinued use of prophylactic study med at least 1-month prior to entry] (BOTOX N = 425; Placebo N = 454) the nominal p-values <0.05 for headache episodes and headache days at the primary timepoint. However among patients with no history of prophylactic headache medication use prior to study entry (BOTOX N = 263; Placebo N = 242) no statistically significant between-group differences were observed at week 24. The results are from post hoc analysis without adjusting for multiplicity.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Allergan's proposed prescribing information for prophylaxis of headache in adults with chronic migraine (b) (4). Please see additional information in section 6.1 of this review and Table 24 regarding Allergan proposed draft language for Section 2.2 Dose and Administration section of the proposed prescribing information.

In both phase 3 studies (191622-079 and 191622-080), the minimum dose of BOTOX that patients were to receive according to the fixed site/fixed dosage treatment regimen was 155 U per treatment cycle (31 sites; each site = 0.1 mL of 5 U BOTOX or 0 U placebo) divided into 7 head/neck muscles. In addition, at the investigator's discretion, *optional additional injections* of BOTOX or placebo could be administered unilaterally or bilaterally using a *follow-the-pain* paradigm of up to 8 injection sites in up to 3 specific

head/neck muscle areas (temporalis, occipitalis, and/or trapezius) for a total additional dose of 40 U. These *optional* additional injections need not be consistent across treatment visits, with respect to dose or number of injection sites, but must still not exceed the maximum dose allowed (195U). The dose injected was fixed for a muscle injection site but the total optional dose injected could vary because of the decision criteria used by Allergan. For example, if tenderness persisted in the Occipitalis muscle, after injecting the required fixed-dose per protocol, then either 5 units in one site or 10 units at two sites could be additionally injected.

The decision on how many additional units to inject took into account the following criteria using Table 19 as a guide:

- Patient-reported usual location of predominant pain
- While palpating the muscle prior to injection, severity of the muscle tenderness
- Clinician's best judgment on the potential benefit of additional doses in the specified muscles (eg, large muscle size)

Evidence of efficacy was evaluated including up to BOTOX 195 U dose. However, there was no standardized approach as shown above whereby a determination could be made about which patients required >155U. The decision on amount of optional additional units to inject was determined by patient-reported usual location of predominant pain, severity of muscle tenderness by muscle palpation prior to injection, and using the clinician's best judgment.

Rationale for dose selection
Initial supportive chronic daily headache studies 191622-038 and 191622-039 identified a BOTOX responsive sub-population (patients with chronic migraine) among patients with chronic daily headache. The doses evaluated ranged from 75 U to 260 U. Allergan stated that there was an apparent dose-response effect observed for a few significant treatment-related adverse events particularly at 225 U. To ensure an optimal risk:benefit safety profile, a maximum dose of < 200 U was therefore selected for further evaluation in the chronic migraine phase 3 studies. And, modifications from the supportive chronic daily headache program was made to the injection paradigm to the chronic migraine phase 3 program to minimize adverse events and further standardize the injection methodology. Allergan stated that the exploratory chronic daily headache studies identified a specific patient population (majority patients with chronic migraine), a well-tolerated dose, treatment paradigm, and clinically meaningful efficacy endpoints to evaluate in the chronic migraine phase 3 trials.

Reviewer Comment
It may be possible that earlier (b) (4) chronic tension type headache studies including supportive chronic daily headache development programs may have been negative because of a failure to identify the correct treatment paradigm. Phase 3

chronic migraine studies involved fixed doses of BOTOX injected into specific muscle sites to demonstrate efficacy. In order to effectively use the product for the indication without losing efficacy such findings are highlighted by the reviewer as important limitations. The reviewer recommends emphasizing the need to Allergan for an educational and training program targeted to any provider treating this condition with BOTOX for consistency and possibly avoiding adverse events from improper use.

Justification for sought dose

Required 155 U

Table 35 and Table 36 details the number of exposures in the phase 3 studies. The mean total dose of BOTOX injected for evaluating primary efficacy at the primary timepoint during the double-blind period of the phase 3 studies ranged from 163 -165 U (Table 37). However, there were no objective criteria to identify candidates for an additional dose, and more importantly the study was not designed to determine the clinical benefit of treatment with a dose higher than 155 U.

(b) (4)

Table 35: BLA 103000/5215 Phase 3 Study 191622-079 Exposures (N) Per Dose by Treatment Cycle

Total Dose injected All Muscles	BOTOX/BOTOX					PLACEBO/BOTOX				
	Day 0	Week 12	Week 24	Week 36	Week 48	Day 0	Week 12	Week 24	Week 36	Week 48
155 U	170	153	138	136	126	166	145	123	127	116
160 U	11	13	17	15	11	18	11	14	17	18
165 U	51	38	39	35	43	44	50	55	41	27
170 U	5	9	8	5	6	8	11	11	8	7
175 U	31	30	25	25	18	42	35	28	22	25
180 U	9	4	11	4	1	6	5	9	7	4
185 U	28	17	20	22	26	22	19	21	10	9
190 U	9	14	11	14	10	8	9	12	11	12
195U	23	25	16	16	15	22	18	13	16	18
>195 U	0	1	0	0	0	0	1	0	0	0
Total Exposures	337	304	285	272	256	336	304	286	259	236

Source: FDA biometrics reviewer analyzed data from Study 191622-079

Table 36: BLA 103000/5215 Phase 3 Study 191622-080 Exposures (N) Per Dose by Treatment Cycle

Total Dose injected All Muscles	BOTOX/BOTOX					PLACEBO/BOTOX				
	Day 0	Week 12	Week 24	Week 36	Week 48	Day 0	Week 12	Week 24	Week 36	Week 48
155 U	211	191	173	154	144	220	212	197	181	164
160 U	16	10	11	9	9	11	20	12	11	8
165 U	33	44	43	43	32	39	34	40	30	24
170 U	10	7	6	6	3	7	6	9	4	7
175 U	30	24	20	22	27	34	24	21	19	20
180 U	3	2	5	2	2	7	4	4	9	3
185 U	19	19	15	16	16	22	21	22	16	16
190 U	5	4	5	4	1	2	1	3	1	1
195U	20	19	26	25	23	15	18	21	20	21
Total Exposures	347	320	304	281	257	357	340	329	291	264

Source: FDA biometrics reviewer analyzed data from Study 191622-080

Table 37: BLA 103000/5215 Phase 3 Studies Mean (SD) Dose Per Muscle Group

Muscle Group	191622-79						191622-080					
	Day 0		Week 12		Week 24		Day 0		Week 12		Week 24	
	BOTOX (N=340)	PLACEBO (N=334)	BOTOX (N=307)	PLACEBO (302)	BOTOX (N=287)	PLACEBO (N=284)	BOTOX	PLACEBO	BOTOX	PLACEBO	BOTOX	PLACEBO
Frontalis	19.9 (1.1)	0	20 (0)	0	20 (0)	20 (0)	20 (0)	0	20 (0)	0	20 (0)	20 (0)
Corrugator	10 (0)	0	10 (0)	0	10 (0)	10 (0)	10 (0)	0	10 (0)	0	10 (0)	10 (0)
Procerus	5 (0)	0	5 (0)	0	5 (0)	5 (0)	5 (0)	0	5 (0)	0	5 (0)	5 (0)
Occipitalis	32.2 (4.5)	0	32.5 (4.3)	0	32.3 (4.1)	32.6 (4.1)	31.6 (3.64)	0	31.6 (3.49)	0	31.6 (3.54)	31.6 (3.39)
Temporalis	43.0 (5.1)	0	42.8 (4.6)	0	42.8 (4.4)	43.3 (4.6)	42.4 (4.0)	0	42.6 (4.2)	0	42.7 (4.2)	42.2 (4.1)
Trapezius	35.1 (7.9)	0	35.5 (8.26)	0	35.4 (7.5)	35.1 (7.1)	34.0 (7.3)	0	33.9 (7.3)	0	34.8 (8.1)	34.5 (7.7)
Cervical Paraspinal Group	19.9 (1.1)	0	19.9 (1.1)	0	20 (0)	20 (0)	20 (0)	0	20 (0)	0	20 (0.6)	20 (0)
TOTAL DOSE	165.1 (15.6)	0	165.8 (14.4)	0	165.5 (13.0)	166.0 (12.6)	163.0 (12.3)	0	163.1 (12.3)	0	164.0 (13.4)	163.3 (12.6)

Modified format only: Module 5.3.5.1.1 Study Report 191622-079; Table 14.1-24 to 14.1-31; Study Report 191622-080; Table 14.1-24 to 14.1-31

4 Pages Immediately Following Withheld - Draft Labeling b(4)

(b) (4)

[redacted]

Subgroup Analysis: Efficacy for Patients who Required Fixed Dose 155U
This was not a pre-specified endpoint for analysis in study 1916220-079 and study 191622-080. As noted in Table 43 nominal p-values <0.05 was observed for efficacy outcomes measured at the primary timepoint during post hoc subgroup analysis for patients who received required fixed dose BOTOX 155U except for change in frequency of headache episodes (p-value = 0.32) in study 191622-079. These results appear consistent with the original efficacy analysis performed. However, please note that all results should be interpreted in the context that the results are from post hoc analysis without adjusting for multiplicity.

Table 43: BLA 103000/5215 SUBGROUP ANALYSIS: Subjects Injected 155U for Both Treatments During Double Blind Phase in Chronic Migraine Phase 3 Studies (191622-079 & 191622-080) Primary and Secondary Efficacy Measurements at Primary timepoint (24 Weeks) LSMean Change from Baseline

Efficacy variable (per 28 days)	191622-079			191622-080		
	BOTOX (N=126)	PLACEBO (N=126)	p-value	BOTOX (N=166)	PLACEBO (N=182)	p-value
Frequency of HA Days[A]	-8.5	-6.7	0.0378	-10.0	-7.0	<0.0001
Frequency of HA Episodes[B]	-6.3	-5.6	0.3211	-6.2	-4.8	0.0073

Total cumulative hours of headache on HA days	-109.4	-67.8	0.0178	-144.0	-91.4	<0.0001
Source: FDA Biometrics reviewer analyzed data from Study 191622-079 and 191622-080 [A] Primary End-point 191622-080, [B] Primary End-point 191622-079						

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

From the summary of efficacy findings shown from Table 28 up to Table 34 it appears the time to onset of treatment effect (for the primary efficacy variables including the secondary measures) may have been around 8-12 weeks although the primary timepoint was pre-specified as 24 weeks and the results were fairly consistent showing persistence of treatment effect over time across multiple endpoints with statistically convincing evidence of clinically meaningful treatment effect except for the reduction in use acute pain medication use.

6.1.10 Additional Efficacy Issues/Analyses

N/A.

7 Review of Safety

Safety Summary

Please refer to review of Dr. Cheryl Graham, MD for sBLA 103000/5215.

9 Appendices

9.1 Literature Review/References

The literature review included studies excluding the trials conducted by Allergan. 7 studies provided information generally relevant to the efficacy of BOTOX in the prophylactic treatment of chronic migraine headache in adults. However, the findings are to be considered within the limited scope of the individual studies. The bulk of data represented by these studies was collected under open-label conditions (311/353 patients treated with BOTOX). The blinded, controlled studies were very small (14 to 41 patients in total) and used a variety of doses, muscles injected, and treatment paradigms that were not similar to the chronic migraine phase 3 studies with BOTOX. The doses used were generally lower than the dose recommended in the proposed labeling submitted with this application, and most studies only evaluated results after a

single treatment cycle. There was little consistency across studies in either the efficacy measures used to evaluate treatment success or the evaluation timepoints. The efficacy results of these studies, while generally supportive of the efficacy of BOTOX in the prophylactic treatment of chronic migraine in adults, cannot be considered as conclusive because of these described limitations and variability.

9.2 Labeling Recommendations

Please see edits proposed for labeling in separate labeling review.

9.3 Advisory Committee Meeting

Not applicable.

9.4 Training Materials for Injection Procedure Used in Phase 3 Chronic Migraine Studies

This was adapted from module 2.7.3, section 2.7.3.6.4 of the sBLA submission.

Corrugator muscle

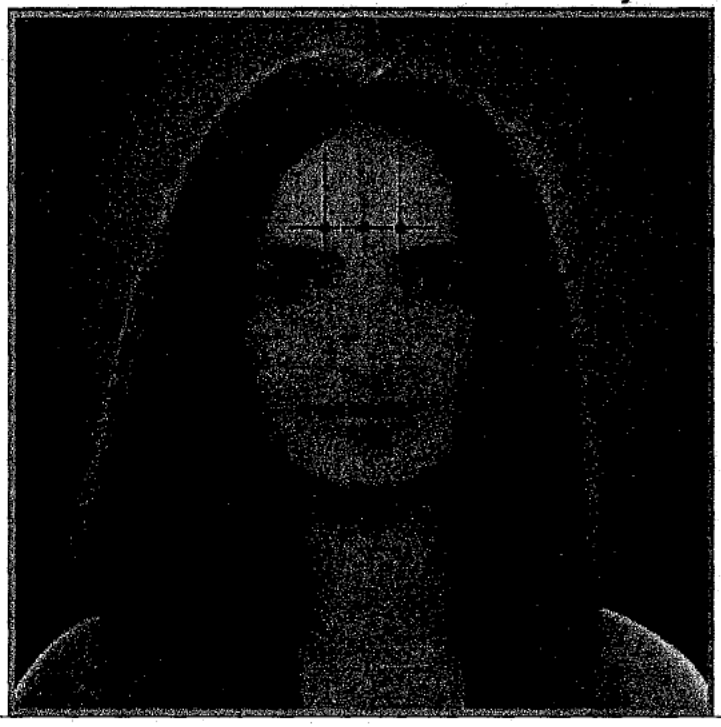
Figure 15: BLA 103000/5215 Corrugator Muscle Injection site

Ref: Module 2.7.3, section 2.7.3.6.4

- The corrugator muscle injection site is located one finger breadth (~ 1.5 cm) above the medial superior edge of the orbital ridge (bony landmark).
- Inject with the needle pointing upwards (i.e., towards the forehead) to avoid ptosis of the eyelid. Repeat this procedure symmetrically on the contralateral side.
- The fixed-site, fixed-dose protocol stipulates that one injection of 0.1 mL of study medication be administered in each the left and right corrugator muscles.
- The total BOTOX dose using the fixed-site, fixed-dose injection paradigm would be 10 U (2 sites).

Procerus muscle

Figure 16: BLA 103000/5215 Procerus Muscle Injection site



Ref: Module 2.7.3, section 2.7.3.6.4

- The procerus muscle injection site is midline on the forehead, approximately one finger breadth (~ 1.5 cm) above and midline to the medial superior aspect of the orbital ridge (bony landmark) of each eye.
- The injection site for this muscle should be approximately midway between the two corrugator injections (visualize a straight, single line connecting all three of these injections).
- The fixed-site, fixed-dose protocol stipulates that one injection of 0.1 mL of study medication be administered in the Procerus muscle.
- The total BOTOX® dose using the fixed-site, fixed-dose injection paradigm would be 5 U (1 site).

Frontalis muscle

Figure 17: BLA 103000/5215 Frontalis Muscle Injection site

Ref: Module 2.7.3, section 2.7.3.6.4

- Locate the frontalis muscle on the left side of the forehead first.
- Draw a line up visually from the medial aspect of the eyebrow.
- The injection site should be about 1.5 cm above the corrugator injection site.
- The next injection is just lateral to the first injection.
- The total BOTOX® dose using the fixed-site, fixed-dose injection paradigm would be 20 U (4 sites).

Temporalis muscle

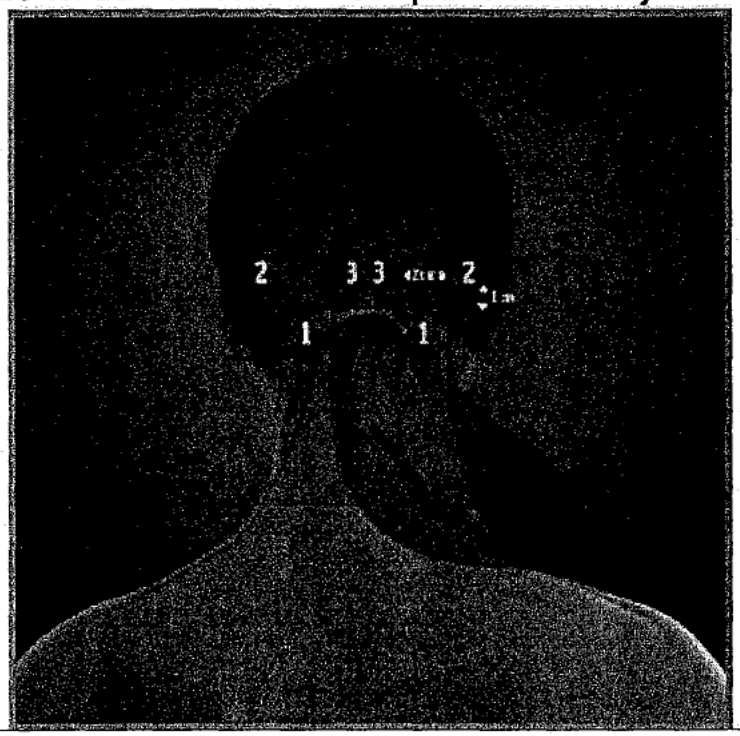
Figure 18: BLA 103000/5215 Temporalis Muscle Injection site

Ref: Module 2.7.3, section 2.7.3.6.4

- Locate the first temporalis injection site on the left side by having the patient clench their teeth.
- Palpate the anterior aspect of the temporalis.
- Make the first injection just behind this point. Try to stay behind the hairline.
- About 1.5 cm posterior and slightly superior to the first injection, make the second injection.
- Along the same line as the first injection, approximately 1.5 cm behind the second injection, make the third injection.
- The fourth injection should be into the medial aspect of the muscle about 1.5 cm inferior to the second injection, in the middle of the muscle.
- Repeat this procedure symmetrically on the contralateral side.
- The fixed-site, fixed-dose protocol stipulates that 4 injections of 0.1 mL of study medication be administered to the right and left temporalis muscles, for a total of 8 injections.
- According to the follow-the-pain, optional dosing paradigm, an additional 2 injections of 0.1 mL of study medication can be distributed between the right and left temporalis muscles.
- The total BOTOX dose using the fixed-site, fixed-dose injection paradigm would be 40 U (8 sites). Optional additional dosing using a follow-the-pain injection paradigm would be 0, 5, or 10 U (0, 1, or 2 sites).

Occipitalis muscle

Figure 19: BLA 103000/5215 Occipitalis Muscle Injection site

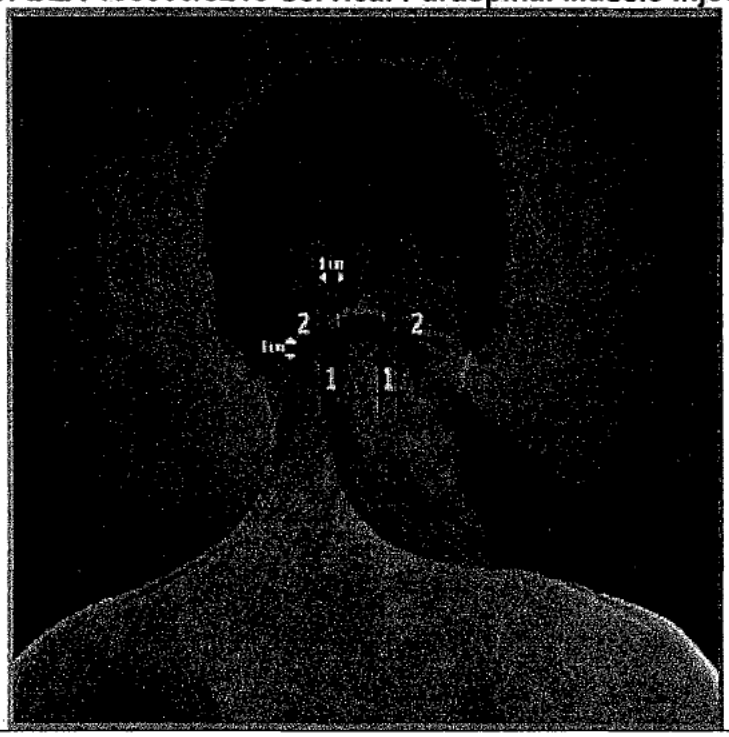


Ref: Module 2.7.3, section 2.7.3.6.4

- To locate the occipitalis muscle, palpate for the external occipital protuberance.
- The occipitalis injections will be superior to the supranuchal ridge on either side of this protuberance.
- The fixed-site, fixed-dose protocol for the occipitalis muscle stipulates that 3 injections be administered to the right and left occipitalis muscles, for a total of 6 injections in all.
- Each injection consists of 0.1 mL of study medication.
- According to the follow-the-pain, optional dosing paradigm, an additional 2 injections of 0.1 mL of study medication can be distributed between the right and left occipitalis muscles, in the areas identified as having maximal tenderness.
- The total BOTOX dose using the fixed-site, fixed-dose injection paradigm would be 30 U (6 sites). Optional additional dosing using a follow-the-pain injection paradigm would be 0, 5, or 10 U (0, 1, or 2 sites).

Cervical Paraspinal muscles

Figure 20: BLA 103000/5215 Cervical Paraspinal Muscle Injection site

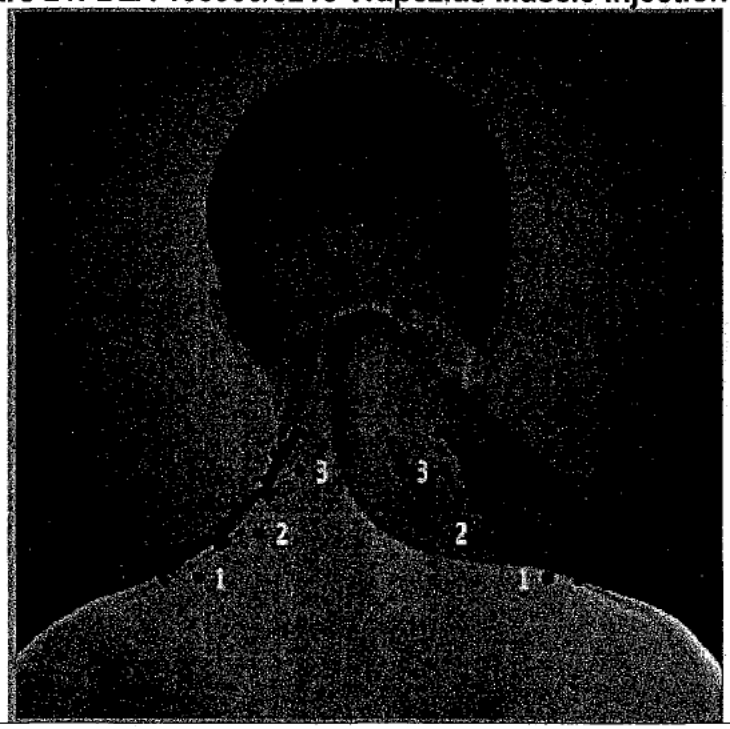


Ref: Module 2.7.3, section 2.7.3.6.4

- Beginning on the left side, locate the cervical paraspinal muscle group injection sites by palpating the cervical spine.
- Administer the first injection lateral to the midline approximately 3 to 5 centimeters inferior to the occipital protuberance.
- The second injection should be administered on the same side 1 cm lateral and superior to the first injection.
- Repeat this procedure symmetrically on the contralateral side.
- The fixed-dose protocol for the cervical paraspinal muscles stipulates that 2 injections be administered to the right and left sides, for a total of 4 injections.
- Each injection consists of 0.1 mL of study medication
- The total BOTOX dose using the fixed-site, fixed-dose injection paradigm would be 20 U (4 sites).

Trapezius muscles

Figure 21: BLA 103000/5215 Trapezius Muscle Injection site



Ref: Module 2.7.3, section 2.7.3.6.4

- Beginning on the left side, divide the muscle into three sections.
- The first injection should be administered in the lateral, inferior aspect of the muscle.
- Move medially, to the middle portion of the trapezius and administer the second injection.
- Move medially and superiorly within the third section of the muscle and administer the third injection.
- Repeat this procedure symmetrically on the contralateral side.
- The fixed-dose protocol stipulates that 3 injections be administered to the right and left trapezius muscles, for a total of 6 injections.
- Each injection consists of 0.1 mL of study medication.
- According to the follow-the-pain, optional dosing paradigm, an additional 4 injections of 0.1 mL of study medication can be distributed between the right and left trapezius muscles, in the areas identified as having maximal tenderness.
- The total BOTOX dose using the fixed-site, fixed-dose injection paradigm would be 30 U (6 sites). Optional additional dosing using a follow-the-pain injection paradigm would be 0, 5, 10, 15, or 20 U (0, 1, 2, 3, or 4 sites).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	BLA103000 / SN 5215
Drug Name:	BOTOX
Indication(s):	prophylaxis of headaches in adults with chronic migraine
Applicant:	Allergan
Date(s):	Sep 28, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiang Ling, Ph.D. 7/6/2010
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader 7/6/2010
	Kooros Mahjoob, Ph. D., Deputy Director Kooros Mahjoob
Medical Division:	Division of Neuropharmacological Drug Products, HFD-120
Clinical Team:	Suhail kasim, M.D.
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	Russell Katz, M.D., Division Director
Project Manager:	Lana Chen

Keywords: analysis of covariance

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data seem to provide some support for the efficacy of BOTOX as headache prophylactic treatment to migraine patients with 15 or more headache days per 4-week period. In both pivotal studies, BOTOX resulted in statistically significantly greater reduction in headache days compared to placebo.

1.2 Brief Overview of Clinical Studies

The primary evidence of efficacy was based on two phase 3 chronic migraine studies (191622-080 and 191622-079). They were randomized, multicenter studies evaluating the efficacy and safety of BOTOX as headache prophylaxis in adult chronic migraine patients. Study 080 was conducted in US, Germany, Canada, UK, Croatia, and Switzerland and Study 079 was conducted in US and Canada. A total of 1,384 patients (679 patients from study 079 and 705 from study 080) were randomly allocated at a 1:1 ratio to receive either BOTOX or placebo.

For both phase 3 studies, the original primary efficacy endpoint was the change from baseline at week 24 in the frequency of headache episodes per 4 weeks and the key secondary efficacy measure was the change from baseline in the frequency of headache days. However, after the completion of study 079 and prior to the primary database lock and treatment unblinding for study 080, the primary endpoint for study 080 was changed to frequency of headache days. The change was primarily based on results from study 079.

1.3 Statistical Issues and Findings

Change in the frequency of headache days
This was a secondary endpoint in study 079 and the primary endpoint in study 080. The results were positive for both studies. P-values were 0.006 for study 079 and <0.001 for study 080. Results were robust across subgroups except that for the small subgroup of Canada in study 079, BOTOX had numerically less reduction in headache days compared with placebo.

Change in the frequency of headache episodes
This was the primary endpoint in study 079 and an exploratory endpoint in study 080. In study 079, it was not statistically significant (p=0.344). There was significant treatment by country interaction. In the US where majority of patients were enrolled, BOTOX group had numerically greater reduction in frequency of headache episodes (p=0.0662); while in Canada with only a total of 42 patients, BOTOX had significantly less reduction compared to placebo in headache episodes (p=0.0104). Given the small sample size, the results were likely driven by extreme observations. In study 080, significant difference favoring BOTOX over placebo was observed (p=0.0034), and the result was robust across subgroups.

'Headache days' was regarded likely a more sensitive endpoint for evaluating headache prophylaxis treatment efficacy in patients with chronic migraine. The Agency recommended

'headache days' as the primary endpoint in the pre-phase 3 meeting, commenting that "in frequent chronic headache, it is difficult to distinguish between two or three shorter headaches occurring back to back vs. one headache with duration of several days. This has the potential to confound interpretation of the study results."

In addition, the studies enrolled subjects with at least 15 headache days and at least four headaches per the 4-week baseline period. Some patients may have only a few headache episodes that each last for days at baseline, and continue to have about the same number of headache episodes but of shorter durations at the primary efficacy timepoint. In this case, the efficacy of the drug cannot be characterized by headache frequency. Including the treatment-by-baseline headache episodes interaction in the ANCOVA model showed that the interaction was statistically significant for the frequency of headache episodes in both study 079 and 080 ($p = 0.0884$ and 0.001 respectively). Therefore, headache episodes may not be a good measure of the overall treatment effect for this study.

2. INTRODUCTION

2.1 Overview

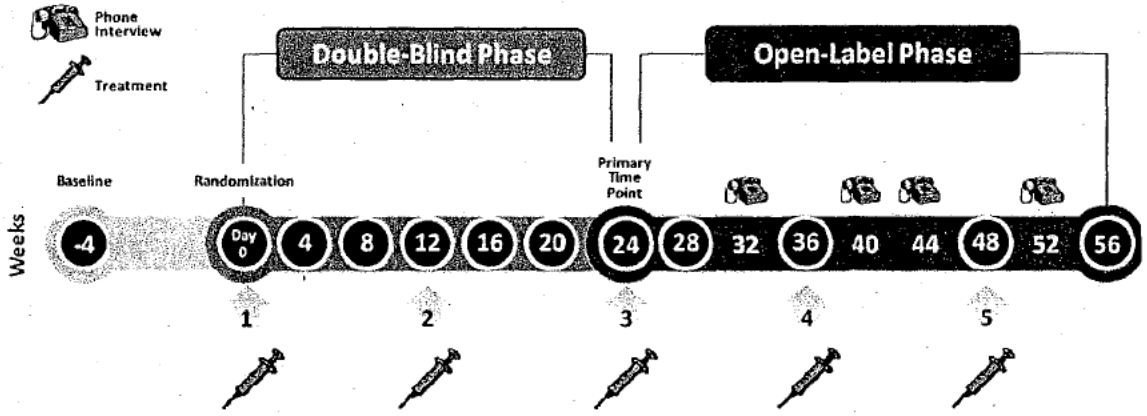
Allergan filed IND 7480 to FDA in December 1997 to support BOTOX clinical development for (b) (4) Allergan and FDA reached agreement on the design and corresponding analysis plans of the two phase 3 protocols (191622-079 and 191622-080) in August 2005. The pre-sBLA meeting was held with the US FDA in June 2009.

The primary evidence of efficacy was based on two phase 3 chronic migraine studies (191622-080 and 191622-079). Supportive evidence of efficacy was provided from the phase 2 subgroup of patients who met key phase 3 criteria.

Phase 3 Studies

The phase 3 studies had the same study design; they were randomized, multicenter studies evaluating the efficacy and safety of BOTOX as headache prophylaxis in adult chronic migraine patients. Each study included a 4-week screening/baseline phase, followed by a 24-week, double-blind, randomized, placebo-controlled, parallel-group phase, which was then followed by a 32-week open-label extension phase where all patients received Botox. There were 2 treatment cycles during the double-blind phase and 3 treatment cycles during the open-label phase. Each treatment cycle was 12 weeks in duration (Figure 1). The dose range was 155 U to 195 U administered IM to 31 to 39 injection sites, respectively, across 7 head and neck muscle groups. Validated electronic diaries using a telephone IVRS system were utilized to collect specific study data, including specific headache characteristics and acute headache medication use.

Figure 1. Schematic of Phase 3 Study Design



* In-office visits were conducted every 4 weeks, except when noted by telephone.
Source: Sponsor's ISE Report Figure 2.7.3.1-3.

A total of 1,384 patients (679 patients from study 079 and 705 from study 080) were randomly allocated to receive either BOTOX or placebo at a 1:1 ratio, stratified by overuse of acute headache pain medications (yes/no) at baseline based on the frequency of acute headache medicine use.

The target population included patients who had: 1) history of migraine; 2) long-lasting headaches (≥ 4 hours) that occurred on 15 or more days per 28 days; 3) an indication that most headache days were migraine in origin; and 4) four or more intermittent, long-lasting headaches per the 4-week baseline period. Patients also had to have no headache prophylaxis treatment within 28 days prior to the start of the baseline period.

Phase 2 Chronic Migraine Studies

The supportive chronic migraine phase 2 studies (191622-038 and 191622-039) were multicenter, randomized, double-blind, placebo-controlled, parallel-group exploratory phase 2 studies evaluating multiple treatments of BOTOX and placebo in 1057 patients. The duration of each phase 2 study was a maximum of 11 months, including a 30-day baseline period, treatment 1 (placebo run-in period) with a 30-day follow-up period, and treatments 2, 3, and 4 (BOTOX or placebo), each with 90-day follow-up periods. The dose range used in study 191622-038 was from 105 U up to 260 U (using a follow-the-pain injection paradigm) and the doses used in study 191622-039 were 75, 150, and 225 U (following a fixed-site fixed-dose injection paradigm).

The target population defined a broader population. Allergan identified a subgroup of patients from the chronic migraine phase 2 studies who met key phase 3 study criteria (referred to as the 'phase 2 subgroup', 154 patients from study 191622-038 and 168 patients from 191622-039) that most closely aligned with the patient population and dose/treatment paradigm in the phase 3 studies which provided the additional data for Allergan's application for prophylaxis of chronic migraine.

2.2 Data Sources

The data files are located in the following directory:
\\cbsap58\M\eCTD_Submissions\STN103000\0072\m5\datasets

The study reports are located in the following directory:
\\cbsap58\M\eCTD_Submissions\STN103000\0072\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

3.1.1. Study 079

Study 079 was initiated on 22 February 2006 (first patient enrolled) and completed on 16 July 2008 (last patient exit date). There was 1 amendment to the original protocol to incorporate minor administrative changes. The original protocol was approved on 06 September 2005 and Amendment 01 was approved on 13 June 2007. The primary analysis database (ie, week 24 data) was locked on 08 February 2008 and the treatment code was unblinded on 11 February 2008.

3.1.1.1. Study Design

Study 079 was a multicenter study conducted at 51 US and 5 Canadian study centers. On day 0, following a 4-week baseline phase, patients meeting the inclusion/exclusion criteria were assigned in a blinded fashion to the study treatment in the strata of medication overuse (yes/no), as determined by the frequency of use of acute headache pain medications during the baseline phase. Within each stratum within each investigator site, patients were randomly allocated to receive either BOTOX or placebo in a 1:1 ratio within blocks of 4.

All patients were to receive either 2 treatments with BOTOX or 2 treatments with placebo during the double-blind phase (day 0 and week 12). Each treatment consisted of a dose ranging from 155 U to 195 U BOTOX or placebo administered intramuscularly (IM) as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas.

3.1.1.2. Efficacy Measures

Efficacy measures were variables derived from information recorded by patients using a validated electronic headache diary that captured data using a telephone interactive voice response system (IVRS). On a daily basis, patients were to report information on the start/stop time of any headache, headache specific characteristics and symptoms and use of any acute headache pain medication. Patients were able to report headache data for each report date and for the three days immediately preceding the report date as long as information reported is for a time subsequent to the patient's most recent report. This is defined as a three-day "missing-recall" window.

The primary efficacy variable is the frequency of headache episodes in the 28-day period ending with Week 24 (ie, Day 57 to Day 84 inclusive following second injection) compared to the first 28 days of the baseline phase. A headache episode is defined as patient reported headache pain with a start and stop time that indicates that the pain lasted at least 4 continuous hours per patient diary. The number of headaches during the *first* 28 days of the baseline phase serves as the "baseline". The number of headaches is counted in successive and non-overlapping 4-week windows. Headaches that continue into a subsequent 4-week period are counted as occurring in each period.

The secondary efficacy variables are identified as follows:

- Frequency of headache days per 28 day period
- Frequency of migraine/probable migraine days per 28 day period
- Frequency of migraine/probable migraine episodes per 28 day period
- Frequency of acute headache pain medication intakes per 28 day period

A migraine (probable migraine) episode is defined as patient reported headache pain with a start and stop time that indicates that the pain lasted at least 4 continuous hours and meets ICHD-II 1.1 Migraine (ICHD-II 1.6 Probable Migraine) criteria per patient diary.

A headache day is defined as a day (00:00 to 23:59) with 4 or more continuous hours of headache per patient diary. A day with a headache that begins at 8:00 PM and continues to another day will be considered to be a day with a headache of at least 4 hours in duration.

Statistical methods to control the type I error rate for the secondary endpoints were not pre-specified.

3.1.1.3. Statistical Analysis Methods

Analysis Population

The intent to-treat (ITT) population consisting of all randomized patients was used for efficacy data analyses. In efficacy analyses, the patients were analyzed according to randomization assignment, regardless of actual treatment received.

Missing Data Imputation

(1) If any diary window for a patient has at least 20 but less than 28 days of reported data, the prorated approach will be used.

(2) If a patient reports any diary data in less than 10 days of a 28-day period, the score of the period will be imputed by a modified last observation carried forward (mLOCF, mean-change adjusted LOCF) analysis:

$$\text{previous } 28-\text{dayperiod score} * \frac{\text{mean over all treatment groups from current } 28-\text{day period}}{\text{mean over all treatment groups from previous } 28-\text{day period}}$$

(3) If a patient reports any diary data in at least 10 days but less than 20 of a 28-day period, the score of the period will be imputed by taking the average of two estimated scores resulting from the simple prorating method (1) and the mLOCF method (2), respectively, as discussed above and rounded to the nearest whole number.

For both methods (2) and (3) above, the substitution will be iterative by 28-day period, in that imputation of a given 28-day period (eg, Week 8) will follow imputation of the preceding 28-day period (eg, Week 4).

Efficacy Analyses

The primary comparison between treatment groups were done by analysis of covariance (ANCOVA) of the change from baseline, with baseline headache count as the covariate, and treatment group and medication-overuse strata as main effects. Investigator center was originally included as one of the main effects, but was removed from ANCOVA models prior to database lock since the majority of investigator centers enrolled a small number of patients.

For the primary variable, sensitivity analyses were performed using (1) the Wilcoxon rank-sum test, where the rank score was determined after applying the imputation; (2) ANCOVA, using "observed data" (ie, without imputing for missing values when there are less than 20 days of reported data in the headache diary); and (3) ANCOVA on the rank of the change from baseline, with the unranked baseline count as covariate, again where the rank score was determined after imputation. All centers and other strata and subgroups were pooled for these sensitivity analyses.

An examination was made of possible treatment-by-center interaction via a 2-way analysis of variance model with main effect terms for treatment, center, and their interaction. A similar examination was made for treatment-by-subgroup interaction for the medication overuse (yes/no) strata.

The secondary variables were each analyzed in a similar manner as the primary variable. For the frequency of headache days, the full set of sensitivity analyses listed for the primary variable was done. Additional sensitivity analyses for this variable were performed by ANCOVA of the change from baseline for headache days that had (1) at least 6 hours and (2) at least 2 hours of continuous headache during the calendar day.

Primary and secondary efficacy variables were summarized by the following subgroup factors: investigator center, age (< 40 years/≥40 years), gender (male/female), race (Caucasian/non-Caucasian), acute headache pain medication overuse (yes/no); with the overuse group as stratified during randomization assignment), and history of headache pain prophylactic medication use (yes/no). The primary subgroup analysis was ANCOVA of the mean change from baseline, using mLOCF, with baseline score as covariate.

There was no interim analysis. A two-sided test with a p-value less than or equal to 0.05 was considered statistically significant, with the exception of treatment-by-subgroup interactions, which were examined at the 0.10 level.

3.1.1.4. Patient Disposition, Demographic and Baseline Characteristics

Of the 1713 patients screened, 679 patients were enrolled in the study (341 randomized to BOTOX group and 338 to placebo group); 679 patients were included in the ITT population and 674 were included in the safety population. Of the 679 enrolled patients, 461 (68.0%) were stratified to the medication overuse group (66.3% in the BOTOX group and 69.5% in the placebo group).

There were no statistically significant between treatment-group differences with respect to baseline demographic characteristics. Overall, patients were 18 to 65 years of age (mean, 41.7 years), 87.5% were female, and 90.4% were Caucasian (Table 1). A total of 97.5% of patients used acute headache pain medications and 61.9% had previously used other headache prophylactic medications prior to study enrollment (Table 2).

Table 1. Study 079: Baseline Demographic Characteristics (ITT Population)

Demographic Characteristic	BOTOX® (N = 341)	Placebo (N = 338)	Total (N = 679)	P-value
Age, years				
Mean ± SD	41.2 ± 10.49	42.1 ± 10.46	41.7 ± 10.47	0.317 [a]
Median	42.0	42.0	42.0	
Min, Max	19, 65	18, 64	18, 65	
Age, n (%)				
< 40 years	144 (42.2%)	128 (37.9%)	272 (40.1%)	0.246 [a]
≥ 40 years	197 (57.8%)	210 (62.1%)	407 (59.9%)	
Gender, n (%)				
Male	37 (10.9%)	48 (14.2%)	85 (12.5%)	0.187 [a]
Female	304 (89.1%)	290 (85.8%)	594 (87.5%)	
Race, n (%)				
Caucasian	305 (89.4%)	309 (91.4%)	614 (90.4%)	
Black	16 (4.7%)	14 (4.1%)	30 (4.4%)	NA
Asian	1 (0.3%)	2 (0.6%)	3 (0.4%)	
Hispanic	18 (5.3%)	11 (3.3%)	29 (4.3%)	
Other [g]	1 (0.3%)	2 (0.6%)	3 (0.4%)	

Source: Sponsor CSR page 83.

Table 2. Study 079: Baseline Medication Use (ITT Population)

Demographic Characteristic	BOTOX® (N = 341)	Placebo (N = 338)	Total (N = 679)	P-value
Prestudy headache prophylactic medications (yes), n (%)	203 (59.5%)	217 (64.2%)	420 (61.9%)	0.210 [c]
Baseline acute headache medication use, n (%)	335 (98.2%)	327 (96.7%)	662 (97.5%)	0.213 [c]
Baseline acute headache medication overuse, n (%) [e]	226 (66.3%)	236 (69.8%)	462 (68.0%)	0.322 [c]
Simple analgesics (≥ 15 days)	43 (12.6%)	51 (15.1%)	94 (13.8%)	0.350 [c]
Ergotamines (≥ 10 days)	2 (0.6%)	1 (0.3%)	3 (0.4%)	>0.999 [f]
Triptans (≥ 10 days)	78 (22.9%)	81 (24.0%)	159 (23.4%)	0.737 [c]
Opioids (≥ 10 days)	7 (2.1%)	10 (3.0%)	17 (2.5%)	0.450 [c]
Combination analgesics (≥ 10 days)	87 (25.5%)	98 (29.0%)	185 (27.2%)	0.308 [c]
Combined categories (≥ 10 days) [d]	165 (48.4%)	174 (51.5%)	339 (49.9%)	0.420 [c]

Source: Sponsor CSR page 83.

The mean time since onset of frequent migraine was 20.4 years and the mean age of onset was 20.6 years in the total population. At baseline, the BOTOX group had significantly less headache episodes and migraine/probable migraine episodes, as well as significantly more total cumulative hours of headache occurring on headache days compared to the placebo group. The baseline mean number of headache days was similar between the groups, and was composed predominantly of migraine and/or probable migraine days (Table 3).

Table 3. Study 079: Baseline Disease Characteristics (ITT Population)

Disease Characteristic	BOTOX (N = 341)	Placebo (N = 338)	Total (N = 679)	P-value
Headache episodes	12.3 ± 5.23	13.4 ± 5.71	12.8 ± 5.50	0.023
Migraine/probable migraine episodes	11.5 ± 5.06	12.7 ± 5.72	12.1 ± 5.43	0.006
Headache days	20.0 ± 3.73	19.8 ± 3.71	19.9 ± 3.72	0.571
Migraine/probable migraine days	19.1 ± 4.04	19.1 ± 4.05	19.1 ± 4.04	0.978
Moderate/severe headache days	18.1 ± 4.22	18.3 ± 4.23	18.2 ± 4.22	0.674
Total cumulative hours of headache occurring on headache days	295.66 ± 116.811	274.88 ± 110.901	285.32 ± 114.298	0.022
Patients with severe HIT-6 category scores, n (%)	322 (94.4%)	320 (94.7%)	642 (94.6%)	0.888

Values are presented as mean ± SD, with the exception of patients with severe HIT-6 category scores.
Source: Sponsor CSR page 86.

A total of 87.0% of all patients completed the double-blind phase of the study: 86.8% in the BOTOX group and 87.3% in the placebo group. In the ITT population, 3.2% (11/341) of patients in the BOTOX group and 0.6% (2/338) of patients in the placebo group discontinued the double-blind phase due to adverse events.

Table 4. Study 079: Subject Disposition

Disposition	BOTOX/BOTOX (N = 341)	Placebo/BOTOX (N = 338)	Total (N = 679)
Enrolled	341	338	679
Completed double-blind phase	296 (86.8%)	295 (87.3%)	591 (87.0%)
Discontinued prior to week 24	45 (13.2%)	43 (12.7%)	88 (13.0%)
Adverse events	11 (3.2%)	2 (0.6%)	13 (1.9%)
Lack of efficacy	1 (0.3%)	0 (0.0%)	1 (0.1%)
Pregnancy	2 (0.6%)	1 (0.3%)	3 (0.4%)
Lost to follow-up	6 (1.8%)	15 (4.4%)	21 (3.1%)
Personal reasons	12 (3.5%)	11 (3.3%)	23 (3.4%)
Protocol violations	0 (0.0%)	3 (0.9%)	3 (0.4%)
Other	13 (3.8%)	11 (3.3%)	24 (3.5%)

Fourteen patients in the BOTOX group and 3 patients in the placebo group had an AE onset during the double-blind phase that led to study discontinuation, but of these 3 BOTOX patients and 1 placebo patient did not exit the study until the open-label phase and were hence accounted for in the open-label phase.
Source: Sponsor CSR page 78.

3.1.1.5. Sponsor's Efficacy Results

Primary efficacy endpoint results

Comparisons between treatment groups were done by ANCOVA for the change from baseline using mLOCF imputation, with covariate of baseline headache count and main effect of treatment group and medication-overuse strata. BOTOX treatment was not shown to be more effective than placebo for the evaluation of change from baseline for headache episodes at the primary timepoint (p=0.344, Table 5), or at any other post-treatment timepoint. Results from all 3 sensitivity analyses (Wilcoxon rank-sum test, ANCOVA on the rank of the mean change from baseline with the unranked baseline count as covariate, and ANCOVA using observed data) were consistent with the results from the primary efficacy analysis.

Table 5. Study 079: Baseline and Change From Baseline for Frequency of Headache Episodes

Time Period[a]	Statistics	BOTOX/BOTOX (N=341)	Placebo/BOTOX (N=338)	Total (N=679)	P-value
Baseline	N	341	338	679	0.023
	LSMean	11.9	12.8	12.4	
	Mean	12.3	13.4	12.8	
	SD	5.23	5.71	5.50	
	Median	12.0	13.0	12.0	
	Min	4	4	4	
	Max	30	43	43	
Week 24 (Primary Endpoint)	N	341	338	679	0.344
	LSMean	-5.4	-5.0	-5.2	
	Mean	-5.2	-5.3	-5.2	
	SD	5.27	5.85	5.56	
	Median	-4.0	-5.0	-5.0	
	Min	-21	-36	-36	
	Max	12	37	37	

Source: Sponsor CSR Table 14.2-1.

Secondary efficacy endpoint results

For the frequency of headache days, patients treated with BOTOX had a highly statistically significantly greater decrease from baseline (LSMean -7.8) than patients treated with placebo (LSMean -6.4) at the primary time point, week 24 (p = 0.006, Table 6), and at most other time points during the double-blind phase. Sensitivity analyses similar to those for the primary endpoint and addition sensitivity analyses for the change from baseline for headache days that had at least 6 hours of continuous headache and at least 2 hours of continuous headache during the calendar day demonstrated statistically significant between-group differences favoring BOTOX at most time points during the double-blind phase.

Table 6. Study 079: Baseline and Change From Baseline for Frequency of Headache Days

Time Period[a]	Statistics	BOTOX/BOTOX (N=341)	Placebo/BOTOX (N=338)	Total (N=679)	P-value
Baseline	N	341	338	679	0.571
	LSMean	19.9	19.7	19.8	
	Mean	20.0	19.8	19.9	
	SD	3.73	3.71	3.72	
	Median	20.0	19.0	19.0	
Week 24 (Primary Timepoint)	N	341	338	679	0.006
	LSMean	-7.8	-6.4	-7.1	
	Mean	-7.8	-6.4	-7.1	
	SD	6.57	6.69	6.66	
	Median	-8.0	-6.0	-7.0	

Source: Sponsor CSR Table 14.2-6.

For the frequency of Migraine/Probable Migraine days, patients treated with BOTOX had a statistically significantly greater decrease from baseline (LSMean -7.6) than patients treated with placebo (LSMean -6.0) at the primary time point, week 24 ($p = 0.002$, Table 7), and at all other time points during the double-blind phase.

Table 7. Study 079: Baseline and Change From Baseline for Frequency of Migraine/Probable Migraine Days

Time Period[a]	Statistics	BOTOX/BOTOX (N=341)	Placebo/BOTOX (N=338)	Total (N=679)	P-value
Baseline	N	341	338	679	0.978
	LSMean	19.0	19.0	19.0	
	Mean	19.1	19.1	19.1	
	SD	4.04	4.05	4.04	
	Median	18.0	18.0	18.0	
Week 24 (Primary Timepoint)	N	341	338	679	0.002
	LSMean	-7.6	-6.0	-6.8	
	Mean	-7.6	-6.1	-6.9	
	SD	6.51	6.78	6.69	
	Median	-8.0	-6.0	-7.0	

Source: Sponsor CSR Table 14.2-14.

There was a decrease from baseline for the frequency of migraine/probable migraine episodes (Table 8) and acute headache pain medication intakes (Table 9) per 28-day period in the BOTOX and placebo groups. However, there were no statistically significant between-group differences at any timepoint.

Table 8. Study 079: Baseline and Change From Baseline for Frequency of Migraine/Probable Migraine Episodes

Time Period[a]	Statistics	BOTOX/BOTOX (N=341)	Placebo/BOTOX (N=338)	Total (N=679)	P-value
Baseline	N	341	338	679	0.006
	LSMean	11.0	12.1	11.6	
	Mean	11.5	12.7	12.1	
	SD	5.06	5.72	5.43	
	Median	11.0	12.0	12.0	
Week 24 (Primary Timepoint)	N	341	338	679	0.206
	LSMean	-5.0	-4.5	-4.8	
	Mean	-4.8	-4.9	-4.8	
	SD	5.06	5.74	5.41	
	Median	-4.0	-5.0	-4.0	

Source: Sponsor CSR Table 14.2-13.

Table 9. Study 079: Baseline and Change From Baseline for Frequency of Acute Headache Pain Medication Intakes

Time Period[a]	Statistics	BOTOX/BOTOX (N=341)	Placebo/BOTOX (N=338)	Total (N=679)	P-value
Baseline	N	341	338	679	0.709
	LSMean	25.2	25.7	25.5	
	Mean	29.1	30.4	29.7	
	SD	19.27	22.29	20.82	
	Median	25.0	26.0	26.0	
Week 24 (Primary Timepoint)	N	341	338	679	0.795
	LSMean	-10.1	-9.8	-10.0	
	Mean	-10.3	-10.4	-10.4	
	SD	18.67	18.54	18.59	
	Median	-8.0	-9.0	-9.0	

Source: Sponsor CSR Table 14.2-15.

3.1.1.6. Reviewer's Results

The reviewer confirmed the sponsor's analysis results from ANCOVA of the change from baseline, with baseline headache count as the covariate, and treatment group and medication-overuse strata as main effects. The investigator center was originally included as a main effect, but was removed prior to database lock. The ANCOVAs including investigator center as a main effect give similar results.

Table 10. Study 079: Sensitivity Analysis of ANCOVA

Endpoint	Main Effect	BOTOX (N = 341)	Placebo (N = 338)	P-value
Headache Episodes	Excluding CENTER	-5.36	-4.99	0.3445
	Including CENTER	-5.10	-4.74	0.3491
Headache Days	Excluding CENTER	-7.81	-6.40	0.0061
	Including CENTER	-7.93	-6.46	0.0041

Source: FDA Reviewer.

The sponsor used a combination of mean-change adjusted LOCF and prorating method for missing diary data during a particular 28-day period. The reviewer assessed the sensitivity of this mLOCF imputation by using the LOCF method. The results are insensitive to the imputation methods.

Table 11. Study 079: Sensitivity Analysis of Imputation

Endpoint	Imputation Methods	BOTOX (N = 341)	Placebo (N = 338)	P-value
Headache Episodes	mLOCF	-5.36	-4.99	0.3445
	LOCF	-5.29	-5.02	0.5279
Headache Days	mLOCF	-7.81	-6.40	0.0061
	LOCF	-7.66	-6.34	0.0191

Source: FDA Reviewer.

The treatment-by-country interactions were statistically significant for both the frequency of headache episodes and headache days (p-values = 0.0006 and 0.0443 respectively). BOTOX group had smaller reduction in headache episodes (p-value = 0.014) and in headache days (p-value = 0.2889) in Canada subgroup, but has greater decrease in headache episodes (p-value = 0.0662) and in headache days (p-value = 0.0015) in the US subgroup. In conclusion, the results show a qualitative treatment-by-country interaction. At any rate, this observation might be disregarded because there were only a total of 42 patients from 5 sites in Canada. Given the small sample size, the results are likely driven by extreme observations.

Table 12. Study 079: Analysis by Country

Country	Group	N	Change in Headache Episodes	P-value	Change in Headache Days	P-value
CANADA	BOTOX	21	-1.82	0.0104	-0.93	0.2889
	Placebo	21	-6.42		-3.20	
USA	BOTOX	320	-5.60	0.0662	-8.18	0.0015
	Placebo	317	-4.88		-6.52	

Source: FDA Reviewer.

The change from baseline at week 24 for the frequency of headache episodes was designated as the primary efficacy endpoint, despite the Agency's comment in the pre-phase 3 meeting that "in frequent chronic headache, it is difficult to distinguish between two or three shorter headaches occurring back to back vs. one headache with duration of several days. This has the potential to confound interpretation of the study results."

In addition, the study enrolled subjects with at least 15 headache days and at least four headaches per the 4-week baseline period. Some patients may have only a few headache episodes that each last for days at baseline, and continue to have about the same number of headache episodes but of shorter durations at the primary efficacy timepoint. In this case, the efficacy of the drug cannot be characterized by headache frequency. Including the treatment-by-baseline headache episodes interaction in the ANCOVA model showed that the interaction was statistically significant for the frequency of headache episodes ($p = 0.0884$). Therefore, headache episodes may not be a good measure of the overall treatment effect for this study.

On the contrary, the frequency of headache days may be more informative. The treatment-by-baseline headache days was not significant ($p=0.6138$). Based on the reduction of headache days and the totality of evidence, BOTOX was shown to be an effective headache prophylactic treatment in study 079.

3.1.2. Study 080

Study 080 was initiated on 09 March 2006 (first patient enrolled) and completed on 11 August 2008 (last patient exit date). There were 2 amendments to the original protocol. The first amendment incorporated minor administrative changes, and the second amendment incorporated changes to the statistical analyses. The original protocol was approved on 16 September 2005, Amendment 01 was approved on 13 June 2007, and Amendment 02 was approved on 05 August 2008. The statistical analysis plan was also amended on 05 August 2008. The amendment included changes to the primary and secondary endpoints, as well as removal of investigator center from ANCOVA models since the majority of investigator centers enrolled a small number of patients. The primary database (ie, week 24 data) was locked on 20 August 2008, and the treatment code was unblinded on 21 August 2008.

3.1.2.1. Study Design and Efficacy Measures

Study 191622-080 was a multicenter study conducted at 44 US, 8 Germany, 6 Canada, 3 UK, 3 Croatia, and 2 Switzerland study centers. The study design was similar to study 079.

The efficacy endpoints were the same with study 079 in the original protocol. The change from baseline at week 24 (week 20 to week 24) for the frequency of headache episodes was designated as the primary efficacy measure for both phase 3 studies and frequency of headache days was called out in the protocol and analysis plans as the most important secondary efficacy measure.

However, on 05 August 2008, prior to the primary database lock and treatment unblinding for study 080 the protocol and statistical analysis plan were amended to change the primary endpoint to frequency of headache days. The change was primarily based on results from study 079. Study 079 did not demonstrate statistical significance for the prespecified primary endpoint, change from baseline in the frequency of headache episodes at week 24. However, significant improvements from baseline were observed for both headache days and migraine/probable migraine days.

The secondary efficacy variables were changed to: frequency of migraine/probable migraine days; frequency of moderate/severe headache days; total cumulative hours of headache occurring on headache days; proportion of patients with severe headache impact test (HIT-6) category scores; and frequency of headache episodes. The above secondary endpoints were tested sequentially in the stated order to control the type 1 error rate for multiple secondary endpoints.

The counts were each analyzed in a similar manner as the primary efficacy variable, by ANCOVA of the change from baseline, with baseline count as the covariate, using mLOCF, with main effects of treatment group and medication-overuse strata. For most other efficacy analyses, changes from baseline for ordinal variables were analyzed using the Wilcoxon rank-sum test using observed data. For binomial variables, comparisons between treatment groups were done with Pearson's chi-square or Fisher's exact tests.

3.1.2.2. Patient Disposition, Demographic and Baseline Characteristics

Of the 1621 patients screened, 705 patients were enrolled in the study (347 randomized to BOTOX and 358 to placebo). All 705 patients were included in the ITT population and safety population. Of the 705 enrolled patients, 444 (63.0%) were stratified to the medication overuse group.

There were no statistically significant between treatment-group differences with respect to baseline demographic characteristics. Overall, patients were 18 to 65 years of age (mean, 41.0 years), 85.4% (602/705) were female, and 89.8% (633/705) were Caucasian. A total of 97.6% of patients used acute headache pain medications and 65.1% had previously used other headache prophylactic medications prior to study enrollment (Table 13).

Table 13. Study 080: Baseline Demographic Characteristics (ITT Population)

Demographic Characteristic	BOTOX® (N = 347)	Placebo (N = 358)	Total (N = 705)	P-value
Age, years				
Mean ± SD	41.0 ± 10.39	40.9 ± 10.82	41.0 ± 10.60	0.849 [a]
Median	42.0	41.0	41.0	
Min, Max	18, 65	18, 65	18, 65	
Age, n (%)				
< 40 years	149 (42.9%)	160 (44.7%)	309 (43.8%)	0.639 [a]
≥ 40 years	198 (57.1%)	198 (55.3%)	396 (56.2%)	
Gender, n (%)				
Male	48 (13.8%)	55 (15.4%)	103 (14.6%)	0.565 [a]
Female	299 (86.2%)	303 (84.6%)	602 (85.4%)	
Race, n (%)				
Caucasian	312 (89.9%)	321 (89.7%)	633 (89.8%)	
Black	18 (5.2%)	26 (7.3%)	44 (6.2%)	NA
Asian	3 (0.9%)	1 (0.3%)	4 (0.6%)	
Hispanic	9 (2.6%)	8 (2.2%)	17 (2.4%)	
Other [d]	5 (1.4%)	2 (0.6%)	7 (1.0%)	
Prestudy headache prophylactic medication use (yes), n (%)	222 (64.0%)	237 (66.2%)	459 (65.1%)	0.536 [c]
Baseline acute headache medication use, (yes), n (%)	337 (97.1%)	351 (98.0%)	688 (97.6%)	0.423 [c]
Baseline acute headache medication overuse (yes), n (%) [f, g]	220 (63.4%)	224 (62.6%)	444 (63.0%)	0.819 [c]
Simple analgesics (≥ 15 days)	52 (15.0%)	36 (10.1%)	88 (12.5%)	0.048 [c]
Ergotamines (≥ 10 days)	2 (0.6%)	1 (0.3%)	3 (0.4%)	0.619 [h]
Triptans (≥ 10 days)	83 (23.9%)	85 (23.7%)	168 (23.8%)	0.956 [c]
Opioids (≥ 10 days)	3 (0.9%)	4 (1.1%)	7 (1.0%)	>0.999 [h]
Combination analgesics (≥ 10 days)	55 (15.9%)	69 (19.3%)	124 (17.6%)	0.233 [c]
Combined categories (≥ 10 days) [e]	143 (41.2%)	150 (41.9%)	293 (41.6%)	0.853 [c]

Source: Sponsor CSR page 86.

The mean time since onset of frequent migraine was 18.0 years and the mean age of onset was 22.4 years in the total population. The baseline mean number of headache days was 19.8, composed predominantly of migraine and/or probable migraine days (mean 18.9) and moderate/severe headache days (mean, 17.9). The mean number of cumulative hours of headache occurring on headache days was 291.62 hours, and 91.6% of patients had severe HIT-6 category scores at baseline; there were no statistically significant between-group differences for these baseline variables (Table 14).

Table 14. Study 080: Baseline Disease Characteristics (ITT Population)

	BOTOX (N = 347)	Placebo (N = 358)	Total (N = 705)	P-value
Headache days [b]	19.9 ± 3.63	19.7 ± 3.65	19.8 ± 3.64	0.682 [b]
Migraine/probable migraine days [b]	19.2 ± 3.94	18.7 ± 4.05	18.9 ± 4.00	0.156 [b]
Moderate/severe headache days [c]	18.1 ± 4.03	17.7 ± 4.26	17.9 ± 4.15	0.333 [b]
Total cumulative hours of headache occurring on headache days [c]	296.18 ± 121.043	287.20 ± 118.089	291.62 ± 119.551	0.311 [b]
Patients with severe HIT-6 category scores, n (%) [c]	321 (92.5%)	325 (90.8%)	646 (91.6%)	0.408 [a]
Headache episodes [a]	12.0 ± 5.27	12.7 ± 5.29	12.3 ± 5.29	0.067 [b]
Migraine/probable migraine episodes [b]	11.3 ± 4.99	11.7 ± 5.08	11.5 ± 5.04	0.218 [b]

Values are presented as mean ± SD, with the exception of patients with severe HIT-6 category scores.
Source: Sponsor CSR page 88.

A total of 91.5% (645/705) of all patients completed the double-blind phase of the study: 89.6% (311/347) in the BOTOX group and 93.3% (334/358) in the placebo group. A total of 2.3% (8/347) of patients in the BOTOX group and 0.8% (3/358) of patients in the placebo group discontinued the double-blind phase due to adverse events.

Table 15. Study 080: Subject Disposition

Disposition	BOTOX/BOTOX (N = 347)	Placebo/BOTOX (N = 358)	Total (N = 705)
Enrolled [a]	347	358	705
Completed double-blind phase	311 (89.6%)	334 (93.3%)	645 (91.5%)
Discontinued prior to week 24	36 (10.4%)	24 (6.7%)	60 (8.5%)
Adverse events	8 (2.3%)	3 (0.8%)	11 (1.6%)
Lack of efficacy	4 (1.2%)	1 (0.3%)	5 (0.7%)
Pregnancy	1 (0.3%)	1 (0.3%)	2 (0.3%)
Lost to follow-up	7 (2.0%)	8 (2.2%)	15 (2.1%)
Personal reasons	7 (2.0%)	5 (1.4%)	12 (1.7%)
Protocol violations	1 (0.3%)	0 (0.0%)	1 (0.1%)
Other	8 (2.3%)	6 (1.7%)	14 (2.0%)

An additional 4 patients in the BOTOX group had an AE onset during the double-blind phase that led to discontinuation, but these patients did not discontinue the study until the open-label phase.
Source: Sponsor CSR page 80.

3.1.2.3. Sponsor's Efficacy Results

Sponsor's primary efficacy endpoint results

Comparisons between treatment groups were done by ANCOVA for the change from baseline using mLOCF imputation, with baseline headache days as the covariate, with main effect of treatment group and medication-overuse strata. The primary endpoint was met whereby there

was a statistically significant mean between-group difference favoring BOTOX (LSMean -9.2) over placebo (LSMean -6.9; $p < 0.001$) in the frequency of headache days.

Table 16. Study 080: Baseline and Change From Baseline for Frequency of Headache Episodes

Time Period[a]	Statistics	BOTOX/BOTOX (N=347)	Placebo/BOTOX (N=358)	Total (N=705)	P-value
Baseline	N	347	358	705	0.682
	LSMean	19.8	19.7	19.8	
	Mean	19.9	19.7	19.8	
	SD	3.63	3.65	3.64	
	Median	19.0	19.0	19.0	
Week 24 (Primary Timepoint)	N	347	358	705	<0.001
	LSMean	-9.2	-6.9	-8.0	
	Mean	-9.0	-6.7	-7.8	
	SD	6.54	6.67	6.70	
	Median	-9.0	-7.0	-8.0	

Source: Sponsor CSR Table 14.2-6.

Sensitivity analyses were performed for the primary efficacy variable using the Wilcoxon rank-sum test, ANCOVA on the rank of the mean change from baseline with the unranked baseline count as covariate, and ANCOVA using observed data. Results from all 3 analyses were consistent with the results observed for the primary efficacy analysis. Additional sensitivity analyses for the change from baseline for headache days that had at least 6 hours of continuous headache and at least 2 hours of continuous headache during the calendar day consistently demonstrated statistically significant mean reductions from baseline favoring BOTOX over placebo at all timepoints during the double-blind phase.

Secondary efficacy endpoint results

For the frequency of Migraine/Probable Migraine days, patients treated with BOTOX had a highly statistically significantly greater decrease from baseline (LSMean -8.8) than patients treated with placebo (LSMean -6.5) at the primary time point, week 24 ($p < 0.001$, Table 17), and at all other time points during the double-blind phase.

Table 17. Study 080: Baseline and Change From Baseline for Frequency of Migraine/Probable Migraine Days

Time Period[a]	Statistics	BOTOX/BOTOX (N=347)	Placebo/BOTOX (N=358)	Total (N=705)	P-value
Baseline	N	347	358	705	0.156
	LSMean	19.1	18.7	18.9	
	Mean	19.2	18.7	18.9	
	SD	3.94	4.05	4.00	
	Median	18.0	18.0	18.0	
Week 24 (Primary Timepoint)	N	347	358	705	<0.001
	LSMean	-8.8	-6.5	-7.7	
	Mean	-8.7	-6.3	-7.5	
	SD	6.64	6.71	6.78	
	Median	-9.0	-6.0	-7.0	

Source: Sponsor CSR Table 14.2-14.

For the frequency of Moderate/Severe headache days, patients treated with BOTOX had a highly statistically significantly greater decrease from baseline (LSMean -8.4) than patients treated with placebo (LSMean -6.0) at the primary time point, week 24 ($p < 0.001$, Table 18), and at all other time points during the double-blind phase.

Table 18. Study 080: Baseline and Change From Baseline for Frequency of Moderate/Severe Headache Days

Time Period[a]	Statistics	BOTOX/BOTOX (N=347)	Placebo/BOTOX (N=358)	Total (N=705)	P-value
Baseline	N	347	358	705	0.333
	LSMean	18.0	17.6	17.8	
	Mean	18.1	17.7	17.9	
	SD	4.03	4.26	4.15	
	Median	18.0	17.0	18.0	
Week 24 (Primary Timepoint)	N	347	358	705	<0.001
	LSMean	-8.4	-6.0	-7.2	
	Mean	-8.3	-5.8	-7.0	
	SD	6.37	6.59	6.60	
	Median	-8.0	-5.0	-7.0	

Source: Sponsor CSR Table 14.2-70.

For the total cumulative hours of headache occurring on headache days, patients treated with BOTOX had a highly statistically significantly greater decrease from baseline (LSMean -134) than patients treated with placebo (LSMean -95) at the primary time point, week 24 ($p < 0.001$, Table 19), and at all other time points during the double-blind phase.

Table 19. Study 080: Baseline and Change From Baseline for Cumulative Hours of Headache Occurring on headache days Headache Days

Time Period[a]	Statistics	BOTOX/BOTOX (N=347)	Placebo/BOTOX (N=358)	Total (N=705)	P-value
Baseline	N	347	358	705	0.311
	LSMean	299.09	289.99	294.47	
	Mean	296.18	287.20	291.62	
	SD	121.043	118.089	119.551	
	Median	275.50	270.03	273.00	
Week 24 (Primary Timepoint)	N	347	358	705	<0.001
	LSMean	-134.15	-94.54	-114.03	
	Mean	-132.41	-90.01	-110.88	
	SD	130.216	133.758	133.627	
	Median	-123.61	-83.38	-103.23	

Source: Sponsor CSR Table 14.2-71.

At baseline, the HIT-6 assessment demonstrated that 91.6% (646/705) of the study population was categorized as "severely impacted" from their migraine. Significantly fewer BOTOX-treated patients were categorized as severely impacted (66.3%) compared with placebo-treated patients (76.5%) at week 24 ($p = 0.003$).

For the frequency of headache episodes, patients treated with BOTOX had a highly statistically significantly greater decrease from baseline (LSMean -5.6) than patients treated with placebo (LSMean -4.6) at the primary time point, week 24 ($p = 0.003$, Table 20), and at all other time points during the double-blind phase.

Table 20. Study 080: Baseline and Change From Baseline for Frequency of Migraine Episodes

Time Period[a]	Statistics	BOTOX/BOTOX (N=347)	Placebo/BOTOX (N=358)	Total (N=705)	P-value
Baseline	N	347	358	705	0.067
	LSMean	11.7	12.4	12.1	
	Mean	12.0	12.7	12.3	
	SD	5.27	5.29	5.29	
	Median	11.0	12.0	12.0	
Week 24 (Primary Timepoint)	N	347	358	705	0.003
	LSMean	-5.6	-4.6	-5.1	
	Mean	-5.3	-4.6	-5.0	
	SD	5.12	4.84	4.98	
	Median	-5.0	-5.0	-5.0	

Source: Sponsor CSR Table 14.2-1.

3.1.2.4. Reviewer's Results

The reviewer confirmed the result of sponsor's analysis results from ANCOVA of the change from baseline, with baseline headache count as the covariate, and treatment group and medication-overuse strata as main effects. The investigator center was originally included as a main effect, but was removed prior to database lock. The ANCOVAs including investigator center as a main effect give similar results.

Table 21. Study 080: Sensitivity Analysis of ANCOVA

Endpoint	Main Effect	BOTOX (N = 347)	Placebo (N = 358)	P-value
Headache Episodes	Excluding CENTER	-5.60	-4.61	0.0034
	Including CENTER	-4.87	-3.89	0.0036
Headache Days	Excluding CENTER	-9.21	-6.92	<0.0001
	Including CENTER	-8.92	-6.72	<0.0001

Source: FDA Reviewer.

The sponsor used a combination of mean-change adjusted LOCF and prorating method for missing diary data during a particular 28-day period. The reviewer assessed the sensitivity of this mLOCF imputation by using the LOCF method. The results are insensitive to the imputation methods.

Table 22. Study 080: Sensitivity Analysis of Imputation

Endpoint	Imputation Method	BOTOX (N = 347)	Placebo (N = 358)	P-value
Headache Episodes	mLOCF	-5.60	-4.61	0.0034
	LOCF	-5.57	-4.50	0.0028
Headache Days	mLOCF	-9.21	-6.92	<0.0001
	LOCF	-9.19	-6.69	<0.0001

Source: FDA Reviewer.

Including the treatment-by-baseline headache episodes interaction in the ANCOVA model showed that the interaction was statistically significant for the frequency of headache episodes (p value = 0.001). Therefore, headache episodes may not be a good measure of the overall treatment effect for this study.

The treatment-by-country interactions were statistically significant for the frequency of headache episodes (p = 0.0611), but not for the frequency of headache days (p = 0.3639). Botox is numerically or significantly better than placebo in all 3 countries with reasonable sample size (Table 23). The other 3 European countries are pooled together because of small sample sizes (9 to 17).

Table 23. Study 080: Analysis by Country

Country	Treatment	N	Change in Headache Episodes	P-value	Change in Headache Days	P-value
USA	BOTOX	266	-5.77	0.0066	-9.39	0.0002
	Placebo	274	-4.75		-7.26	
CANADA	BOTOX	31	-5.57	0.8664	-8.31	0.3750
	Placebo	32	-5.37		-6.85	
GERMANY	BOTOX	36	-6.06	0.0486	-9.37	0.0113
	Placebo	28	-3.48		-5.11	
CHE, GRB, HRV	BOTOX	36	-1.75	0.3856	-7.62	0.2452
	Placebo	28	-2.92		-5.33	

Source: FDA Reviewer.

Statistically significant differences favoring BOTOX over placebo were demonstrated for the primary efficacy endpoint and all 5 of the secondary efficacy endpoints. BOTOX was shown to be an effective headache prophylactic treatment in study 080.

3.1.3. Phase 2 studies 038 and 039

The chronic migraine phase 2 studies (191622-038 and 191622-039) were multicenter, randomized, double-blind, placebo-controlled, parallel-group exploratory phase 2 studies evaluating multiple treatments of BOTOX and placebo in 1057 patients. The duration of each chronic migraine phase 2 study was a maximum of 11 months, including a 30-day baseline period, treatment 1 (placebo run-in period) with a 30-day follow-up period, and treatments 2, 3, and 4 (BOTOX or placebo), each with 90-day follow-up periods. The dose range used in study 191622-038 was from 105 U up to 260 U (using a follow-the-pain injection paradigm) and the doses used in study 191622-039 were 75, 150, and 225 U (following a fixed-site fixed-dose injection paradigm).

The original results from phase 2 studies were largely negative. The study 039 result was against BOTOX (Table 24).

Table 24. Mean Change from Baseline at Day 180 Primary Timepoint for Key Efficacy Results from Phase 2 Chronic Migraine Studies; Original Analyses

	Study 191622-038			Study 191622-039				
Efficacy parameters (per 28 days)	BOTOX 105~260 U N = 173	Placebo N = 182	P-value	BOTOX 225 U N = 182	BOTOX 150 U N = 168	BOTOX 75 U N = 174	Placebo N = 178	P-value
Frequency of headache days	-8.2	-6.5	0.200	-8.0	-8.6	-9.4	-8.7	0.646
Frequency of headache episodes	-7.1	-3.7	<0.001	-7.2	-6.2	-7.6	- 7.9	0.683
Frequency of M/PM days	-6.9	-6.0	0.387	-6.6	-7.6	-8.4	-6.5	0.402
Frequency of M/PM episodes	-5.8	-3.0	0.002	-5.5	-4.6	-6.1	-5.2	0.224
Frequency of acute	-13.1	-11.2	0.237	-15.0	-10.7	-12.7	-13.0	0.632

Efficacy parameters (per 28 days)	Study 191622-038 BOTOX 105~260 U N = 173	Placebo N = 182	P-value	Study 191622-039 BOTOX 225 U N = 182	BOTOX 150 U N = 168	BOTOX 75 U N = 174	Placebo N = 178	P-value
headache pain medication intakes								
Proportion of patients with 50% reduction in headache days	40.3%	25.3%	0.050	34.3%	42.1%	39.3%	38.6%	0.737
Proportion of patients with 50% reduction in headache episodes	54.2%	38.0%	0.046	45.5%	52.6%	53.3%	50.6%	0.680

Source: ISE Table 2.7.3.2–3

The target population defined a broader population. Allergan identified a subgroup of patients from the chronic migraine phase 2 studies who met key phase 3 study criteria (referred to as the 'phase 2 subgroup', 154 patients from study 191622-038 and 168 patients from 191622-039) that most closely aligned with the patient population and dose/treatment paradigm in the phase 3 studies which provided the additional data for Allergan's application for prophylaxis of chronic migraine. The results from the pooled phase 2 subgroup favor BOTOX group (Table 25). However, adhoc subgroup analysis is not considered supportive of primary efficacy.

Table 25: Phase 2 Subgroup Primary and Secondary Efficacy Measurements at Primary timepoint (24 Weeks) Mean Change from Baseline

Efficacy variable (per 28 days)	BOTOX N=181	PLACEBO N=141	p-value
Frequency of HA Days	-9.8	-7.9	0.008
Frequency of HA Episodes	-5.4	-4.6	0.090
Frequency of M/PM HA days	-8.9	-7.3	0.027
Frequency of M/PM HA Episodes	-4.8	-3.9	0.062
Total cumulative hours of headache on HA days	-127.73	-124.50	0.294
Proportion of patients with 50% reduction in HA days	50%	36.8%	0.129
Proportion of patients with 50% reduction in HA episodes	53.8%	50.9%	0.733
Frequency of acute HA pain medication intake	-13.2	-10.7	0.178

Source: ISE Table 2.7.3.3–5

3.2. Evaluation of Safety

Please see the clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race and Age

Table 26 shows the reviewer's subgroup analysis result for age, gender and race subgroups. Majority of the patients are 40 years old or older (58%), Caucasian (90%), female (86%). The treatment effect appears consistent across the subgroups.

Table 26. Treatment Effect by Age, Gender and Race in Pooled Population from Study 079 and Study 080

Subgroup	Treatment	N	Change in Headache Episodes	P-value	Change in Headache Days	P-value
40 or Greater	BOTOX	395	-5.34	0.0024	-8.05	0.0001
	Placebo	408	-4.27		-6.17	
Less Than 40	BOTOX	293	-5.54	0.7907	-9.04	0.0026
	Placebo	288	-5.45		-7.38	
Female	BOTOX	603	-5.50	0.0047	-8.56	0.0000
	Placebo	593	-4.72		-6.56	
Male	BOTOX	85	-5.41	0.9406	-8.38	0.4217
	Placebo	103	-5.36		-7.60	
Caucasian	BOTOX	617	-5.58	0.0065	-8.53	<0.0001
	Placebo	630	-4.84		-6.67	
Non-Caucasian	BOTOX	71	-4.68	0.9712	-8.58	0.2902
	Placebo	66	-4.66		-7.30	

Source: FDA Reviewer.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Change in the frequency of headache days

This was a secondary endpoint in study 079 and the primary endpoint in study 080. The results were positive for both studies. P-values were 0.006 for study 079 and <0.001 for study 080. Results were robust across subgroups except that for the small subgroup of Canada in study 079, BOTOX had numerically less reduction in headache days compared with placebo.

Change in the frequency of headache episodes

This was the primary endpoint in study 079 and an exploratory endpoint in study 080. In study 079, it was not statistically significant (p=0.344). There was significant treatment by country interaction. In the US where majority of patients were enrolled, BOTOX group had numerically greater reduction in frequency of headache episodes (p=0.0662); while in Canada with only a total of 42 patients, BOTOX had significantly less reduction in headache episodes (p=0.0104). Given the small sample size, the results were likely driven by extreme observations. In study 080, significant difference favoring BOTOX over placebo was observed (p=0.0034), and the result was robust across subgroups.

'Headache days' was regarded likely a more sensitive endpoint for evaluating headache prophylaxis treatment efficacy in patients with chronic migraine. The Agency recommended 'headache days' as the primary endpoint in the pre-phase 3 meeting, commenting that "in frequent chronic headache, it is difficult to distinguish between two or three shorter headaches occurring back to back vs. one headache with duration of several days. This has the potential to confound interpretation of the study results."

In addition, the studies enrolled subjects with at least 15 headache days and at least four headaches per the 4-week baseline period. Some patients may have only a few headache episodes that each last for days at baseline, and continue to have about the same number of headache episodes but of shorter durations at the primary efficacy timepoint. In this case, the efficacy of the drug cannot be characterized by headache frequency. Including the treatment-by-baseline headache episodes interaction in the ANCOVA model showed that the interaction was statistically significant for the frequency of headache episodes in both study 079 and 080 ($p = 0.0884$ and 0.001 respectively). Therefore, headache episodes may not be a good measure of the overall treatment effect for this study.

5.2 Conclusions and Recommendations

The data overall seem to provide some support for the efficacy of BOTOX as headache prophylactic treatment to migraine patients with 15 or more headache days per 4-week period. In both pivotal studies, BOTOX resulted in statistically significantly greater reduction in headache days compared to placebo.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Initial REMS Approval: 7/2009
Most Recent Modification: 10/2010

BLA 103000 BOTOX® / BOTOX® Cosmetic (OnabotulinumtoxinA)

Allergan, Inc.
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goals of the REMS are to:

- minimize the risks of medication errors related to the lack of interchangeability of **BOTOX®/BOTOX® Cosmetic** Units with those of licensed botulinum toxins of other manufacturers; and
- inform prescribers and patients about the potential occurrence of spread of toxin effect beyond the injection site.

II. REMS ELEMENTS

The **BOTOX®/BOTOX® Cosmetic** REMS includes a Medication Guide for patients and a Communication Plan for Healthcare Providers.

A. Medication Guide

In accordance with 21 CFR 208.24, a Medication Guide will be dispensed with each BOTOX prescription.

Please see appended Medication Guide in Appendix 1.

B. Communication Plan

Allergan will implement a communication plan to healthcare providers to support implementation of the modified REMS with the addition of prophylaxis of headaches in patients with chronic migraine indication. This will consist of a revised Dear Healthcare Provider Letter (DHCPL), with the updated labeling for **BOTOX®** and Medication Guide for **BOTOX®/BOTOX® Cosmetic.** The DHCPL will be distributed 6 weeks after REMS approval to physician specialists, specifically headache specialists, neurologists, and pain management specialists. These specialists currently represent the majority of physicians who are diagnosing and treating chronic migraine, and who will potentially treat chronic migraine patients with **BOTOX®.** See Appendix 3 for the second DHCPL.

Allergan distributed a Dear Healthcare Provider Letter (DHCPL) in September 2009 with the FDA-approved labeling and Medication Guide for **BOTOX®/BOTOX® Cosmetic** to all purchasers of **BOTOX®** and **BOTOX® Cosmetic** based on Allergan's Customer Lists. These include neurologists, dermatologists, and other specialists who prescribe botulinum toxin products.

See Appendix 2 for the DHCPL.

E. Timetable for Submissions of Assessments

Allergan will submit REMS assessments to FDA 18 months, 3 years and 7 years from the date of initial approval of the REMS (July 31, 2009). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before submission date for that assessment. Allergan will submit each assessment so it will be received by the FDA on or before the due date.

APPENDIX 1: Medication Guide

MEDICATION GUIDE
BOTOX®
BOTOX® Cosmetic
(Boe-tox)
(onabotulinumtoxinA)
for Injection

Read the Medication Guide that comes with **BOTOX** or **BOTOX Cosmetic** before you start using it and each time it is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

What is the most important information I should know about BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

- **Problems swallowing, speaking, or breathing. These problems can happen hours to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.
- People with certain breathing problems may need to use muscles in their neck to help them breathe. These patients may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
    - loss of strength and muscle weakness all over the body
    - double vision
    - blurred vision and drooping eyelids
    - hoarseness or change or loss of voice (dysphonia)
    - trouble saying words clearly (dysarthria)

- loss of bladder control
- trouble breathing
- trouble swallowing

These symptoms can happen hours to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic.**

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX** or **BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines.

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:

- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary).

It is not known whether **BOTOX** is safe or effective in patients younger than:

- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX and BOTOX Cosmetic** are safe or effective to prevent headaches in patients with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

Who should not take BOTOX or BOTOX Cosmetic?

Do not take **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc®*, *Dysport®, or Xeomin®*
- have a skin infection at the planned injection site

What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?

Tell your doctor about all your medical conditions, including if you have:

- a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- a breathing problem, such as asthma or emphysema
- swallowing problems
- bleeding problems
- plans to have surgery
- had surgery on your face
- weakness of your forehead muscles, such as trouble raising your eyebrows
- drooping eyelids
- any other change in the way your face normally looks
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*® (rimabotulinumtoxinB), *Dysport*® (abobotulinumtoxinA), or *Xeomin*® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles or skin.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.

What should I avoid while taking BOTOX or BOTOX Cosmetic?

BOTOX and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, or vision problems within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic. If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.

- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic.** For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about BOTOX and BOTOX Cosmetic:
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic.** If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for healthcare professionals. For more information about **BOTOX** and **BOTOX Cosmetic** call Allergan at 1-800-433-8871 or go to www.botox.com.

What are the ingredients in BOTOX and BOTOX Cosmetic?
Active ingredient: botulinum toxin type A
Inactive ingredients: human albumin and sodium chloride

Issued: 10/2010

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc.
2525 Dupont Dr.
Irvine, CA 92612

U.S. Patents 6,974,578; 6,683,049; and 6,896,886

Myobloc® is a registered trademark of Solstice Neurosciences, Inc.
Dysport® is a registered trademark of Ipsen Biopharm Limited Company.
Xeomin® is a registered trademark of Merz Pharma GmbH & Co KGaA.

APPENDIX 2: Initial Dear Healthcare Provider Letter

Dear Healthcare Provider:

Allergan, Inc. would like to inform you of 1) updated safety information regarding the risk of possible spread of botulinum toxin effects to sites distant from the injection site that appears in the prescribing information for Allergan's **BOTOX®/BOTOX® Cosmetic** as with all botulinum toxin products, 2) the introduction of a new established nonproprietary name for **BOTOX®/BOTOX® Cosmetic**, onabotulinumtoxinA, that replaces the previous common nonproprietary name botulinum toxin type A, and 3) the introduction of a Risk Evaluation and Mitigation Strategy (REMS) that includes a **BOTOX®/BOTOX® Cosmetic** Medication Guide to provide to your patients receiving **BOTOX®/BOTOX® Cosmetic**. The REMS has been implemented to ensure that the benefits of **BOTOX®/BOTOX® Cosmetic** treatment outweigh the potential risks of **BOTOX®/BOTOX® Cosmetic** treatment.

The goals of the **BOTOX®/ BOTOX® Cosmetic** REMS are to:

- minimize the risks of medication errors related to the lack of interchangeability of **BOTOX®/ BOTOX® Cosmetic** Units with those of licensed botulinum toxins of other manufacturers; and
- inform prescribers and patients about the potential occurrence of spread of toxin effect beyond the injection site.

You are advised to discuss the risks associated with **BOTOX®/BOTOX® Cosmetic** therapy outlined in the enclosed Medication Guide with patients and caregivers. In addition, please share the Medication Guide and Dear Healthcare Provider Letter materials with anyone in your practice who is involved in the preparation, prescribing and/or injection of **BOTOX®/BOTOX® Cosmetic**.

Per FDA regulations, a copy of the Medication Guide must be distributed directly to each patient every time he/she receives a BOTOX®/BOTOX® Cosmetic injection. Copies of the **BOTOX®/BOTOX® Cosmetic** Medication Guide are enclosed and if you wish to obtain additional copies of the Medication Guide for distribution to your patients please call 1-800-433-8871 or print copies directly from our Web sites (www.botoxmedical.com or www.botoxcosmetic.com). A copy of the Medication Guide will also be present in every carton of **BOTOX®/BOTOX® Cosmetic.**

Botulinum toxin products are not interchangeable
Because there are currently multiple marketed botulinum toxin products with different dose to potency ratios, there is a concern about medication errors such as overdosing based on incorrect unit administration from interchanging the products. It is important to understand that **BOTOX®/BOTOX® Cosmetic** (onabotulinumtoxinA, Allergan, Inc.), MYOBLOC® (rimabotulinumtoxinB, Solstice), and DYSPORT™ (abobotulinumtoxinA, Ipsen Biopharm Limited/Medicis Corporation) are unique biologic products that are **not interchangeable** with each other. Therefore, the Units of biological activity of **BOTOX®/BOTOX® Cosmetic** cannot be compared to nor converted into units of any other botulinum toxin product. Additionally, **BOTOX®/BOTOX® Cosmetic** has multiple indications which all require specific dosing. Caution should be taken to ensure that the dosing, dilution, injection volume, and injection pattern are appropriate for the product.

Information on the lack of interchangeability between the botulinum toxin products (WARNINGS: Lack of Interchangeability between Botulinum Toxin Products) is provided in the enclosed copy of the FDA-approved **BOTOX®/BOTOX® Cosmetic** Full Prescribing Information as well as below.

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX®/BOTOX® Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX®/BOTOX® Cosmetic cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method (see DESCRIPTION).

Other changes have been made in the CLINICAL PHARMACOLOGY and OVERDOSAGE sections of the prescribing information.

To help differentiate these products and address the concern for medication errors and non-interchangeability of the multiple botulinum toxin products, Allergan, in conjunction with the Food and Drug Administration and the United States Adopted Names Council, has adopted the established name onabotulinumtoxinA that is specific to **BOTOX®** and **BOTOX® Cosmetic.** This uniquely established nonproprietary name replaces the previous common terms Botulinum Toxin Type A and differs from the established name for DYSPORT™ (abobotulinumtoxinA). Nothing about Allergan's unique **BOTOX®** and **BOTOX® Cosmetic** products, its formulation or approved uses have been changed in conjunction with the change in nonproprietary name. The change in the nonproprietary name for **BOTOX®** and **BOTOX® Cosmetic** will enable continued tracking of product for patient safety purposes and addresses the challenges healthcare practitioners may face in distinguishing information, long associated with **BOTOX®** and **BOTOX® Cosmetic**, with that of other toxin products.

Risk of possible spread of botulinum toxin

Information on the spread of toxin effect (Boxed Warning and Warnings: Spread of Toxin Effect, Pre-existing Neuromuscular Disorders, Dysphagia and Breathing Difficulties in the Treatment of Cervical Dystonia; Precautions: Information for Patients) is provided in the enclosed copy of the FDA-approved **BOTOX®/BOTOX® Cosmetic** Full Prescribing Information as well as below.

DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of **BOTOX®/BOTOX® Cosmetic** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of toxin effect have occurred at doses comparable to those used to treat cervical dystonia and at lower doses.

Spread of Toxin Effect

Postmarketing safety data from **BOTOX®/BOTOX® Cosmetic** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and

may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX®/BOTOX® Cosmetic** at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX®** for blepharospasm at the recommended dose (30 Units and below) or for strabismus at the labeled doses have been reported.

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX®/BOTOX® Cosmetic** (see **ADVERSE REACTIONS**).

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX®** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved (see **WARNINGS**).

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post marketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin (see **WARNINGS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY**).

Information for Patients:
The physician should provide a copy of the FDA-Approved Patient Medication Guide and review the contents with the patient. Patients should be advised to inform their doctor or pharmacist if

they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens.

Patients should be counseled that if loss of strength, muscle weakness, or impaired vision occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Adverse event information may be reported directly to Allergan Inc. by phone to 800-433-8871, by facsimile to 714-246-5295 or by email to IR-Pharmacovigilance@allergan.com. In addition, adverse event reports may also be reported to the FDA MedWatch Reporting System by the following methods:

- Online at www.fda.gov/medwatch/report.htm
- Phone at 1-800-FDA-1088
- Fax at 1-800-FDA-0718, using the MedWatch Form 3500 (available at www.fda.gov/medwatch/getforms.htm)
- Mail, using the postage-paid MedWatch Form 3500 to:
  MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787

Please carefully review this information and the revised prescribing information. If you have any questions about this information or the safe and effective use of **BOTOX®/BOTOX® Cosmetic** please contact Allergan at 1- 800-433-8871 or via facsimile at 1-714-246-4971 or email at http://www.allergan.com/contact and we will be glad to assist you.

Sincerely,

Mitchell Brin, MD

Mitchell F. Brin, M.D.
Senior Vice President, Global Drug Development
Chief Scientific Officer, BOTOX®

Enclosures: **BOTOX®/BOTOX® Cosmetic** Medication Guide, **BOTOX®** USPI, **BOTOX® Cosmetic** PI

APPENDIX 3: Second Dear Healthcare Provider Letter

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Provider:

Allergan, Inc. would like to inform you that the FDA has approved **BOTOX®** (onabotulinumtoxinA) for the prophylaxis of headaches in adults with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer). This letter provides important prescribing information, including safety and efficacy for this new indication, and also highlights relevant safety information on the use of **BOTOX®**.

The recommended dosing regimen for treating chronic migraine is 155 Units administered intramuscularly, as 0.1 mL (5 Unit) injections per site divided across 7 head/neck muscles, repeated every 12 weeks. Allergan will make training available to physicians regarding appropriate patient selection and proper injection of **BOTOX®** for chronic migraine.

Botulinum toxin products are not interchangeable
Because there are currently multiple marketed botulinum toxin products with different dose to potency ratios, there is a concern about medication errors such as overdosing based on incorrect unit administration from interchanging the products. It is important to understand that **BOTOX®** (onabotulinumtoxinA, Allergan, Inc.), *Myobloc®* (rimabotulinumtoxinB, Solstice), and *Dysport®* (abobotulinumtoxinA, Ipsen Biopharm Limited/Medicis Corporation) are unique biologic products that are **not interchangeable** with each other, and do not all have the same FDA-approved indications. The units of biological activity of **BOTOX®** cannot be compared to nor converted into units of any other botulinum toxin product. Additionally, **BOTOX®** has multiple indications which all require specific dosing. Caution should be taken to ensure that the dosing, dilution, injection volume, and injection pattern are appropriate for the product.

Information on the lack of interchangeability between the botulinum toxin products is provided in the enclosed copy of the FDA-approved **BOTOX®** Full Prescribing Information as well as below.

Lack of Interchangeability between Botulinum Toxin Products
The potency units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Risk of possible spread of botulinum toxin
Information on the spread of toxin effect for the general use of **BOTOX®** (Boxed Warning, Warnings and Precautions: Spread of Toxin Effect, Pre-existing Neuromuscular Disorders; and Patient Counseling Information) is provided in the enclosed copy of the FDA-approved **BOTOX®** Full Prescribing Information as well as below.

DISTANT SPREAD OF TOXIN EFFECT
Postmarketing reports indicate that the effects of **BOTOX®** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

Spread of Toxin Effect
Postmarketing safety data from **BOTOX®** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX®/BOTOX® Cosmetic** at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX®** for blepharospasm at the recommended dose (30 Units and below), strabismus, or for chronic migraine at the labeled doses have been reported.

Patient Counselling Information
You are advised to discuss the risks associated with **BOTOX®** therapy outlined in the enclosed Medication Guide with patients and caregivers. In addition, please share the Medication Guide and this Dear Healthcare Provider Letter with anyone in your practice who is involved in the preparation, prescribing and/or injection of **BOTOX®**.

Per FDA regulations, a copy of the Medication Guide must be distributed directly to each patient every time he/she receives a BOTOX® injection. Copies of the **BOTOX®** Medication Guide are enclosed and if you wish to obtain additional copies of the Medication Guide for distribution to your patients please call 1-800-433-8871 or print copies directly from our Web sites (www.botoxmedical.com or www.botoxcosmetic.com). A copy of the Medication Guide will also be present in every carton of **BOTOX®**.

Adverse event information may be reported directly to Allergan Inc. by phone to 1-800-433-8871, by facsimile to 1-714-246-5295 or by email to IR-Pharmacovigilance@allergan.com. In addition, adverse event reports may also be reported to the FDA MedWatch Reporting System by the following methods:

- Online at www.fda.gov/medwatch/report.htm
- Phone at 1-800-FDA-1088
- Fax at 1-800-FDA-0718, using the MedWatch Form 3500 (available at www.fda.gov/medwatch/getforms.htm)
- Mail, using the postage-paid MedWatch Form 3500 to:
  MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787

Please carefully review this information and the revised prescribing information. If you have any questions about this information or the safe and effective use of **BOTOX®** please contact Allergan at 1- 800-433-8871 or via facsimile at 1-714-246-4971 or email at http://www.allergan.com/contact and we will be glad to assist you.

Sincerely,

Mitchell Brin, MD

Mitchell F. Brin, M.D.
Senior Vice President, Global Drug Development
Chief Scientific Officer, BOTOX®

Enclosures: **BOTOX®/BOTOX® Cosmetic** Medication Guide, **BOTOX®** USPI

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 30, 2010
To:	Russell Katz, MD, Director Division of Neurology Products (DNP)
Thru:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK) Claudia B Karwoski 8/30/10
From:	BOTOX Review Team Marcia Britt, PhD., Health Education Reviewer (DRISK) Kendra Worthy, Pharm.D., Drug Risk Management Analyst (DRISK) Suzanne Robottom, Pharm.D., Team Leader (DRISK)
Subject:	Modification of Botox REMS in response to supplemental BLA for proposed migraine indication
Drug Name(s):	Botox® (onabotulinumtoxinA)
Submission Number:	5215
Application Type/Number:	BLA 103000
Applicant/sponsor:	Allergan, Inc.
OSE RCM #:	2009-2376

1 INTRODUCTION AND BACKGROUND

This review follows a request from the Division of Neurology Products (DNP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to review and comment on a modified Risk Evaluation and Mitigation Strategy (REMS) for Botox (onabotulinumtoxinA) for the proposed indication of prophylaxis of headaches in adults with chronic migraine. Botox is currently approved for cervical dystonia in adults, severe primary axillary hyperhidrosis, the treatment of strabismus, blepharospasm associated with dystonia, and upper limb spasticity.

The REMS for Botox was approved on July 31, 2009, to address the risk(s) of medication errors related to the lack of interchangeability of Botox units and the spread of toxin effect beyond the injection site. The REMS consists of a Medication Guide, Communication Plan (Dear Healthcare Provider Letter disseminated within 6 weeks of REMS approval), and Timetable for Submission of Assessments (18 months, 3 years, and 7 years) of the REMS. Similar REMS are approved for all currently marketed botulinum toxin products to address these risks as they affect the entire class.

The modified REMS to include the indication for upper limb spasticity was approved March 9, 2010.

Allergan submitted another REMS modification September 29, 2009, with the proposed indication of prophylaxis of headaches in adults with chronic migraine. An assessment was not submitted with the REMS, citing it was too soon to assess the REMS at that time. This proposed REMS modification by Allergan is the subject of this review.

The Medication Guide review was completed August 24, 2010.

2 MATERIAL REVIEWED

The following document(s) were reviewed:

- Allergan's revised REMS supporting document July 14, 2010
- Allergan's proposed REMS modification submission with the addition of chronic migraine prophylaxis submitted July 6, 2010
- Allergan's BOTOX REMS approved on March 9, 2010 with the following components:
  - Supporting Document
  - Dear Healthcare Provider Letter
- www.botoxmedical.com

3 PROPOSED MODIFIED REMS

The addition of the prophylaxis of headaches in adults with chronic migraine indication to the Botox label has impact on the approved REMS warranting changes to the text of the Medication Guide and modifying the communication plan to include a revised Dear Healthcare Provider Letter (DHCPL) distributed to additional healthcare provider specialties not previously targeted. Headache specialists, neurologists, and pain management specialists will receive the DHCPL within 6 weeks of REMS approval. Allergan will use professional societies such as the American Headache Society, the American Academy of Neurology, and the American Board of Pain Medicine as sources for obtaining information on the appropriate prescribers.

The REMS supporting document states [redacted] (b) (4)

4 DISCUSSION

Upon initial REMS discussions, DNP expressed concern regarding physicians' understanding of proper technique in administering Botox for migraine prophylaxis. In particular, this new indication expands the Botox prescriber base and introduces Botox to physicians who have not previously injected it. The administration for migraine prophylaxis involves bilateral injections into at least seven muscle areas. Proper injection technique is necessary primarily for efficacy but does impact the risk of spread of toxin. [redacted] (b) (4)

DRISK explored Allergan's non-REMS educational components for the currently approved indications and present the materials to DNP. Allergan has an extensive multimedia approach for residents/fellows, new injectors, and experienced injectors. They offer preceptorships with expert injectors, hands-on, and virtual simulators to build injections skills. They also conduct outreach at numerous meetings and workshops.

The two REMS options presented to DNP were:

1. Maintain current REMS approach with modifications to the MG and communication plan (distribute the DHCPL to additional specialties) to accommodate for this new indication.

2. [redacted] (b) (4)

[redacted] (b) (4)

Therefore, the team agreed that Option #1, the existing REMS format with the Dear Healthcare Provider Letter, is sufficient [redacted] (b) (4) at this time.

DRISK provided brief interim comments on the REMS to Allergan on June 22, 2010. These comments conveyed that the REMS modification should include a communication plan with a revised target audience, a Dear Healthcare Provider Letter with information regarding the expanded indication, and a (b) (4) DRISK and DNP also requested that Allergan prepare to discuss their plan on how they propose to educate HCPs (outside of the REMS) about proper injection.

5 ASSESSMENT OF THE REMS

The Timetable for Submission of Assessments of the REMS should remain consistent with the timetable in the original REMS approval. We do note that the assessment methodology will need to be revised to include the additional specialties included in the modified REMS communication plan.

Information needed for assessment should be addressed in the REMS approval letter and discussed in the REMS supporting document. The REMS assessments will include the following information:

a. Results of a survey of patients' understanding of the serious risks of Botox/Botox Cosmetic.

b. Results of a survey of prescribers' understanding of the serious risks of Botox/Botox Cosmetic.

c. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

d. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.

e. An assessment of use data, including:

- extent of use (denominator estimates)
- number of patients by age

f. A summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection with Botox/Botox Cosmetic.

g. A summary of reports of all medication errors involving interchangeability of Botox/Botox Cosmetic units with those of other licensed botulinum toxin products.

6 CONCLUSION

The Division of Risk Management and the OSE Botox Review Team find the modified REMS for Botox (onabotulinumtoxinA) acceptable once the sponsor accepts the recommended changes in the REMS document and DHCPL. Both are included in Appendices A-B, respectively.

Comments to Allergan:

1. See Appendix A for the tracked changes version of the Proposed.
2. See Appendix B for the tracked changes version of the DHCP letter to be distributed within 6 weeks of approval of the modified REMS.
3. FDA has determined that your specific plan to distribute the MG is more appropriate for the REMS Supporting Document.
4. The assessment methodology in your REMS Supporting Document will need to be revised to include the additional specialties included in the modified REMS communication plan.

7 pages immediately following withheld - b(4)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 21, 2010
To:	Russell Katz, M.D., Director **Division of Neurology Products (DNP)**
Through:	Mary Willy, PhD, Deputy Director 6/21/10 **Division of Risk Management (DRISK)**
From:	Brian Gordon, M.A., Social Science Reviewer 6/21/2010 **Division of Risk Management (DRISK)**
Subject:	Review of proposed REMS assessment survey instruments and methodologies
Drug Name(s):	Botox/Botox Cosmetic (onabotulinumtoxinA)
Application Type/Number:	BLA 103000
Applicant/sponsor:	Allergan, Inc.
OSE RCM #:	2010-1176

1 INTRODUCTION

This review is in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the proposed methodologies and survey instruments that will be used to assess the effectiveness of the Risk Evaluation and Mitigation Strategies (REMS) for Botox/Botox Cosmetic (onabotulinumtoxinA). The REMS includes a Medication Guide and Communication Plan. Please send these comments to the Applicant, but let us know if you would like a meeting to discuss these comments before sending to the Applicant.

2 MATERIAL REVIEWED

- Patient and caregiver survey protocol submitted on February 26, 2010
- Prescriber survey protocol submitted on February 26, 2010
- Botox/ Botox Cosmetic REMS approval letter dated July 31, 2009; REMS modification dated March 9, 2010 with original 18 month assessment requirement
- Botox/Botox Cosmetic Medication Guide dated March 2010

3 DISCUSSION AND RECOMMENDATIONS

We have the following comments and recommendations for the Applicant:

Patient survey:

- Clarify if healthcare providers who recruit patients for the first survey are eligible to recruit patients in future surveys
- Clarify if healthcare providers who recruit patients are compensated
- Reword question #4 to the following:
    - Which of the following are possible serious side effects of Botox or Botox Cosmetic? (Select all that apply)
        - Trouble breathing or swallowing
        - Trouble speaking
        - Trouble sleeping
        - Blurred or double vision
        - Liver failure
        - I don't know
- Add a question that asks what a patient should do if they experience a serious side effect. For example:
    - If you have trouble breathing, swallowing or speaking after an injection of Botox or Botox Cosmetic you should
        - Rest and see if the problem goes away
        - Call your doctor or get medical help right away
        - Wait two days then call your doctor

        - I don't know
- Re-word question #7 to the following:
    - After a treatment with Botox or Botox Cosmetic, problems breathing or swallowing can happen … (Read List) (Check all that apply)
        - Within hours of the injection
        - Within days of the injection
        - Within weeks of the injection
        - I don't know
- Add a question that asks if Botox and Botox Cosmetic can cause serious side effects which can be life threatening. For example:
    - Botox and Botox Cosmetic may cause serious side effects that can be life threatening. True/False/I don't know

Prescriber survey

- Move question #4 and #5 to the end of the survey
- Split question #6 into multiple questions. For example:
    - The units of Botox/Botox Cosmetic are specific to Botox/Botox Cosmetic and cannot be used for other botulinum toxin products. True/False/I don't know
    - 100 units of Botox/Botox Cosmetic are the same as 100 units of other botulinum toxins. True/False/ I don't know
- Combine question 8a, 8b and 8c into one multiple choice question. For example:
    - Botox/Botox Cosmetic should be used with caution in patients … (select all that apply)
        - with Lambert-Eaton syndrome
        - with pre-existing swallowing or breathing difficulties
        - with diabetes
        - being treated with aminoglycosides or other agents interfering with neuromuscular transmission
        - I don't know
- Change the answer choices in question 9 from Agree/Disagree/Don't know to True/False/Don't know
- Re-word questions #10 to the following:
    - After a treatment with Botox or Botox Cosmetic, muscle weakness, blurred vision and problems breathing or swallowing can happen … (Read List) (Check all that apply)
        - Within hours of the injection
        - Within days of the injection
        - Within weeks of the injection
        - I don't know

- Add a question that asks if Botox and Botox Cosmetic can cause serious side effects which can be life threatening. For example:
    - Botox and Botox Cosmetic may cause serious side effects that can be life threatening. True/False/I don't know
- Add questions that ask if the prescriber received and read the Dear Healthcare Provider Letter. For example:
    - Did you receive a Dear Healthcare Provider Letter about Botox/Botox Cosmetic?
        - Yes
        - No
        - I don't know
    - Did you read the Dear Healthcare Provider Letter about Botox/Botox Cosmetic?
        - Yes
        - No
        - I don't know

Please let us know if you have any questions.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: 8/27/10

To: Eric Basting, MD
Deputy Director
Division of Neurology Products (DNP)

From: Quynh-Van Tran, PharmD, BCPP (Professional)
Beth Carr, PharmD (Direct-to-Consumer)
Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications (DDMAC)

Cc: Lana Chen, Regulatory Project Manager, DNP
Andy Haffer, Group Leader, DDMAC
Aline Moukhtara, Group Leader, DDMAC

Subject: DDMAC comments on BOTOX® (botulinum toxin type A) PI for the chronic migraine indication

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Thank you for the opportunity to review the proposed updated PI for Botox for the new chronic migraine indication (dated 8/13/2010).

Please see attached PI with our comments incorporated therein.

28 pages immediately following withheld - b(4) Draft Labeling

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 24, 2010
To:	Russell Katz, MD, Director
	Division of Neurology Products
Through:	Mary Willy, PhD, Deputy Director 8/24/10
	Division of Risk Management (DRISK)
	LaShawn Griffiths, MSHS-PH, BSN, RN
	Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
From:	Steve L. Morin RN, BSN
	Patient Labeling Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide),
Drug Name(s):	Botox Cosmetic (onabotulinumtoxin A) for Injection
Application Type/Number:	BLA 103000
Submission Number:	S-5215
Applicant/sponsor:	Allergan Inc.
OSE RCM #:	2009-2376

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Botox Cosmetic (onabotulinumtoxin A) for Injection.

Botox Cosmetics was initially approved in 1989, supplement number 5215 is being submitted for an added indication (b) (4) of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours or longer).

Please let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will provided to DNP under separate cover.

2 MATERIAL REVIEWED

- Draft Botox Cosmetic (onabotulinumtoxin A) for Injection Prescribing Information (PI) submitted September 29, 2009 revised by the Review Division throughout the current review cycle and provided to DRISK on August 16, 2010.
- Draft Botox Cosmetic (onabotulinumtoxin A) for Injection Medication Guide (MG) submitted on September 29, 2009 and provided to DRISK on August 16, 2010.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

10 pages immeidately following withheld - b(4) Draft Labeling

CC List:

DNP
Russell Katz
Eric Basting
Lena Chen
Alice Hughes
Kelly Summers

OSE
Mary Willy
Mary Dempsey
LaShawn Griffiths
Laurie Kelley

DDMAC
Wayne Amchin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

OTHER REVIEW(S)

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

BLA:	103000/5215
Drug:	OnabotulinumtoxinA (Botox)
Indication:	Prophylaxis of chronic migraine
Sponsor:	Allergan
Submission Date:	9/28/2009
Review Date:	9/20/2010
Reviewer:	Sally Usdin Yasuda, Safety Team Leader Neurology Drug Products, HFD-120

S Yasuda 9/20/10

1. Background

Botox (onabotulinumtoxinA) has been approved for treatment of strabismus and for blepharospasm since 1989, and has additional indications for treatment of cervical dystonia, glabellar lines, severe axillary hyperhidrosis, and treatment of upper limb spasticity. Among those indications, the highest total single recommended dose is 360 units distributed across muscles of the wrist, finger, and elbow for treatment of upper limb spasticity in adults. The indication that may be most relevant to chronic migraine because of the site of administration is cervical dystonia for which the highest total single dose is 300 units. Among the safety issues of concern is distant spread of toxin effect after administration of botulinum toxin products, including Botox, was the focus of a change to the Botox label that was approved July 31, 2009.

This memorandum primarily summarizes the findings of Dr. Graham's primary safety review of the Botox BLA for prophylaxis of chronic migraine in adults. Among the primary issues addressed by Dr. Graham are exposure, dosing regimen, distant spread of toxin effect, and exacerbation of migraine. Please refer to Dr. Graham's review for more detail.

2. Summary of Findings from the Safety Review

2.1 Sources of Data

The clinical data evaluated in the safety review are primarily from studies submitted as part of the BLA. This includes 9 placebo controlled clinical trials in episodic migraine (EM) , chronic tension-type headache, chronic daily headache (CDH), and chronic migraine (CM). The major focus of Dr. Graham's review is on data from the two Phase 3 studies (Protocols 79 and 80). The remainder of the studies were Phase 2 studies. These include Protocol 039 in a chronic daily headache (CDH) population that used a different dose and injection scheme that brackets the dose range used in the Phase 3 trial, as well as Protocol 38 that is a flexible dose Phase 2 trial in CDH. In addition, Dr. Graham identified a placebo controlled study (027) (b) (4) that she has included in the safety review, as it is relevant for a dose-response consideration.

Pooled safety analyses include the Phase 3 chronic migraine studies, the pooled CM/CDH studies, and the pooled CM/CDH/EM studies. Dr. Graham considers the studies by dosing scheme in order to better characterize the adverse event profile.

Exposure – The patient population in the pooled CM trials was approximately 88% female and 90% Caucasian. The mean age (range) was 41 years (18-65), with approximately 43% < 40 y.o., 57% ≥ 40 y.o. and only approximately 4% ≥ 60 y.o. Patients previously treated with botulinum toxin therapy of any serotype or immunized to any botulinum toxin serotype were excluded from the CM trials.

Trials 079 and 080 were multicenter trials with a 24-week, double blind, randomized, placebo-controlled, parallel-group phase followed by a 32-week open-label extension phase. In the double-blind phase, patients received either two treatments of BOTOX® or 2 treatments of placebo. In the open-label phase, patients received 3 treatments with BOTOX®. The minimum total BOTOX dose was 155 units injected at 31 protocol-specified sites for seven muscle groups bilaterally, and an additional 49 units could be injected in three of the seven muscle groups.

ICH guidelines recommend that 1500 patients should be treated overall in a drug development program, 300-600 for 6 months, and 100 for at least 1 year at the dose or dose range believed to be efficacious. In the overall integrated safety database, there were 3235 patients with CM, CDH, or EM who received at least one dose of BOTOX ranging from a single dose of 6 units to 260 units. In the Phase 3 trials in CM, there were a total of 1300 patients with at least 1 treatment with BOTOX, 1092 with at least 3 treatment cycles, and 518 with 5 treatment cycles (with 12 weeks between doses). Dr. Graham notes, however, that only 27 of the 518 patients with multiple treatment cycles received ≥4 consecutive cycles of 195 units of BOTOX. Thus, there is limited experience with long-term CM treatment above 155 units. (b) (4)

(b) (4)

Capture of Adverse Events – Adverse event data were collected at clinic visits between baseline and study exit. Vital signs and laboratory data were collected at baseline and upon exit from the trial. No ECG data were collected. According to protocols 079 and 080, adverse events were monitored following the first injection and at each post-baseline visit by having the investigator query for adverse events by asking a general question, followed by directed questioning and examination as appropriate. The Sponsor did not use a checklist of specific adverse events was not used and some events might have been missed without such directed questioning.

2.3 Significant Safety Findings

2.3.1 Deaths

There was one death among the 4076 clinical trial subjects from the trials included in the sBLA. This was a 60 y.o. placebo treated subject in Phase 2 trial 038 who suffered a syncopal episode and stopped breathing 54 days after the third treatment with placebo.

2.3.2 Nonfatal Serious Adverse Events (SAEs)

Overview of SAEs in the pooled safety population – Dr. Graham reports that that 4.2% (136/3235) of subjects who received BOTOX in the integrated safety database had a nonfatal serious adverse event (SAE). In the pooled double blind placebo controlled (DBPC) safety database, 3.3% (83/2532) of subjects who received Botox had a SAE compared with 2.3% (36/1544) of placebo-treated subjects. In those studies, the System Organ Class (SOC) groupings with the most SAEs after exposure to Botox (n=2532) and greater than placebo were Nervous system disorders (0.7% vs 0.3%), Gastrointestinal disorders (.4% vs 0.2%), Neoplasms (0.4% vs 0.2%), Hepatobiliary disorders (0.2% vs 0.1%), and Psychiatric Disorders (0.2% vs 0%). Dr. Graham notes that only reports coded to Migraine, Headache, and Depression/Major Depression were reported more frequently for Botox than for placebo. Four of the 5 migraine SAE reports in the Botox-treated subjects in the placebo-controlled trials occurred in the pooled Phase 3 CM studies. One of those events was considered by the investigator to be possibly treatment related, and Dr. Graham has included that narrative in her review. This was a 44 year old patient who reported intractable migraine beginning 7 days after her first treatment with Botox (165 units) in Study 080. It is not possible to determine whether this is related to treatment.

SAEs in Pooled Phase 3 trials in CM - Dr. Graham reports that during the DBPC portion of the Phase 3 trials in CM, 4.8% (33/687) of Botox-treated subjects and 2.3% (16/692) of placebo-treated subjects reported a SAE. These were consistent with the findings in the overall DBPC database. The imbalance

occurred in Neoplasms (1% vs 0.3%), Nervous system disorders (1.3% vs 0.3%) that included migraine (0.6% vs 0.1%), and Infections & infestations (1% vs 0.7%). In that latter SOC there were 2 reports of pneumonia (0.3%) in the Botox-treated group and 1 (0.1%) in the placebo-treated group (further considered under Dropouts). During the open label period of the phase 3 trials for SAEs reported by 2 or more patients, there was no SOC with SAEs reported more frequently than in the double-blind period.

Overall for patients exposed to Botox in the pooled Phase 3 CM trials (n=1300), 5.8% (75/1300) had a SAE. Those that were reported by 2 or more patients were migraine (n=8), uterine leiomyoma (n=5), pneumonia (n=4), non-cardiac chest pain (n=4), breast cancer (n=3), and small intestinal obstruction, intervertebral disc protrusion, basal cell carcinoma, squamous cell carcinoma, and depression that each occurred in 2 patients.

Human carcinogenicity is discussed in section 2.3.10 of this memo.

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

2.3.3 Dropouts and/or Discontinuations

Dr. Graham has considered dropouts and discontinuations from the Pooled Phase 3 CM Trials and from Protocol 039 in CDH. She states that the design of the CRFs for the Phase 2 trials did not capture the adverse event leading to discontinuation.

Overall, in the pooled Phase 3 trials, approximately 12% of subjects randomized to Botox and approximately 10% of subjects randomized to placebo in the DBPC period discontinued prior to week 24 during the DBPC period, and 25.4% of Botox/Botox subjects and 29.3% of placebo/Botox subjects discontinued the entire study. The most common causes for discontinuation were personal reasons, adverse events, and other. Dr. Graham reports that the most frequent reason for discontinuation listed as "other" was lack of efficacy. She notes that the dose of BOTOX received by patients discontinuing BOTOX was 155 units for all treatment cycles in about half of the cases, with the rest receiving between 155 and 190 units.

In the pooled Phase 3 trials, 3.8% (26/687) of Botox treated subjects and 1.2% (8/692) placebo-treated subjects had adverse events leading to discontinuation. In the DBPC portion of the studies, in the Botox group these events that occurred in at least 2 subjects included neck pain (4 subjects), muscular weakness, headache, and migraine (each in 3 subjects), eyelid ptosis and breast cancer (each in 2 subjects). These did not result in discontinuations in the placebo group except for headache and migraine that were reported in one patient each. In the open-label exposure, adverse events leading to dropout in at least 2

subjects were muscle spasm and joint stiffness each occurring in 2 subjects in the group originally randomized to Botox, and neck pain (4 subjects), muscular weakness (3 subjects), and muscle spasms, muscle tightness, musculoskeletal pain, headache, and migraine (each occurring in 2 subjects) in the group that received Botox in the open label after receiving placebo in the DBPC portion. As Dr. Graham notes, pain (including neck pain for some indications) and muscular weakness are well-documented adverse events associated with other indications for Botox.

Among the discontinuations due to adverse events in 1 subject each were worsening of depression, depression, tachycardia, and cerebral infarction. Dr. Graham has provided the narratives for these. I agree with her assessment that these cases could be reasonably attributed to pre-existing conditions. There was also 1 discontinuation due to bilateral pneumonia that is discussed below.

The case of bilateral pneumonia occurred in a 28 y.o. subject who received her first dose of 155 units of Botox on (b) (6) and was hospitalized 14 days later with pneumonia after failing outpatient therapy for bronchitis. She recovered and was discharged from the hospital on (b) (6) According to the narrative, the patient's symptoms started six weeks prior to hospitalization and consisted of flu-like symptoms with fever of 103 to 104 degrees, chills and generalized malaise. She was diagnosed by her primary care physician as having bronchitis and was treated with prednisone and albuterol, but the patient's symptoms did not improve. According to the narrative "She developed right-sided pleuritic chest pain about a week later and went to the urgent care center, where she was diagnosed with pneumonia and started on Levaquin for five days and was also given Toradol@ once". Dr. Graham notes the discrepancy in the narrative regarding the time course of events. According to the narrative, the Levaquin was started on (b) (6) The patient also had a history of gastroesophageal reflux disease since 2000, animal allergies for which she used albuterol prn since 1996, and "minimal wheezing with left lower base cleared with cough" on (b) (6) that was considered resolved. It appears that the symptoms began prior to administration of Botox. However, the symptoms worsened after administration of Botox. The role of Botox in exacerbating the event is unknown, although I agree with Dr. Graham that an action of Botox on respiratory muscles could be involved.

There was also 1 discontinuation reportedly due to tightness in the back of the neck in a 49 y.o. patient (10038-10103) 6 days after administration of 170 units of Botox. The patient also experienced dysphagia at the same time, and lasting for 18 days, but this was apparently not considered to be the cause of the discontinuation. Both were described as moderate in severity, required no treatment and resolved without sequelae. In addition there was one case of dyspnea in a 54 y.o. patient (10015-50282) who reportedly discontinued due to "non-cardiac chest pain". This patient had a history of degenerative joint disease and herniated cervical disc treated with tizanidine on the day she received her

first treatment with Botox 185 U in Study 080 in June 2006. Two days after injection she complained of intermittent moderate shortness of breath and nasal congestion; she was not treated for shortness of breath, and that resolved 15 days later. She had 2 positive rechallenges in September 2006 and December 2006 in which shortness of breath occurred 2 days after the injection. The event after the 3rd treatment was described as moderate shortness of breath along with moderate non-cardiac chest tightness. Although the discontinuation was ascribed to "noncardiac chest pain", it appears related to the shortness of breath. Both the dysphagia and the dyspnea events could be reasonably due to Botox administration.

Dr. Graham has reviewed discontinuations from the Phase 2 fixed dose trial in CDH, protocol 039. She notes that the discontinuation rate reported by the Sponsor for adverse events for the 150 unit (7.7%) and 225 unit (5.9%) Botox dosing group exceed that in the pooled phase 3 trials. She also finds, based on her review, that there were actually 13/130 patients (10%) in the 150 unit group who discontinued due to adverse events rather than 10 as reported by the Sponsor. According to Dr. Graham's table 19, among the adverse events leading to discontinuation are dysphagia, ptosis, and facial numbness, and a variety of other events that I agree are consistent with the overall adverse event profile. Dr. Graham also reports a case of discontinuation for hypoesthesia (numbness and tingling from shoulder to toes) 48 days after an injection of Botox (225 units) in a patient who had a history of back pain for which she received tramadol. She was incidentally found to have a "low B12" and her symptoms are consistent with that finding. She started taking vitamin B12 and by approximately 4 months later, the symptoms had resolved although she noted bilateral numbness in legs and feet. It is not clear how this is related to Botox. Dr. Graham also describes a case of discontinuation in a patient (3071-2426) with migratory polyarthralgias and lower extremity weakness within 2 weeks of receiving 150 units of Botox, and with no clear causes for this event.

I agree with Dr. Graham's conclusion that discontinuations were largely related to adverse events commonly associated with botulinum toxin injections for other indications and attributable to the pharmacological activity. The role of Botox in several serious cases (including the serious cases in 039 described above and the case of bilateral pneumonia) is unknown.

2.3.4 Significant Adverse Events and Submission Specific Primary Safety Concerns

Adverse events of special interest identified by Dr. Graham are spread of toxin effect, falls, exacerbation of migraine, and lack of efficacy. I will summarize her findings here. Please refer to her review for a more detailed discussion.

Spread of Toxin Effect– Dr. Graham notes that the sponsor conducted an analysis of the entire safety database using a set of MedDRA codes intended to

signal distant spread of toxin (effect). These terms were identical to the terms used in the analyses by the manufacturers of all botulinum toxin products reviewed in 2009, with the exception of the specific term "muscle paresis" that was included in the earlier set, and "extraocular muscle paresis" that was not.

Dr. Graham reports that of the 4076 subjects included in the analysis, 34/1544 (2.2%) placebo-treated subjects and 658/2532 (25.9%) of Botox treated subject had an adverse event report corresponding to a least one of the spread of toxin effect terms. Ten of the 17 terms with adverse event reports were interpreted by the Sponsor as associated with local adverse events. These included eyelid ptosis, diplopia, vision blurred, extraocular muscle paresis, facial palsy, facial paresis, dysarthria, dysphagia, dry mouth, and hypotonia. I agree with that assessment.

Dr. Graham has reviewed the reports that appeared inconsistent with local spread. These terms were dyspnea, aspiration pneumonia, respiratory failure, muscular weakness, bradycardia, urinary retention, and constipation. Dr. Graham reports that the respiratory failure and aspiration pneumonia occurred in one patient secondary to a carotid artery occlusion and cerebral infarction. The case of urinary retention was confounded by medical history and concomitant use of an anticholinergic drug. The case of bradycardia occurred 76 days after a Botox dose. Dyspnea was reported in 10 subjects treated with Botox and 2 with placebo (1 of the 10 had a positive rechallenge and that case is described under discontinuations in this memo; the other 9 did not have a recurrence after repeat dosing). As Dr. Graham notes, dyspnea is included in the current PI for Botox as being associated with treatment of cervical dystonia, and I agree with her that since there is overlap between the muscle groups injected for treatment of cervical dystonia and CM, it is not surprising that there are reports of dyspnea in this analysis. Dr. Graham reports that there were 228 reports of muscular weakness in patients receiving Botox (9%) and 7 in placebo (0.5%). She also notes that only 5 of the reports in Botox treated subjects involved muscle weakness outside the muscles injected. She considers only 1 of those potentially related to Botox treatment, and that case (3071-2426) has been described under discontinuations. Twelve patients on Botox (0.5%) and 2 on placebo (0.1%) reported constipation. The average dose in these cases was 114 units (range 9-204 units) and the events occurred on average 42 days after the dose (1-98 days). All reports occurred without other events potentially associated with spread of toxin effect. No positive rechallenge was reported. Dr. Graham states that the events were confounded by a medical history or with concurrent use of medications associated with bowel symptoms including constipation. Given the known pharmacology of the botulinum toxins and effects observed in other indications with similar sites of administration, I agree with Dr. Graham's assessment that in general none of these events are unexpected.

Falls – Dr. Graham notes that during the open label exposure period of the pooled Phase 3 trials, there was an excess of falls reported in the chronically

treated group (up to 5 treatment cycles) compared to the group that received placebo for 2 of the 5 treatment cycles. She notes that falls could be an indicator of Botox-related effects including visual effects or muscular weakness. Dr. Graham has reviewed the individual reports of fall in the Phase 3 trials and examined adverse events secondary to "fall" in Trial 039, and these are presented in Tables 22 and 23 in her review. I agree with her assessment that the available data do not suggest an increase in falls related to Botox treatment.

Exacerbation of Migraine and Lack of Efficacy– Migraine is among the most common adverse events in the DBPC database of the pooled Phase 3 trials, occurring in 3.8% of the Botox treated subjects and 2.6% of the placebo treated subjects. Dr. Graham has explored the adverse event of exacerbation of migraine after noting the number of subjects hospitalized or discontinuing treatment because of migraine headache. She reports that in the Phase 3 trials there were 15 reports of migraine in the Botox-treated group and 2 (0.3%) in the placebo group. Nine of the 15 Botox reports (1.3% of the 687 subjects exposed to Botox) had events that occurred during the double-blind phase, and 6 of those occurred within the first week of treatment (as did 4 of the 6 cases that occurred in the open label period. The remainder occurred within 7 to 9 weeks after treatment. I agree that there are too few cases in the placebo group to characterize the time course in the absence of Botox exposure.

According to Dr. Graham, 76 subjects discontinued treatment due to lack of efficacy, headache, or migraine. She finds that in the double blind period 16/687 (2.3%) of patients randomized to Botox discontinued due to "Drug ineffective", headache, or migraine and 6/692 (0.9%) of placebo-treated subjects discontinued for those reasons. In the open label period, she finds that 20 patients (2.9%) in the Botox/Botox group discontinued due to drug ineffective, and 34 patients (4.9%) who received placebo in the double blind period and Botox in the open label period discontinued due to drug ineffective or due to migraine while receiving Botox.

I acknowledge the excess in the adverse event of migraine as well as discontinuations for migraine or lack of efficacy in the Botox-treated group compared to the placebo-treated group in the Phase 3 trials. I also note the severity of these cases, with 10 of the 15 Botox-treated cases of migraine resulting in hospitalization. However, in a population being treated for chronic migraine, it is very difficult to know whether this is an adverse event due to the treatment. In addition, the subjects are likely to be incompletely blinded due to the nature of the pharmacological effects of Botox, and it is difficult to know what role this might play in perceived events related to headache.

2.3.5 Common Adverse Events

Overall, in the pooled, placebo controlled trials, 429/687 (62.4%) of Botox-treated subjects and 358/692 (51.7%) of placebo treated subjects experienced adverse events. Among the most common adverse events (≥ 2% and greater than

placebo) in the controlled trials were eyelid ptosis (3.5% vs 0.3%), injection site pain (3.3% vs 2%), bronchitis (2.5% vs 1.6%), neck pain (8.7% vs 2.7%), musculoskeletal stiffness (3.6% vs 0.9%), muscular weakness (3.5% vs 0.3%), myalgia (3.1% vs 0.9%), musculoskeletal pain (2.6% vs 1.4%), muscle spasms (1.9% vs 0.9%), headache (4.7% vs 3.2%), migraine (3.8% vs 2.6%), facial paresis (2.2% vs 0%). I note that (b) (4) bronchitis (b) (4) this event was observed in the adult spasticity trials with a frequency of 3% for 251-360 units, 2% for 150-250 units, 0 for less than 150 units, and 1% for placebo, according to the approved label. Other events noted by Dr. Graham that occur at a frequency of less than 1% but greater than placebo include vertigo (3 patients vs 0), dry eye (3 patients vs 0), eyelid edema (3 patients vs 0), dysphagia (5 patients vs 1), cellulitis (3 patients vs 0), eye infection (3 patients vs 0), and jaw pain (5 patients vs 0).

In the open label extension the adverse event profile was generally similar to that observed in the DBPC period. Dr. Graham notes that several events occurred more frequently in the newly exposed group (Placebo/Botox) compared to the group with a longer exposure to Botox. These included influenza-like illness, AST increased, depression, insomnia, and anxiety as well as bronchitis and muscular weakness, muscle tightness, musculoskeletal stiffness, musculoskeletal pain, and myalgia, headache, facial paresis and rash. Dr. Graham suggests that the increased frequency in the newly exposed group could be due to tolerance over time. I agree that tolerance may be an explanation, but this could also be due to dropouts from the Botox group after the DBPC period, with more tolerant subjects remaining in the open label extension. Abdominal pain, fatigue, non-cardiac chest pain, fall, back pain, and hypoesthesia were reported more frequently in the chronically treated patients (Botox/Botox) compared to the placebo/Botox patients, and not seen in the DBPC period. I agree with Dr. Graham's hypothesis that these could reflect adverse events associated with repeated exposure.

Dr. Graham has reviewed the most common adverse events in the Phase 2 Trials 309 and 038 in CDH. These are similar to those observed in the Phase 3 trials. In Study 039 with doses of placebo, 75 units, 150 units, and 225 units of Botox, she finds a dose response relationship for many of these events including muscular weakness, neck rigidity, and blepharoptosis.

2.3.6 Laboratory findings, Vital Signs, and Electrocardiograms (ECGs)
Chemistry and Hematology – As previously mentioned, routine blood sampling for hematology and chemistry were only done at baseline and at trial exit, and in some trials a sample was taken prior to the next injection. Dr. Graham reports no reproducible pattern across the studies. Because most effects of botulinum toxin would be expected to have dissipated at trial exit (12 weeks after the last dose in the DBPC portion of the studies), this approach does not seem very useful. The same approach was used for *vital signs*, and the finding of no notable differences

between treatment groups is not unexpected given the timing of the measurements. Routine ECGs were not included in the protocols in this submission.

2.3.7 Immunogenicity

The Sponsor was to measure neutralizing antibodies using the mouse protection assay for Trials 37, 38, and 39 as well as 509, although based on lack of evidence of the presence of neutralizing antibodies in Trials 37, 38, and 39, the sponsor did not test the samples from 509. There were 496 analyzable samples from Botox-treated subjects. Dr. Graham reports no clearly positive results and 1 inconclusive result. Antibodies were not measured for the Phase 3 trials.

2.3.8 Other Safety Explorations

Dose Dependency for Adverse Events – Dr. Graham has examined in detail the dose and injection schemes in the Phase 3 trials and their basis in the previous trials using different dose and injection schemes. Please refer to her review for details. This history begins with Protocol 005 in EM comparing 0, 25, and 75 units of Botox injected in facial and temporal muscles at 11 sites in 4 muscles (frontal, temporal, corrugator, procerus), progressing to the regimen in 079 and 080 in the present submission. Dr. Graham points out that because of this progression with variability in dosing scheme and injection site, there is no dose response information with regard to number of injections, site of injections, or amount of Botox per injection. She has considered bridging Protocols 79 and 080 to the fixed dose comparison studies, particularly Protocol 039 that had a total dose of 150 units as the middle dose and included a population most closely resembling the population of CM patients. Protocol 039 used 150 units or 225 units in 20 injections, compared to Phase 3 Protocols 079 and 080 that had a mean dose of 165 units in 31 or more injections. Although there are limitations in comparing adverse events across studies, the injection scheme in the Phase 3 studies had a lower rate of common adverse events across most adverse events, including muscular weakness (24-30% in 039 vs 3% in 079/080), eyelid ptosis (4%-6% in 039 vs 3% in 079/080), and dysphagia (3%-6% in 039 vs 0.6% in 079/080). In addition, Dr. Graham notes that the placebo rate of adverse events was also reduced in the Phase 3 trials compared to Protocol 039 (51% vs 37%). I agree that this suggests that the number of injections and volume of injections are associated with tolerability effects.

Dr. Graham has evaluated time dependency of adverse events. In Table 38 of her review some events such as muscle pain, headache, eyelid ptosis, and muscular weakness diminish in frequency with each cycle; reports of migraine occurred relatively consistently throughout the study beyond the second dose.

2.3.9 Drug Interactions

Dr. Graham has reviewed drug-demographic interactions. Musculoskeletal adverse events were infrequently reported by men and in women they were

reported at a greater rate with Botox than placebo. Neck pain, headache, eyelid ptosis, migraine, and injection site pain did not differ substantially between genders. Only 4% of the Phase 3 population was greater than 65 years old and no one in the Phase 2 population was in this age group; I agree that it is not feasible to conduct an analysis based on age. When compared in patients > 40 y.o. vs less than or equal to 40 y.o., there was not an apparent difference in most adverse events although there is a slightly greater frequency of some events including neck pain, musculoskeletal stiffness, and musculoskeletal pain in patients greater than 40 y.o.

There was no drug-disease analysis conducted and there was no drug-drug interaction analysis conducted.

2.3.10 Human Carcinogenicity

There were 17 reports of a neoplasm in the sBLA. These include 6 uterine leiomyoma (fibroids) that are common findings in this age group of women. There were 3 reports of breast cancer; 1 occurred approximately 5-6 months after the first dose of Botox and 2-3 months after the second dose, and 2 months after a normal mammogram. The second occurred within 1 month of a dose of Botox in a patient who had a prior history of breast induration with previous mammogram and ultrasound inconclusive. The 3rd was diagnosed following an abnormal mammogram within 2 months of the Botox dose. There was 1 case of melanoma in situ and 1 case of malignant melanoma diagnosed within 2 months after the 2nd or 4th dose of Botox. There were single cases of brain neoplasm and parathyroid adenoma. There was one case of diverticulitis miscoded as colonic neoplasm. I agree with Dr. Graham that the safety data in this sBLA does not suggest a cancer risk associated with Botox.

2.3.11 Human Reproduction and Pregnancy Data

Eighteen women became pregnant during the Phase 3 trials. Eight occurred during the DBPC portion of the trials (5 in Botox treated patients and 3 in placebo treated patients. The placebo treated patients delivered healthy babies. Two in the Botox group were lost to follow-up, one delivered a healthy baby, one delivered a baby with metatarsus adductus, and one experienced a spontaneous abortion. Nine women became pregnant during the open label portion; 7 delivered healthy babies, one had a miscarriage, and one experienced a placenta abruption at 25 weeks. Overall, 12 Botox-treated women who were known to become pregnant had a known outcome (9 during the open label and 3 in the DBPC portion).

Dr Graham calculates that at least 17 patients (1.6% of 1042 women) in the Phase 3 trials became pregnant during the trial, where there were requirements for contraception. I agree with her assumption that a higher rate in the postmarketing setting can be expected. She calculates that based on the known

outcomes, 75% of the 12 pregnancies in the women treated with Botox resulted in live births. Dr. Graham points out that this is crudely consistent with 2004 US data that 64% of pregnancies resulted in a live birth, 17% in fetal loss, and 19% in an induced abortion. She points out that the lost-to follow up cases could easily change the live birth population. Dr. Graham argues that women of childbearing potential are prime candidates for the use of Botox in the treatment of migraine, and that there is sufficient evidence of regional and systemic side effects of botulinum toxins to raise concern about the use of BOTOX in women of childbearing potential. The Maternal Health Team was consulted and did not recommend either a pregnancy registry. This consideration was due to their consideration of the unlikely possibility the botulinum toxin A would cross the placenta, inadequate data to determine whether events of spontaneous abortions and placental abruptions occur at rates higher than the background rates in the general population, and the lack of utility of a pregnancy registry as a data collection tool to detect signals for adverse effects on the placenta and results on fetal outcomes (e.g. spontaneous abortion).

2.3.12 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no specific reports of overdose in the ISS. There is already language in the Botox label in the overdose section, including information about the availability of antitoxin. With respect to abuse potential, there were no trials investigating potential for abuse, and I agree that based on the known botulinum toxin actions there is no pharmacological rational for suspecting potential abuse. There were no spontaneous reports of rebound with worse headaches in the absence of treatment.

2.3.13 Postmarketing Experience
I agree with Dr. Graham's assessment that the majority of events observed when Botox is used for migraine in the postmarketing experience (1990-2008 and 1/1/09-10/31/09) are similar to those reported during the phase 3 trials in CM. These included eyelid ptosis, dysphagia, dyspnea, and dysphonia. There were also cases of hypersensitivity, pruritus, urticaria, and swelling face. I note that hypersensitivity reactions are described in the approved Botox labeling in section 5.3 (Warnings and Precautions).

2.3.14 Summary of Significant Safety Concerns:
Dr. Graham has evaluated the safety data for Botox for chronic migraine. She has specifically evaluated safety issues of concern with the botulinum class of products including distant spread of toxin effect. The adverse events after administration of Botox for this indication are similar to those previously reported, particularly for indications involving injections in muscles of the neck. She has not identified other safety concerns in this submission that have not been already identified for botulinum toxin products. However, she does note an excess of headache and migraine in the Botox treated patients compared to placebo. She is concerned about the widespread use in women of childbearing potential, but

MHT does not believe that a pregnancy registry would address this concern. Dr. Graham is also concerned about the provision of proper training that will be required in order to adhere to the dosing regimen used in the phase 3 trials to minimize dose-related adverse effects and to achieve efficacy. I also note that there is very limited experience with doses above 155 units in chronic migraine, (b) (4)

2.3.15 Postmarketing Risk Management Plan

A REMS, including a MedGuide and a Communication plan (DHCP letter), is in place for Botox and will require revision to include the new indication if approved. Dr. Graham recommends modification of the REMS to include (b) (4) I would recommend that OSE reviewers with expertise in such assessments be involved in the review of this approach.

2.3.16 Conclusions

I agree with Dr. Graham's assessment that the application for Botox for chronic migraine allowed for an adequate safety review, and no safety concerns that would preclude approval were identified should Botox be found to be effective for chronic migraine. However, I recommend considering (b) (4)

I recommend assessment of the Sponsor's educational program regarding the dosing regimen in order to determine whether prescribers adhere to the guidance that is designed to provide an effective dose and minimize toxicity. The sponsor's proposed approach to assessment of this program should be evaluated by OSE reviewers with expertise in that type of assessment.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: August 18, 2010 **Date Consulted:** July 5, 2010

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D. LLM for Karen Feibus 8/18/2010
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D. LLM 8/18/2010
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Neurology Products (DNP)

Drug: Botox (onabotulinumtoxin A), BLA 103000/5215

Subject: Pregnancy Registry

Materials Reviewed:

- Draft Botox Clinical Review (Safety), July 1, 2010

Consult Questions:

1. Do you agree with a PMR for a pregnancy registry?
2. If answer to #1 is yes, then please suggest wording for including this request in the Action Letter.
3. If the answer to #1 is no, the please explain your rationale.

INTRODUCTION

Allergan submitted a Supplemental Biologics Licensing Application (BLA 103000/5215) on September 29, 2009, for Botox (onabotulinimtoxin A), for the prophylaxis of headaches in adults with chronic migraines.

The majority of patients enrolled in the Botox Phase 3 clinical trials for the prophylaxis of headaches in adults with chronic migraines were women of childbearing potential. Eighteen of these women became pregnant with most delivering healthy babies. One delivered a baby with metatarsus adductus; one had a spontaneous abortion; and two were lost to follow-up. An additional nine women became pregnant during the open label portion of the Botox trial. Seven of these women delivered healthy babies; however, one had a spontaneous abortion, and one had a placental abruption at 25 weeks gestation. The Division of Neurology Products (DNP) recommends a postmarketing requirement for a pregnancy registry to record pregnancy outcomes because of the likely increased use of Botox in women of childbearing potential with the approval of this indication and the likelihood of pregnancies in this population while receiving the drug.

DNP consulted the Maternal Health team (MHT) to determine the appropriateness of requesting a pregnancy registry for Botox as a postmarketing requirement and to respond to the following questions:

1. Do you agree with a PMR for a pregnancy registry?
2. If answer to #1 is yes, then please suggest wording for including this request in the Action Letter.
3. If the answer to #1 is no, the please explain your rationale.

BACKGROUND

Onabotulinumtoxin A

Onabotulinimtoxin A is a neuromuscular blocking agent that blocks neuromuscular transmission by binding to acceptor sites on motor sympathetic nerve terminals, inhibiting the release of acetylcholine. Onabotulinimtoxin A also blocks efferant autonomic fibers to smooth muscles and to exocrine glands. Direct central nervous system effects are not seen, as onabotulinimtoxin A does not cross the blood-brain barrier.[1] When injected intramuscularly at therpeutic doses, a partial denervation of the muscle occurs resulting in a localized reduction in muscle activitiy. The muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. Botulinim toxin effects (spread of toxin effect) may be observed beyond the site of local injection.

Botox (onabotulinimtoxin A) was first licensed in the United States on December 29, 1989, for the treatent of blepharospasm in patients and with dystonia $\geq$ 12 years of age, and for the treatment of strabismus in patients $\geq$ 12 years of age. Both of these indications were orphan product designation. FDA also approved the following indications between 2001 and 2010:

[1] Dressler D, Saberi F, Barbosa E. Botulinum toxin: mechanism of action. Arq Neuropsiquiatr. 2005 Mar;6391):180-5

- Reduce the severity of abnormal head position and neck pain (orhan product) in adults with cervical dystonia (December 21, 2001).

- Severe axillary hyperhydrosis that is inadequately managed by topical agents in adult patients was approved (July 19, 2004)

- Upper limb spasticity (March 9, 2010).

In addition, FDA approved Botox Cosmetic (onabotulinimtoxin A) for the treatment of glabellar lines on April 12, 2002.

DISCUSSION

DNP consulted the Maternal Health team (MHT) to determine the appropriateness of requesting a pregnancy registry for Botox as a postmarketing requirement and to respond to the following questions:

1. Do you agree with a PMR for a pregnancy registry?
2. If answer to #1 is yes, then please suggest wording for including this request in the Action Letter.
3. If the answer to #1 is no, the please explain your rationale.

Before responding to this question about a pregnancy exposure registry for Botox, the Maternal health team (MHT) will discuss characteristics of the botulinum toxin A molecule, pregnancy exposure registries, spontaneous abortions, congenital malformations, placental abruptions, and available animal and human data.

Botulinum toxin A is a large molecule with a molecular weight of approximately (b) (4) daltons. The current approved Botox labeling states that using available analytical technology; it is not possible to detect Botox in the peripheral blood following intramuscular injections at recommended clinical doses.[2]

Transfer of drugs across the placenta requires the presence of the drug in the maternal circulation. If a drug is present in the maternal circulation, then drug placental passage can occur via several mechanisms, including passive diffusion (molecular weight < 500 daltons), facilitated diffusion, and active transport. Facilitated diffusion requires the presence of a carrier substance but does not involve the transfer of energy and often the maternal and fetal plasma concentrations equalize. Active transport is mediated by drug transporters (specific proteins) that require energy and can occur against a concentration gradient.[3]

Pregnancy Exposure Registries

A pregnancy exposure registry[4] is a prospective observational cohort study that actively collects information on a medical product exposure during pregnancy and associated pregnancy outcomes. It is one method of collecting data on drug exposure during pregnancy

[2] See current approved Botox labeling, June 3, 2010
[3] Wang J, Newport D, et al. The emerging importance of transporter proteins I the psychopharmacological
[4] See Guidance for Industry – Establishing Pregnancy Exposure Registries, August 2002

before pregnancy outcomes are known. The main goal of pregnancy exposure registries is to collect data about the presence or absence of drug-associated fetal adverse developmental effects when a drug is used during pregnancy. This data is used in labeling to inform clinician and patient decision making regarding use of the product.

The decision to establish a pregnancy exposure registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the registry. In order to collect meaningful data, the sample size of a pregnancy exposure registry should be large enough to either detect a difference or show no difference between the exposed and control groups.

Spontaneous Abortions
All pregnancies have a spontaneous abortion (SAB) background rate of approximately 15 to 18 percent, regardless of drug exposure. A spontaneous abortion is defined as a pregnancy loss that occurs less that 20 weeks gestation. The reason for any SAB is varied and in many cases, the cause cannot be identified.

Congenital Malformations
All pregnancies have a 2 to 4 percent background risk of a birth defect or adverse outcome, regardless of drug exposure. Metatarsus adductus (the one reported malformation from the migraine prophylaxis Phase 3 clinical trials) is the most common congenital foot deformity. It occurs in 1- 2 per 1000 live births and is thought to result from the fetus's position in the uterus.[5]

Placental Abruptions
Placental abruption, or the partial or complete detachment of the placenta prior to birth, occurs in approximately 0.6 to 1 percent of all pregnancies and is usually unpredictable and unpreventable. The etiology of placental abruption is not well understood; however, suspected key mechanisms include impaired placentation, placental insufficiency, intrauterine hypoxia, uroplacental underperfusion, or a manifestation of an inflammatory process that could affect the placental vascular bed. In most cases, placental abruption appears to result from a long-standing process that may date back to early pregnancy.[6]

Animal Data
Adverse outcomes occurred in animals when Botox was administered during the period of organogenesis; however, most adverse fetal effects occurred in the presence of maternal toxicity. Animal studies conducted in the 1960's failed to demonstrate detectable levels of botulinum toxin A in the placentas or fetuses of pregnant rabbits that received intravenous botulinum toxin A at lethal doses.[7]

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[5] See http://www.fpnotebook.com/Ortho/Peds/MtrsAdcts.htm
[6] Tikkanen M. Etiology, clinical manifestations, and prediction of placental abruption. Acta Obstetrica and Gynecologica. 2010;89:732-40
[7] Morgan, J, Iyer S, Moser E, et al. Botulinum toxin A during pregnancy: a survey of treating physicians. L Neurol Neurosurg Psychiatry 2006:77:117-19

Another animal study was conducted to analyze the effect of Botox on pregnant myometrium activity in vitro. Botox depressed the amplitude and frequency of myometrial contractions and eventually totally abolished contractions in rat myometrial tissue at most concentrations studied. The effects were reversed by a complete wash-out of the tissue bath. The authors concluded that Botox consistently inhibited myometrial activity in a potentially reversible fashion and may prove to be valuable in preventing preterm labor after fetal surgery.[8]

Human Pregnancy Outcome Data

The effects of botulinum toxin A on human pregnancy are largely unknown, and a brief literature search conducted by the MHT did not identify any signal for adverse fetal outcomes. One article reported the results of a survey sent to 900 physicians who used botulinum toxin A in females of childbearing potential. The authors reported on 19 pregnancies, and the only adverse outcome was a SAB in a woman with a history of SABs.[9] In addition, there are several case reports of botulism poisoning in pregnant woman with no evidence of adverse fetal effects. In one case, the mother was completely paralyzed and receiving mechanical ventilation; however, fetal movement was normal.[10] The infant's serum was tested immediately after birth, and there were no measurable levels of botulinum toxin detected, suggesting that the toxin was not transported across the placenta.

REPROTOX[11] also reports that botulism during pregnancy has not been associated with transfer of botulinum toxin to the fetus. This information is based on case reports of either maternal botulism poisoning during pregnancy or the therapeutic use of botulinum toxin A during pregnancy.

Furthermore, The Drug and Lactation Database (Lactmed)[12] reports that no data are available on the therapeutic use of botulinum toxin A during lactation. There was one reported case of a women who breastfed while hospitalized with maternal botulism. No botulinum toxin was detected in either the mother's milk or infant; however, it was detected in the mother's blood and stools.

CONCLUSIONS

Based on available animal and human data reviewed by the MHT, botulinum toxin A is not detected in the maternal circulation when injected intramuscularly at therapeutic doses. Case reports in pregnant and lactating women infected with Clostridium botulinum suggest that botulinum toxin A does not cross the placenta (or into human milk), most likely explained by its large molecular weight. Because of these findings, botulinum toxin A does not appear to have a direct effect on a developing fetus. However, it is possible that botulinum toxin A

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[8] Garza J, Downard C. Clostridium botulinum toxin inhibits myometrial activity in vitro: possible application on the prevention of preterm labor after fetal surgery. J Pediat Surg. 2003; Mar;38(3):511-13

[9] Morgan, J, Iyer S, Moser E, et al. Botulinum toxin A during pregnancy: a survey of treating physicians. L Neurol Neurosurg Psychiatry. 2006:77:117-19

[10] Yim J, Weir C. Botulinum toxin and pregnancy – a cautionary tale. Strabismus. 2010;18(2):65-6

[11] REPROTOX® is a subscription information system on environmental hazards to human pregnancy, reproduction and development developed by the Reproductive Toxicology Center for its members. REPROTOX contains summaries on the effects of medications, chemicals, infections, and physical agents on pregnancy, reproduction, and development.

[12] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

could have an indirect effect on the developing fetus through a possible placental effect. Spontaneous abortions and placental abruptions have been reported after botulinum toxin A exposure during pregnancy; however, the data are inadequate to determine whether these events occur at rates higher than the background rates in the general population. Botulinum toxin A binds to acceptor sites on motor sympathetic nerve terminals and inhibits the release of acetylcholine. Therefore, botulinum toxin A effects could potentially impact placental vasculature and placental perfusion if toxin spread systemically after a distal intramuscular injection. Botulinum toxin A abolished myometrial contractions in an in vitro rat myometrial study;[13] and may have a similar effect on the human myometrium. In vitro models using human placenta can be useful in in assessing the both the transfer of a drug across the placenta as well as any placental effects.[14]

If botulinum toxin A does not cross the placenta, direct adverse fetal develpmental effects are unlikely to occur. A pregnancy exposure registry (prospective observational cohort study) would not be the appropriate data collection tool to detect signals for adverse effects on the placenta and any resulting fetal adverse outcomes. The Sponsor should provide data on the placental transfer of onabotulinimtoxin A and any direct placental effects. If data demonstrate a placental transfer of onabotulinimtoxin A, then a pregnancy exposure registry should be considered for Botox. Botox pregnancy labeling should be revised to include information regarding placental transfer, any placental effects, and available human pregnancy data.

RECOMMENDATIONS

The MHT does not recommend a postmarketing requirement for a pregnancy registry for Botox at this time until further information is provided for review regarding placental transfer and placental vasculature and perfusion effects.

Comment for the review division:

1. To address the uncertainty for the potential of Onabotulinimtoxin A to cross the placenta and the concern for potential effects on the function of the placenta that may lead to loss of pregnancy or result in placental abruption, consider requesting the Sponsor to consult with placental experts about the use of in vitro models utilizing human placenta to assess the transfer of agents across the placenta as well as direct effects on the placenta and require the Sponsor to conduct an appropriatey designed study.

Please convey the following information requests to the Sponsor:

1. Does botulinum toxin A transfer across the placenta? Provide all relevant human and animal data for review.

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[13] Garza J, Downard C. Clostridium botulinum toxin inhibits myometrial activity in vitro: possible application on the prevention of preterm labor after fetal surgery. J Pediat Surg. 2003; Mar;38(3):511-13

[14] Miller R. What is the role of the placenta—Does it protect against or is it a target for insult? Teratology Primer, 2nd Edition. http://connection.teratology.org/p/cm/ld/fid=6

2. Provide a literature review of pregnancy outcomes in women who were either administered or infected with botulinum toxin during pregnancy.

3. Submit revised Botox pregnancy subsection labeling for review that incorporates information regarding placental transfer, direct placental effects, and available human pregnancy data.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 1, 2010

TO: Lana Chen, Regulatory Health Project Manager
Suhail Kasim, M. D., Medical Officer
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 103000/5215

APPLICANT: Allergan, Inc.

DRUG: BOTOX (botulinum neurotoxin type A)

NME: Yes. Original BLA

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of patients with migraine headache

CONSULTATION REQUEST DATE: December 19, 2009

DIVISION ACTION GOAL DATE: June 29, 2010

PDUFA DATE: June 29, 2010

I. BACKGROUND:

The Sponsor, Allergan, Inc. has submitted a BLA application for marketing approval of BOTOX (Botulinum Toxin Type A) as prophylaxis for treatment of patients with 15 or more headache days per 4-week period. Chronic migraine headache is a common neurological disorder, which is defined as migraine lasting more than 4 hours per day and occurring 16 or more days per month. Botulinum Toxin Type A purified Neurotoxin Complex appears to act both peripherally (directly) and centrally (indirectly) on the sensory nerves. Botox blocks the release of neurotransmitters associated with genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as confirmed by clinical and pre-clinical studies. Clinical evidence suggests that Botox reduces or prevents local neuropeptide (NP) release and thus reduces NP-induced sensitization of peripheral nocioceptive (pain-conducting) nerve fibers, thereby reducing peripheral pain signals to the central nervous system.

The results of two pivotal studies were submitted in support of the application, Protocol 191622-079-01 entitled: "A Multicenter Study Evaluating the Efficacy and Safety of BOTOX (Botulinum Toxin Type A) Purified Neurotoxin Complex as Headache Prophylaxis in Migraine patients with 15 or more Headache Days per 4-week Period, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Phase followed by a 32 –week Open-label Extension Phase"; and 191622-080-02 entitled: " A Multicenter Study Evaluating the Efficacy and Safety of BOTOX (Botulinum Toxin Type A) Purified Neurotoxin Complex as Headache Prophylaxis in Migraine Patients with 15 or more Headache Days per 4-Week period in a 24-week, Double-Blind, Placebo-Controlled, Randomized, Parallel Group Phase followed by a 32-Week Open –Label Extension Phase". Both Protocols describe studies that are of 60 weeks in duration; the duration of treatment includes a 4-week baseline phase, followed by a 24 –week, double blind phase, prior to subjects entering a 32-week, open-label extension phase. A brief description of the study objectives are presented below.

Study Protocol 191622-079-01 primary objective was to evaluate the safety and efficacy of Botulinum Toxin Type A purified neurotoxin complex compared with placebo as headache prophylaxis in migraine patients with 15 or more headache days per 4-week period. The study duration is approximately 60 weeks. The treatment included male and female subjects over 18 years of age.

Study Protocol 191622– 080-02 primary objective was to evaluate the efficacy and safety of Botulinum Toxin Type A purified complex with placebo as headache prophylaxis in migraine patients with 15 or more headache days per 4-week period. The study duration is about 60 weeks. The treatment included both male and female subjects over 18 years of age.

The review division requested inspection of four clinical investigators in Protocols 191622-078-01 and 191622-080-02 as data from the two studies are considered essential to the approval decision. Two domestic clinical investigators were selected from Protocol 191622-07901 and two clinical investigators were selected from Protocol 191622-080-02, one foreign investigator and one domestic. These sites were targeted for inspection due to enrollment of a relatively large number of subjects and a significant primary efficacy results pertinent to decision- making.

II. RESULTS (by protocol/site):

Name of CI, site # and location	**Protocol and # of subjects**	**Inspection Dates**	**Final Classification**
Dennis Riff, M.D Advanced Clinical Research Institute a 1211 West La Palma Avenue, Ste. 602 &303 Anaheim, CA, 92801 Site# 10032	Protocol 191622-079-01 Number of subjects listed 24	3/24 and 4/1/10	VAI
Paul Winner, DO. Premier research Institute at Palm Beach Neurology 4631 Congress Avenue, Ste. 200 West Palm Beach, FL 33407	Protocol 191622-079-1 Number of subjects listed 32	3/22-26/10	NAI
Constance Johnson, M.D. Neurological Medicine Headache Care Center 311 Landrum Place, Ste. B400 Clarksville, TN 37043 Site # 10018	Protocol 191622-080-02 Number of subjects listed 23	3/29 and 4/7/10	NAI
Harmut Gobel, M.D. Kiel Pain Center Heikendorfer Weg 9-27 D-24149 Keil, Germany Site# 12506	Protocol 191622-080-02 Number of subjects listed 22	5/24-28/10	NAI/pending

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol 191622-079-1

1. **Dennis Riff, M.D.**
   Anaheim, CA 92801

   a. What Was Inspected: At this site, a total of 82 subjects were screened, 58 subjects were reported as screen failures, 24 subjects randomized, 21 subjects completed the study, and 3 subjects withdrew consent. There were no deaths reported at this site. Informed consent documents, for all records reviewed, verified that subjects signed prior to enrollment.

   A review of the medical records/source documents was conducted. The medical records for 24 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, IRB records and sponsor correspondence, and use of concomitant medications; source documents were compared to case report forms and to data listings, including primary efficacy endpoints and adverse events.

   b. General observations/commentary: At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Riff. Our investigation found that adverse events and the use of concomitant medications by subjects were not reported on the respective case report forms for some subjects. Four subjects experienced sleepiness, right shoulder pain and muscle weakness (10356), muscle tightening (10692), eyebrow paralysis (10954), and constipation (11256). In addition, 4 subjects took concomitant medications that were not reported in there respective case report forms such as acetaminophen (10455), Theraflu (10463), Fioricet (10580), and Taztia (10954). The clinical investigator acknowledged the inspectional findings in a written response dated April 9, 2010, in which he stated that corrective action plan will be instituted and promised to be vigilant in the oversight of his staff.

   c. **Assessment of Data Integrity:** Although regulatory violations were noted, the findings are unlikely to affect data integrity as they appear to be isolated occurrences and not systemic in nature; however, the review division may choose to consider the AEs as outlined above that were not reported on the case report forms in their assessment of safety. The remaining data generated from Dr. Riff's site are considered reliable and appear acceptable in support of the application.

2. **Paul Winner, DO.**
   West Palm Beach, Florida

   a. What Was Inspected: At this site, a total of 53 subjects were screened, twenty one (21) subjects were reported as a screen failures, 32 subjects were randomized, and 29 subjects completed the study. There were no deaths and five adverse events reported. Informed consent documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 10 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, inclusion/exclusion criteria, adverse events, concomitant medications, IRB files, and laboratory results; source documents were compared to data listings, to include primary efficacy endpoints and adverse events. A Form FDA 483 was not issued and the medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data.

b. General Observations/Commentary: Our investigation found no evidence of under reporting of adverse events.

The medical records/source document reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data, In general, the records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity

The data from Dr. Winner's site are considered reliable and appear acceptable in support of the pending application.

Protocol 191622-080-02

3. **Constance Johnson, M.D.**
   Clarksville, TN 37043-6319

a. What Was Inspected: At this site, a total of 40 subjects were screened, 17 subjects were reported as screen failures, 23 subjects were randomized into the study, and two subjects withdrew from the study late prior to study completion. There were no death and adverse events were reported. Informed consent documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 12 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, use of concomitant medications, and protocol deviations; source documents were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events.

b. General Observations/Commentary: Our investigation found no evidence of under reporting of adverse events. No significant violations were noted and a Form FDA 483 was not issued.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. There were no known limitations to this inspection.

c. **Assessment of Data Integrity:** The data from Dr. Johnson's site are considered reliable and appear acceptable in support of the pending application.

4. **Harmut Gobel, M.D.**
Keil, Germany D-24149

a. **What was Inspected:** At this site, a total of 28 subjects were screened, 6 subjects were reported as screen failures, 22 subjects were randomized, one subject withdrew consent and 21 subjects completed the study. Informed consent documents, for all subjects reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for 22 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB files, prior and current medications, inclusion/exclusion criteria, and the use of concomitant medications; source documents were compared to case report forms and to data listings, to include primary efficacy endpoint and adverse events. There were no deaths and one subject was reported to have an SAE (uterine myoma), which was noted as not drug related.

b. **General Observations/Commentary:** Although no Form FDA 483 was issued, the FDA investigator discussed with the clinical investigator minor discrepancies related to not reporting the use of concomitant medications by a few subjects on the respective case report forms for the treatment of headache episodes. Subject 50959 received naratriptan that was not reported in the source document (diary). Two subjects had headache episodes listed in their respective diaries, 50031 and 50900, but were not reported in the data listings. The clinical investigator acknowledged the discrepancies and promised corrections in the future. The medical records reviewed disclosed no adverse findings that would negatively on the reliability of the data. In general, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

c. **Assessment of Data Integrity:** Although isolated minor deficiencies were noted, the findings are unlikely to affect data integrity. The data from Dr. Gobel's site are considered reliable and appear acceptable in support of the pending application.

Note: Observations noted above are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three domestic clinical investigators and one foreign investigator were inspected in support of this application. The inspections of Drs. Riff, Winner, Johnson and Gobel revealed no significant problems that would adversely impact data acceptability. Overall the data submitted from these sites are acceptable in support of the pending application.

Note: Observations noted for Dr. Gobel's site are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

/Antoine El-Hage, Ph.D./
Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

/Tejashri Purohit-Sheth, M.D./
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	August 25, 2010
Application Type/Number:	BLA #: 103000/5215
To:	Russell Katz, MD, Director Division of Neurology Products
Through:	Denise P. Toyer, PharmD, Deputy Director D.P. Toyer 8/26/2010 Division of Medication Error Prevention and Analysis
From:	Walter Fava, RPh, MSEd, Safety Evaluator Walter Fava 8-25-10 Division of Medication Error Prevention and Analysis
Subject:	Labeling Review
Drug Name:	Botox (OnabotulinumtoxinA) 50 units/vial, 100 units/vial, 200 units/vial
Applicant:	Allergan
OSE RCM #:	2010-1231

CONTENTS

1 INTRODUCTION

This review responds to a June 2, 2010 request from the Division of Neurology Products for an evaluation of the labels and labeling for the product, Botox (BLA # :103000/5215) pursuant to a submission from the Licensee on April 9, 2010 for approval of the indication of migraine headaches.

2 REGULATORY HISTORY

Botox was approved December 9, 1991. The established name was subsequently revised from Botulinum Toxin Type A to Onabotulinumtoxin A. DMEPA reviewed the container labels and carton labeling that reflected the change in established name in OSE review 2009-989, dated May 21, 2010. Supplement 5197, approved August 21, 2009, provided for extension of the post-reconstitution in-use shelf life from four hours to 24 hours for the 50 unit and 100 unit vials. Supplement 5219, approved June 3, 2010, provided for the post-reconstitution in-use shelf life for the 200 unit vials (OSE Review # 2010-872). This supplement, 5215, provides for information concerning the indication of migraine headaches.

3 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the insert labeling submitted on April 9, 2010. DMEPA also referenced our previous reviews of the carton and insert labeling for Botox 50 unit, 100 unit, and 200 unit vials (OSE Reviews 2009-989 and 2010-872) to determine if any of the recommendations in those reviews are applicable.

4 RECOMMENDATIONS

Our evaluation of the labeling finds that the presentation of information in the insert labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations in Section 4.1 *Comments to the Division*.

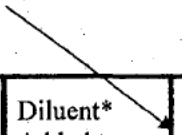
Please copy the Division of Medication Error Prevention and Analysis on any communication to the Licensee with regard to this review. If you have further questions or need clarifications on this review, please contact Laurie Kelley, Project Manager, at 301-796-5068.

4.1 COMMENTS TO THE DIVISION

A. Package Insert Labeling

1. In the Highlights section we note *units* is spelled out where it first appears in the text followed by '(U)', however, the abbreviation, 'U' is on the Institute of Safe Medication Practices list of 'Error-Prone Abbreviations, Symbols and Dose Designations', as the letter 'u' has been mistaken for the numbers '0' or '4' and has resulted in 10 fold overdoses or greater. Revise the abbreviation 'U' and replace with 'Units' throughout the package insert.
2. Ensure that units of measure immediately follow each numerical strength notation throughout the package insert. For example, in the dosage and administration section in Highlights, revise the dosage range statement, (b) (4)

3. Revise the Dilution Table in Section 2.1 to improve readability and minimize confusion by:
    - changing the heading of the table to read 'Dilution Instructions for Botox Vials (50 units, 100 units, and 200 units)
    - revising '*0.9% Sodium Chloride Injection Only' in the footnote to read 'Preservative-free 0.9% Sodium Chloride Injection, USP Only'
    - decreasing the thickness of the vertical line separating the last two columns on the far right associated with the 200 unit vial (see sample representation below)



Diluent* Added to **50 Unit** Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to **100 Unit** Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to **200 Unit** Vial	Resulting Dose Units per 0.1 mL

4. Revise each of the recommended doses presented in Table 1 from (b) (4)
5. Revise Table 2 in section 2.3, Upper Limb Spasticity, to include (b) (4)
6. Revise the sentence in section 2.3 which reads, '…and no more than 50 units per site should generally be administered.' (b) (4) '.

5 REFERENCES

5.1 REVIEWS

1. *OSE Review # 2009-989, Label and Labeling Review for Botox and Botox Cosmetic (OnabotulinumtoxinA), Walter Fava, June 17, 2009.*
2. *OSE Review # 2010-872, Labeling Review for Botox (OnabotulinumtoxinA), Kristina Arnwine, June 1, 2010.*

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000 S-5215

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Chen, Lana Y

From: Bastings, Eric
Sent: Wednesday, September 29, 2010 2:02 PM
To: Chen, Lana Y
Cc: Ware, Jacqueline H
Subject: Botox ac

Attachments: risk-mgmt-plan-migraine.pdf; BLA 103000 5215 APPROVAL LETTER (chronic migraine) final (0929).doc


risk-mgmt-plan-migraine.pdf (1...


BLA 103000 5 APPROVAL LET

Lana,

Here is the Botox action letter, and the REMS.

Note that there are a couple of minor edits to the Medication Guide that may be negotiated with the sponsor, and as the REMS include the Med Guide as an appendix, that appendix may need to be modified. It is really minor, though.

As soon as I hear from Rusty regarding labeling, we'll send Allergan our final labeling comments.

Hopefully, we can take the action at the end of next week.

A press release is going through clearance, and we will have to coordinate the action with them.

Thanks.

Eric

24 Pages Immediately Following Withheld - b(4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BLA 103000/5125

July 15, 2010

Allergan
Attention: Mary O'Sullivan, MPH
2525 Dupont Dr
PO Box 19534
Irvine, CA 92623-9534

Dear Ms. O'Sullivan:

Please refer to your supplement to your biologics license application submitted under section 351 of the Public Health Service Act for Botox (onabotulinumtoxinA).

We received your July 1, 2010 amendment to this supplement on July 1, 2010 and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to October 29, 2010, to provide time for a full review of the amendment.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Lana Chen, at (301) 796-1056.

Sincerely,

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA STN 103000\5215

PREA WAIVER DENIED

April 15, 2010

Allergan
Attention: Mary O'Sullivan, MPH
2525 Dupont Dr
PO Box 19534
Irvine, CA 92623-9534

Dear Ms. O'Sullivan:

Please refer to your submission dated September 29, 2009, requesting a waiver of pediatric studies for Botox (onabotulinumtoxinA) under 505B(a)(4) of the Federal Food, Drug, and Cosmetic Act (the Act).

We have reviewed your submission and do not agree that a waiver of pediatric studies in patients from birth to 17 years is justified for Botox (onabotulinumtoxinA) for (b) (4) (b) (4).

We are denying this waiver for the following reasons:

> We have reviewed your request for full waiver of all pediatric studies in patients from birth to 17 years, submitted in your supplemental BLA application (sBLA) under FDA review, for the indication of prophylaxis of headache in adults with chronic migraine. In your sBLA you include the following justification for requesting a full waiver of pediatric studies: (a) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act) (b) Necessary studies are impossible or highly impracticable (section 505B(a)(4)(A)(i) of the Act).
>
> Currently there is no approved treatment for the prophylactic treatment of chronic migraine in pediatric patients, and there is an unmet medical need for that population. There also appears to be a substantial number of adolescent patients age 12-17 years with chronic migraine, who may benefit from a prophylactic treatment. Therefore, we disagree that a study is impossible or highly impracticable.

You must submit a revised pediatric plan, to assess the safety and efficacy of BOTOX for the prophylactic treatment of chronic migraine in pediatric patients age 12-17 years. Please include

with your plan timelines for submission of the study protocol(s), completion of the proposed study(ies), and submission of the study report(s), with appropriate justification if necessary.

The Division believes that a waiver for patients age 0-11 years is acceptable.

We request that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your supplement is not approvable. Review of other sections of your supplement is continuing. Please submit the revised pediatric plan no later than May 3, 2010.

If you have any questions, call the Regulatory Project Manager, Lana Chen, at (301) 796-1056.

Sincerely,

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Chen, Lana Y

From: Mulinde, Jean
Sent: Tuesday, February 02, 2010 9:47 AM
To: Kasim, Suhail; Bastings, Eric
Cc: Chen, Lana Y; El Hage, Antoine N; Purohit-Sheth, Tejashri
Subject: DSI Consult for BLA 103000

Importance: High

Suhail and Eric,
Can you please advise as to status to consult request to DSI for this application? If CI audits are to be completed we need final list of site selects and rationale for each site select to complete assignments for issuance.
Regards,
Jean

Jean Mulinde, M.D.
Lead Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations
CDER, FDA
(301)796-0768

DSI CONSULT: Request for Clinical Inspections

Date: January 13, 2010 COMPLETED JAN 2 8 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Suhail Kasim, MD, Clinical Reviewer, Division of Neurology Products (DNP)
Eric Bastings, MD, Deputy Division Director, DNP
Russell Katz, MD Division Director, DNP

From: Lana Chen, RPh, Project Manager, DNP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: BLA 103000/5215 Prophylaxis of Chronic Migraine Headache
Applicant/ Applicant contact information (to include phone/email):

Mary O'Sullivan, MPH
Senior Director, Global Regulatory Affairs,
Neurology and Pain
714/246-2904
OSullivan_Mary@Allergan.com

Drug Proprietary Name: Botox
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Migraine

PDUFA: 6/29/10
Action Goal Date: 6/29/10
Inspection Summary Goal Date: 5/29/10

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site No: 12506 Kiel Pain Center Heikendorfer Weg 9-27 D-24149 Kiel, GERMANY Tel: +49 431-2009965 Fax: +49 431-2009935 Email: kiel@schmerzklinik.de PI: Harmut Gobel, MD Sub PI: (b) (6)	191622-080	22	Prophylaxis of chronic migraine
Site No: 10018 Neurological Medicine Headache care center 311 Landrum Place, Suite B400 Clarksville, TN 37043 Tel : 931-647-2828 Fax :931-906-0938 PI: Constance Johnson, MD Sub PI : (b) (6)	191622-080	23	Prophylaxis of chronic migraine

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site No: 10032 Advanced Clinical Research Institute 1211 West La Palma Avenue, Suite 602 & 303 Anaheim, CA 92801 Tel : 714-774-7777 Fax: 714-778-0667 PI : Dennis Riff, MD FACG Sub PI : (b) (6)	191622-079	24	Prophylaxis of chronic migraine
Site No: 10005 Premier Research Institute at Palm Beach Neurology 4631 Congress Avenue, Suite 200 West Palm Beach, FL 33407 Tel: 561-845-0500 Fax: 561-845-1794 PI: Paul Winner, DO FAAN Sub PI: (b) (6)	191622-079	32	Prophylaxis of chronic migraine

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

These sites had high enrollers with greater treatment effect on primary efficacy measure.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
__X__ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

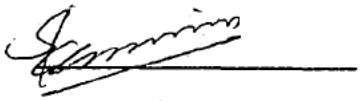
____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Enrollment of large numbers of study subjects with greater treatment effect on primary efficacy measure.

IV. Tables of Specific Data to be Verified (if applicable)

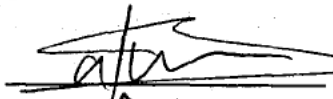
If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Lana Chen, RPM 301-7961056 or Suhail Kasim, MD at 301-796-2077.

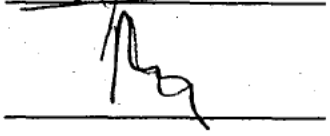
Concurrence: (as needed)



Medical Reviewer



Medical Team Leader



Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*