STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Novel concepts for OnabotulinumtoxinA (Botox) mechanisms of action: role in altering the molecular environment in which pain fibers exist

NCT number: 3381261
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DETAILED STUDY DESCRIPTION

TITLE OF PROTOCOL	**Novel concepts for OnabotulinumtoxinA (Botox) mechanisms of action: role in altering the molecular environment in which pain fibers exist**

Version date: 6/7/22

1. PURPOSE OF PROTOCOL

Specific Aim

To compare Botox-treated and Botox-untreated symptomatic tissues (defined as areas where the head hurts and the pain is felt) of CM patients using targeted transcriptome and genome-wide epigenome analysis. This aim will test the hypothesis that Botox reverses the abnormal expression of inflammatory genes in headache-affected regions and pericranial muscles, fascia, and perineurium of nerves supplying them.

2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Background and Rational

The broad objective of this proposal is to understand better how Botox works and determine whether it can attenuate inflammation. Based on our preliminary findings, we expect the proposed research to vastly expand the understanding of Botox MOA, both in migraine prophylaxis and somatic pain conditions associated with inflammation. Scientifically, we expect to gain new insight into the role played by Botox in environments that surround relevant peripheral nociceptors – potentially by attenuating local expression of pro-inflammatory molecules (mRNA) and their post-transcriptional regulators (non-coding RNA). In the context of migraine, such tissues include the calvarial periosteum, galea aponeurotica, pericranial muscles and fascia surrounding extracranial nerves (e.g., occipital, supraorbital, auriculotemporal nerves). In the context of other somatic pains, such tissues include muscles, fascia, and the perineurium. The potential impacts of the proposed research is that if successful, it will broaden the clinical use of Botox. Equally important, it will define a novel framework for conceptualizing about Botox MOA and consequently, why and how it may be used to treat other pains and possibly conditions associated with abnormal inflammatory and immune responses.

The goals of the proposed research will be achieved by studying tissues commonly discarded during nerve decompression surgeries performed to alleviate neck and head pain in chronic migraineurs. These goals were formulated on the basis of two sets of preliminary clinical findings. The first showed that gene transcripts (mRNA) that promote immune and inflammatory responses are significantly upregulated in calvarial periosteum of CM patients (as compared to control subjects) and that gene transcripts (mRNA) that reduce immune and inflammatory responses are significantly down-regulated in calvarial periosteum of CM patients (as compared to control subjects).

In more detail, there is new evidence of extracranial origins of migraine headache. Clinically, there is data that describes an imploding headache (extracranial) versus exploding headache (intracranial) [1]. There is evidence that expression of proinflammatory genes (eg, CCL8, TLR2) in the calvarial periosteum is significantly increased in CM patients, whereas expression of genes that suppress inflammation and immune cell differentiation (eg, IL10RA, CSF1R) is decreased. It is well known that anti- inflammatory drugs improve migraine attacks. It has further been shown that extracranial administration of OnabotulinumtoxinA is effective in reducing the number of migraine days per month in patients who testified to having ‘imploding’, but not in those who testified to having ‘exploding’ headache [2]. The identification of extracranial pathophysiologies in chronic migraine patients whose headaches are most commonly perceived as imploding, and the finding that imploding migraine patients are those who benefit most from prophylactic treatment with OnabotulinumtoxinA [1], gave rise to a theory that Botox may help patients with imploding headache due to anti-inflammatory properties.

1. Jakubowski M, McAllister PJ, Bajwa ZH, Ward TN, Smith P, Burstein R (2006) Exploding vs. imploding headache in migraine prophylaxis with Botulinum Toxin A. Pain 125 (3):286-295. doi:10.1016/j.pain.2006.09.012
2. Burstein R, Dodick D, Silberstein S (2009) Migraine prophylaxis with botulinum toxin A is associated with perception of headache. Toxicon 54 (5):624-627. doi:10.1016/j.toxicon.2009.01.009

3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Overall study design:

Patients diagnosed with chronic migraine (fulfill criteria for CM as defined in the ICHD-3 beta), especially those complaining about chronic muscle tenderness, are routinely considered good candidate to benefit from a surgery in which trapped nerves are decompressed. In routine clinical care, such patients are referred to Dr. Austen (plastic surgeon performing these procedures) to determine whether or not they fit to undergo the nerve decompression procedure. Of great importance to the evaluation of the proposed study is the fact that the decision on whether or not to operate is unrelated to and independent of any academic study. Those deemed good candidate for the surgery, which include fulfilling all inclusion/exclusion criteria, would be presented with an option to hear about the study from a research nurse. Those interested in hearing about the study will be presented with all the necessary details required and then given the option to sign (or not to sign). They will be given as much time as needed to sign the consent form and have the option to take the consent form home and call in interested.

Since the surgery itself is unrelated to the proposed study, all patients (those who sign the informed consent and those who chose not take part in the study) are booked for the surgery. Usual waiting time is 3-6 month.
Those who agree to participate in the study, will be asked to fill out a 15min headache questionnaire that contains questions about their headaches. Subjects will also be asked to complete a headache diary 3 months prior to botox injections.

Enrolled subjects will be booked for another visit to Dr. Austen's clinic 30 days prior to their planned surgery. In this visit, they will be injected with 40 units of Botox in one side of their head/neck as detailed below.

During surgery, calvarial periosteum, pericranial muscles and fascia surrounding nerves that are routinely removed and discarded, will be collected by Dr. Austen, stored in in RNAlater Solution, Ambion, CA, de-identified, frozen, and shipped overnight to Dr. Burstein's lab at BIDMC, where each sample will be recorded, verified, prepared for processing, and analyzed for targeted transcriptome and epigenome involved in inflammatory and immune responses.

Clinical Site Study Procedures
The following research study activities will take place exclusively at MGH:

Those who agree to participate in the study, will be asked to fill out a 15min headache questionnaire that contains questions about their headaches. Subjects will also be asked to complete a headache diary 3 months prior to botox injections.

The headache diary will be filled out every day for 3 months prospectively prior to botox injection. Subjects will indicate whether they had migraines that day (check date box), what severity the migraines were (on a scale of 0-10), what the duration was (hours), what the location was, which other symptoms they experienced, which medications they took, how often they went to the ED, saw doctors or missed work and how much the total cost was. The total time spent every day filling out the diary should not exceed 5min.

Enrolled subjects will be injected with Botox on one side of the back of the head. The FDA-approved injection paradigm includes 7 muscles (Frontalis, Corugator, Procerus, Occipitalis, temporalis, Trapezius, and the Cervical Paraspinal muscle group), 31 sites and 155 units divided as follows: Frontalis – 4 sites, 5 units in each; Corrugator – 2 sites, 5 units in each; Procerus – 1 site, 5 units; Occipitalis – 6 sites, 5 units at each; Temporalis – 8 sites, 5 units in each; Trapezius – 6 sites, 5 units at each; Cervical

Paraspinal – 4 sites, 5 units in each.

Of these muscles, sites and doses, patients will be injected (from a 100 Unit vial of OnabotulinumtoxinA reconsituted per product manufacturer label instructions) as follows:

(A) 2 sites in the Occipitalis muscle (5 units each)
(B) 4 sites in the Cervical Paraspinal muscle group (5 units each)
(C) 2 sites in the Trapezius muscle (5 units each)

These injections will be given into one side only. This deviates from the standard of care, as Botox is usually injected on both sides if pain is experienced on both sides. The selection will be random based on subject number. Odd numbers will be injected on the right and even numbers on the left.

The current standard of care for screening for migraine surgery includes injection of Botox to identify nerve triggers. In the occipital region, botox is either injected unilaterally or bilaterally depending on where pain occurs. When pain occurs bilaterally, Botox is injected on both sides. Subjects included in this study have bilateral occipital pain and would therefore as part of routine standard care be injected on both sides. As per this protocol, subjects will only be injected on one side. The risks of unilateral injection of botox (in addition to the risk of Botox in general outlined by the FDA) include continued pain on the uninjected side and/or injected side and one- sided muscle weakness, one- sided bruising, one sided infection on the injected side. More generally, botox injections may cause the formation of anti-botox antibodies, which may decrease the effectiveness of botox treatment in other areas.

Subjects will be informed that they have the option to be injected with Botox on the uninjected side if any unwanted symptoms are experienced on the uninjected side. The cost of injection on the other side will be covered by the study funds.

Because the standard surgical procedure involves removal of equal amount of corresponding tissues from both sides of the head, an opportunity is created here to analyze identical Botox-treated and Botox-untreated tissues. Importantly, all analyzed tissues are discarded as a part of the surgery and none is collected for the sake of the study.

Note that this injection paradigm does not deviate from the currently approved FDA paradigm and that it is given to chronic migraine patients (i.e., for the indication it was approved by the FDA). Also note that one of the standard clinical criteria that these patients must fulfill in order to qualify for the surgical decompression procedure (which is unrelated to the study) is to demonstrate that they have failed at least 3 attempts to treat their chronic migraine with prophylactics – one of which is Botox. Thus, all those who qualify for the study would have been treated with Botox at least twice before as per the FDA approved protocol.

Thirty days later, patients will undergo a study-unrelated nerve decompression surgery. This procedure involves the removal of different tissues surrounding trapped branches of the occipital nerve. These tissues include muscles, fascia, and periosteum (discarded tissue). The amount of tissue removed at each area is many folds larger than the amount of tissue needed for sampling (less than the size of 1 grain of rice.

From the time of informed consent and for 3 months following injection, all sellf-reported adverse events will be reviewed by the study physician at each patient contact(patients are followed every 4 weeks after botox injection and one week, one month, three months, one year and after that yearly after surgery). All serious adverse events will be reported to the IRB and designated safety monitor within 24 hours of awareness of the event.

There will be two visits:
Screening visit: Patients will be screened for eligibility. This will be performed during the regular clinical assessment for surgery. The study visit will take 30min. The subject will be asked to complete

a 15 min questionnaire and will be asked to fill out a 3m headache diary which may take up to 5min a day.
Preoperative visit: will be injected with Botulinum Toxin. This will take 30 minutes.

There will be further routine clinical visits postoperatively (one week, 3 months and 12 months). However, these visits are not related to the study but are part of regular follow up. No study materials for this study will be collected as part of this visit.

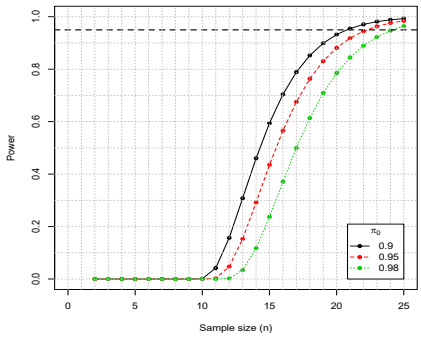
Analysis to be Done at BIDMC

(A) Tissue processing, RNA isolation, genetic processing and mRNA counting will occur in Dr. Burstein's lab at Beth Israel Deaconess Medical Center, Harvard Medical School.
(B) Bioinformatics and biostatistics analyses will be conducted at Dr. Bhasin's lab at Beth Israel Deaconess Medical Center, Harvard Medical School.

B. Statistical Considerations

Statistical power analysis: In doing the power calculation, we control for false discovery rate (FDR), a common method used in genome level analysis to control for multiple testing of a large number of genes. The statistical power is also a function of proportion of non-differentially expressed genes using the method developed by Liu and Hwang in 2007. Based on our feasibility study findings, we used 98% non-differentially genes and effect size of 1.5 for power calculation. With 50 chronic migraine (each serving as his/her own control), we will have 95% statistical power to detect effect size of 1.5, with stringent FDR of 0.001.

Figure 2. Power vs. Sample Size with fdr=0.001 and Δ/σ=1.5038



Statistical analysis for main outcome measure: (A) Comparisons of targeted transcriptome from periosteal, muscles and fascia surrounding nerves will be performed between corresponding injected and not-injecetd tissues using Wilcoxon's Matched Pairs Tests.

Quality controls (QC), normalization and preprocessing analysis of genomics profiling data : Tissues genomics profiling data will be analyzed using the following major steps:

(a) Quality control: We will first assign a quality measure for each sample based on nanostring standard QC criteria such as FOV counted, binding density, array mean signal, average background, and scaling factor using expert bioinformatician supervision. We will also check for reproducibility of the samples using correlation and signal-to-noise ratio (SNR) methods for replicate arrays. Low quality arrays will be excluded from further analysis.

(b) Normalization: Normalization is the most critical step in the analysis, which is a transformation of signal values so that different chip results become comparable. The normalization will be performed in three steps: (i) Positive Spike in controls based normalization that will take care of signal variation due to different amounts of input RNA, (ii) Negative Spike in controls based background correction, (iii) Normalization based of signal values of house keeping genes from the experiments to bring all

the chips onto a similar expression level. The different normalizations and QCs will be performed using the Bioconductor R packages workflows.

(c) Unsupervised analysis: To identify unbiased patterns of similarity, outlier arrays and batch effects, unsupervised learning technique will be performed on the normalized expression profiles of all genes. The unsupervised learning will be carried out using the Unweighted Pair Group Method with Arithmetic Mean (UPGMA), also referred to as hierarchical clustering. The assumption underlying these clustering techniques is that expression profiles that are proximate in Euclidean or correlation space are mechanistically related. Additionally attempt to identify outliers will be done using principal component analysis.

Identification of Botox signatures: In this analysis, we will consider the gene expression as the dependent variable and the indicator variable of group (e.g. Botox vs. No Botox) as the independent variable. The analysis will be performed using Linear Models for Microarray Data (LIMMA) as it employs an empirical Bayes approach for parameter estimation. To reduce the false positive, the significantly differentially expressed genes will be obtained using Benjamini and Hochberg multiple test corrected P value. The genes with P value < 0.01 and absolute fold change of at least 2 folds will be considered as differentially expressed. Due to differences in level of expression of gene in different tissues, we will perform separate normalization and signature identification for each tissue type.

Functional and Pathways analysis: The genes from different tissues will be further analyzed in the context of biological pathways, Gene Ontology (GO) and functional categories. The analysis will be performed using MATLAB, Bioconductor and commercial packages (e.g. Ingenuity pathways Analysis). Identifying significantly over-represented biological pathways is particularly valuable for understanding the underline mechanism of action of Botox.

Identification of tissues and pathways that potentially drive Botox effects: The comprehensive network generated above will be further analyzed to pin-down the involved tissues and pathways. To reach this goal, an effort will be made to find a sub-network with highest number of alterations. Such subnetwork will be identified using HotNet package that considers gene as a unit heat source, and uses a diffusion process to derive “hot" subnetworks that contain more alterations than expected by random chance. *In principle, significant subnetworks are routinely determined by both the frequency of alteration of genes and the local topology of the subnetwork.* To identify a key pathway(s) in a top significant subnetwork, we will use the Biological pathway enrichment analysis. This analysis will be done using various modules of Bioconductor, which uses multiple corrected hypergeometric tests to determine significance of pathway or biological process affected.

C. Subject Selection

Patients diagnosed with chronic migraine (fulfill criteria for CM as defined in the ICHD-3 beta), especially those complaining about chronic muscle tenderness, are routinely considered good candidate to benefit from a surgery in which trapped nerves are decompressed. In routine clinical care, such patients are referred to Dr.Austen to determine whether or not they fit to undergo the nerve decompression procedure. Of great importance to the evaluation of the proposed study is the fact that the decision on whether or not to operate is unrelated to and independent of any academic study. Those deemed good candidate for the surgery would be presented with an option to hear about the study from Dr. Austen, the plastic surgeon responsible for their well-being during the surgery and the one handling the discarded tissues. Those interested in hearing about the study will be presented with all the necessary details required by the Western IRB and then given the option to sign (or not to sign).

Accordingly, up to ~~50~~ 65 chronic migraine patients will be recruited to the study (if they are found fit to undergo the surgery) by Dr. Austen, a certified plastic surgeon with enormous experience in performing these procedures.

Inclusion Criteria:

- Age 18-65 years
- Diagnosis of Chronic Migraine consistent with International Classification of Headache Disorders (ICHD-III) criteria, with a history of bilateral headache pain and chronic tenderness in neck muscles
- Patient is capable and willing to provide informed consent
- Female subjects of child bearing potential must have a negative pregnancy test at enrollment and agree to remain abstinent or use acceptable methods of birth control (i.e., hormonal contraceptives, inrauterindevce, diaphragm with spermicide, cervidal cap or spong, condoms or partner has had a vasectomy) for three months following injections of Botox
- Patients referred by their primary Neurologist to the study surgeon and who are determined to be candidates for surgical decompression of extracranial sensory nerves.
- Patient agrees to abstain from protocol-specific excluded medications (see Appendix A) beginning 14 days prior to the decompression surgery.

Exclusion Criteria:

- Patient has hypersensitivity reactions or other intolerance to Botox
- Patient is pregnant or trying to become pregnant with the timeframe of the study.
- Infection at proposed injection sites

4. POSSIBLE BENEFITS

It is not possible to predict whether participants will benefit directly from participation in this study. However, their participation may help others in the future as a result of knowledge gained from the research

It is important to note that the clinical outcome of the procedure is unrelated to the proposed study. While improvement (or lack of improvement) in headache days per month after the procedure is followed by Dr. Austen, it is outside the scope of the proposed study and as such will not be collected and/or reported.

5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Only subjects who have been selected as a surgical candidate for sensory nerve decompression of chronic headache would have their tissue tested. The taking of the periosteal sample would add no additional risk to the operation, as we are obtaining tissue *discarded* during surgery.

Botox therapy is currently approved by the FDA for preventive treatment of migraines.

All the potential risks of Botox injections as issued by the FDA are as follows. As we are only injecting the back of the occiput, symptoms occurring around the eyes, the oropharynx or generalized symptoms are very unlikely.

A. General:

- There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, after treatment with botulinum toxin.

- *There have also been rare 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.*

- The following events have been reported since the drug has been marketed and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction.

- In general, adverse events occur within the first week following injection of **BOTOX®** and while generally transient may have a duration of several months. Localized pain, tenderness and/or bruising may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin.

- Extraocular muscles adjacent to the injection site can be affected, causing ptosis or 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 are 15.7% and 16.9%, respectively.

- The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection.

B. Side effects and discomforts associated with study treatment that you may experience include the following and some of these effects may last as long as 3 to 4 months:

  - Drooping of the upper lid
  - Swelling of the eyelid
  - Dryness of the eye
  - Irritation/tearing of the eye
  - Difficulty in closing the upper lid
  - Sensitivity to light
  - Double vision
  - Soreness and/or bruising at the injection sites
  - Skin rash
  - Loss of facial wrinkling
  - Localized muscle weakness in the muscles which have been injected
  - Slight weakness in other muscles in the neck
  - Difficulty swallowing
  - Generalized weakness and fatigue

C. If you experience any illness or discomfort during the study, you should notify Dr. *Austen.* Dr. Austen will then evaluate you to determine if you should continue in the study.

D. There may be side effects or discomforts from the study treatment which are not yet known. You could have an allergic reaction to BOTOX. A severe allergic reaction could be life-threatening.

E. Women who are pregnant, nursing a child, or planning a pregnancy during this study period may not participate in this study. You must confirm that, to the best of your knowledge, you are not now pregnant, and that you do not intend to become pregnant during the study. Prior to entering the study, you and the study doctor must agree on the method of birth control you will use during the study. If you suspect that you have become pregnant during the study, you must notify the study doctor immediately. The sponsor of the study may need access to your medical records regarding your pregnancy and the outcome of your pregnancy. In addition, if you are pregnant or become pregnant during the study, there may be a risk of miscarriage or fetal malformation.

F. Treatment with BOTOX for the treatment of migraine headaches may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments with BOTOX for other purposes.

G. Botox injections are associated with pain from the needle prick with pain from the needle prick. A bruise may develop at the site, and there is a small chance you might get an infection.

Overall, we believe the risks of this study are sufficiently low and that the benefits of information to be gained and the potential benefit of improved migraine treatment outweigh the risks in this study.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Patient screening, recruitment and consent will occur at Dr. Austen's clinic (River Oaks Plastic Surgery Center) during a visit that determines their candidacy to undergo the surgery.

Patients are referred to the investigator or schedule an appointment independently for migraine surgery routinely. Subjects will be selected from among the patients that are reffered to the investigator.. A research nurse will initially explain participation in the study prior to the visit with the investigator. The patient will be given the consent forms and can take us much time as needed to consent for the study. The patient can also take the consent form home and call if interested. At the scheduled visit with the investigator he will reinforce that participation is voluntary and with their patients that participation is voluntary, that they do not have to participate, and the decision not to participate will not affect their care, now or in the future. The investigator can answer any questions the subject may have.

Subject Protection

Study subjects will not be employees of the study team.

7. STUDY LOCATION

Clinical Site: Boston

(A) Patient screening, recruitment, and consent will be performed by Dr. Austen at the Division of Plastic and Reconstructive Surgery, MGH
(B) Botox injections will be conducted by Dr. Austen at at the Division of Plastic and Reconstructive Surgery, MGH
(C) Nerve decompression surgery will occur at the MGH operating rooms

Processing Site: Boston

(C) Tissue processing, RNA isolation, genetic processing and mRNA counting will occur in Dr. Burstein's lab at Beth Israel Deaconess Medical Center, Harvard Medical School.
(D) Bioinformatics and biostatistics analyses will be conducted at Dr. Bhasin's lab at Beth Israel Deaconess Medical Center, Harvard Medical School.

8. DATA SECURITY

All clinical study records will be stored in a secure location in the office of Dr. Austen, as all research activities involving patient data will take place at MGH.

De-identified discarded tissue will be transferred to Dr. Burstein's lab at Beth Israel Deaconess Medical Center for processing and analysis. No personally identifiable data (including name, date of birth, age, and gender) will be shared between the clinical site (Boston) and the processing site (BIDMC).

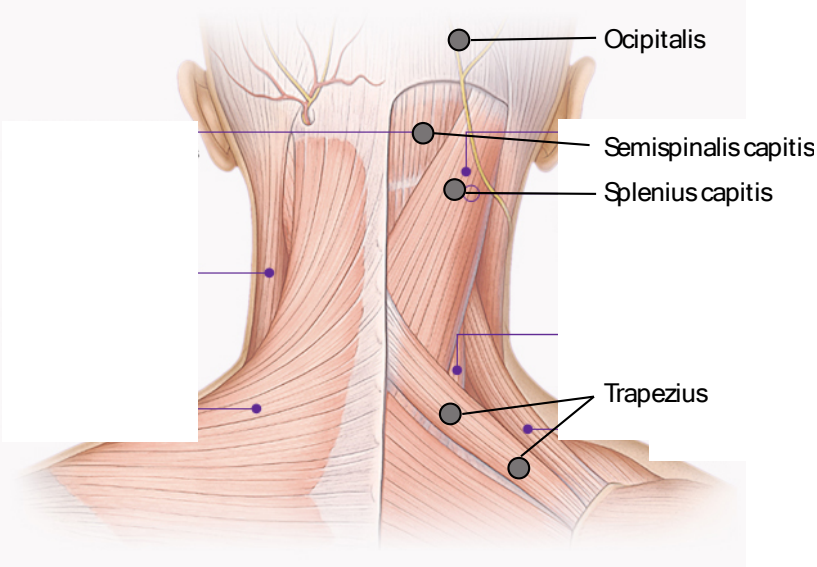
9. Dissemination of Research Results

Dr. Austen will provide participants with the option to learn about findings generated as a result of their participation. A copy of the final published manuscript will be provided to subjects who express interest in receiving a copy of the primary manuscript.

10. Botox administration

Botox Prior to Surgery

As stated above, patients diagnosed with CM affecting both sides of the head who have been deemed candidates for *study-unrelated* surgical decompression of extracranial sensory nerves will be presented with an option to hear about the study and sign the informed consent. Those who agree to participate in the study will be injected with Botox (Fig. 1) on one side of the neck/back of the head per FDA approved guidelines for migraine prophylaxis. Botox treatment will take place 30 days prior to surgery. As before, during surgery, perineurium, fascia, muscle, and periosteum will be collected (in RNAlater Solution, Ambion, CA), de identified, frozen, and shipped overnight for processing and analysis for targeted transcriptome and epigenome involved in inflammatory and immune responses using the advanced nanostring system.



Injection paradigm:
Occipital - 1 injection of 10 units
Trapezius - 2 injections of 10 units each
Semispinalis - 1 injection of 10 units
Splenius Capitis - 1 injection of 10 units

Headache Diary

Month/Year:_____

Participant ID# ___ ___ ___

Date	Maximum Severity (0-10)	Duration (hours)	Location	Nauseau Y N	Vomiting Y N	Sensitive to Light Y N	Throbbing Y N	Muscle Pain Before HA Y N	Muscle Pain During HA Y N	Muscle Pain After HA Y N	Acute HA Medicine (name/s)	No. of Doses	Number of ER & Doctor Visits, Work Days Missed	Total Cost (medications, doctor & ER visits, work days missed)
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Please fill out (in medium blue or black pen) as completely as possible and bring to your first visit.

Patient Name: _____ **Date of Birth:** ____/____/____

Name of Primary Care Physician: _____

PCP Address: _____

_____

Personal and Work:

Which hand do you write with? ☐ Right ☐ Left

Check (√) the following if you:

☐ Smoke	How many packs per week? _____
☐ Drink alcohol	How many drinks per week? _____
☐ Use recreational drugs	How many times per week? _____
☐ Drink caffeine (coffee, tea, soda)	How many cups per day? _____

What kind of work do you do? _____

Have headaches ever caused you to miss work or alter your daily activities? ☐ Yes ☐ No

On average, how many days per month do you miss work because of headaches? _____

How many days per month do you go to work with a headache but cannot work as well? _____

Medical History:

Please list any medical problems you have now: _____

_____

_____

Please list any medical problems you have had in the past: _____

_____

_____

Have you had any **surgeries**? ☐ Yes ☐ No

If Yes, please list: _____

Have you ever been diagnosed with:

☐ Raynaud's Syndrome ☐ Seizures ☐ Mitral valve prolapse

	Yes	No
Have you ever had head trauma (a severe blow to your head)? *If Yes*, when? _____	☐	☐
Did you hit your head directly?	☐	☐
Did you lose consciousness (pass out)?	☐	☐
Were you hospitalized?	☐	☐
Did you have any brain imaging (*e.g.*, X-ray, MRI, etc.) as a result?	☐	☐
Have you had **any** dental work?	☐	☐
Have you been diagnosed with TMJ?	☐	☐
Do you grind your teeth?	☐	☐

Please check (√) if you have had any of the following problems in **the past six months**:

☐ Skin changes	☐ Shortness of breath	☐ Difficulty seeing
☐ Swelling	☐ Muscle weakness	☐ Difficulty hearing
☐ Chest pain	☐ Bowel problems	☐ Difficulty speaking
☐ Neck pain	☐ Bladder problems	☐ Difficulty swallowing
☐ Joint or back pain	☐ Incontinence	☐ Sleep problems
☐ Dizziness	☐ Memory loss	☐ Skin lesions
☐ Palpitations	☐ Depression	☐ Night sweats
☐ Fevers / Chills	☐ Mood changes	

Are you breastfeeding? ☐ Yes ☐ No ☐ N/A
Are you pregnant? ☐ Yes ☐ No ☐ N/A
Are you planning to become pregnant in the near future? ☐ Yes ☐ No ☐ N/A

Headache History:
How old were you when your headaches started? _____

Who in your family has (or had) headaches? _____

Which family members, if any, were diagnosed with migraines? _____

How many migraine attacks do you get each month? _____

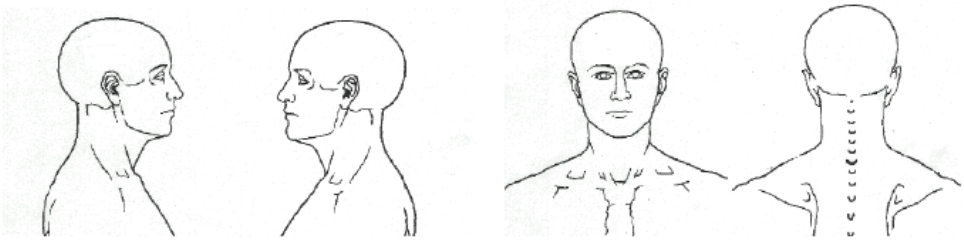
How long do your typical attacks last? _____

Do you get migraines daily? ☐ Yes ☐ No
If Yes, how long ago did they start occurring daily? _____

Have your headaches recently been coming more often? ☐ Yes ☐ No
Have your headaches recently been worse than usual? ☐ Yes ☐ No
On weekends or vacations, are your headaches: ☐ Better ☐ Worse ☐ The same
During stressful times, are your headaches: ☐ Better ☐ Worse ☐ The same

Headache Description:
Are your headaches generally: ☐ On one side ☐ On both sides
If one-sided is it always the same side? ☐ Yes ☐ No
If both-sided, does it usually start on one side? ☐ Yes ☐ No

For the questions below, please think about a typical headache that you experience.
Shade in the areas where you feel the pain. If you have a throbbing pain, place an **X** at the point where the pain throbs.



When your pain throbs, does the throbbing feel like it's: ☐ inside **or** ☐ outside **your skull?**
Which illustration and description below best describes your head pain? Circle one letter or more. If none, skip to next question.

A

Buildup of pressure inside the head as if the skull is about to split open or explode. Something is squeezing the inside of my brain

B

The skull is assaulted by external forces typically described as crushing, clamping or stabbing

C

Eye-popping pain

Describe how your headache feels: _____

_____

_____

Describing the pain, check (√) all that apply:

☐ Pulsating ☐ Throbbing ☐ Pounding ☐ Squeezing ☐ Vise-Like ☐ Tightening
☐ Pressing ☐ Dull ☐ Constricting ☐ Stabbing ☐ Shock-Like

☐ Other: _____

Is the pain made worse by:

Tilting or bending your head? ☐ Yes ☐ No
Coughing or sneezing? ☐ Yes ☐ No
Exertion such as climbing stairs? ☐ Yes ☐ No

On average, how long does it take for your headache to reach its highest level of pain? _____

On a scale of 0 to 10 (**0 is no pain** and **10 is the worst pain** you have ever had), how do your headaches rate: Usual headache: _____ Worst headache: _____

Pain: ☐----------☐
No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain

Please complete this chart in two steps:

Complete **Before Headache** column by Placing an **X** by any symptom you Experience *before* your headache begins.

Complete **During Headache** column by Placing an **X** by any symptom you Experience during your headache.

Symptoms	Before Headache	During Headache
Euphoria (feeling of great happiness)		
Hyperactivity		
Depression		
Anxiety		
Irritability		
Unhappiness		
Yawning		
Food craving		
Disrupted sleep		
Frequent urination		
Muscle tenderness		
Stuffy nose		
One-sided runny nose		
Teary eyes and/or droopy eyelids		
Excessive saliva		
Aura: (check [√] if you have *any* of the following) Blurred vision One-sided loss of vision Flashing or shimmering lights Blackened portion of visual field		
Tingling (fingers, hands or face)		
Numbness (fingers, hands or face)		
One-sided weakness		
Facial flushing		
Skin hypersensitivity		
Difficulty finding words		
Difficulty saying words correctly		
Photophobia (sensitivity to light)		
Phonophobia (sensitivity to sound)		
Osmophobia (sensitivity to smell)		
Dizziness or unsteadiness		
Nausea		
Vomiting		
Difficulty swallowing		
Difficulty hearing		
Ringing in the ears		
Other: (please specify): _____		

After you have the "**Before Headache**" symptoms, how soon does your headache begin? _____

Do you avoid any of the following activities during headache because they hurt you?
(Check (√) all that apply)

- ☐ Combing hair
- ☐ Pulling hair back (*e.g.*, ponytail)
- ☐ Wearing eyeglasses
- ☐ Wearing earrings
- ☐ Wearing necklaces
- ☐ Breathing through your nose on cold days
- ☐ Resting your face on your pillow on the headache side
- ☐ Wearing tight clothes
- ☐ Allowing shower water to hit your face
- ☐ Cooking (to avoid the heat)
- ☐ Wearing something on your arms / wrists
- ☐ Shaving your face

Are you a good sleeper? ☐ Yes ☐ No ☐ I don't know

Does your sleeping pattern change often? ☐ Yes ☐ No

When you have a headache, does sleep usually relieve the headache? ☐ Yes ☐ No

Does anything in particular bring on the headache? Check (√) all that apply:

- ☐ Menstrual Cycle
- ☐ Stress
- ☐ Post-stress
- ☐ Skipping a meal
- ☐ Sleeping too little
- ☐ Bright lights
- ☐ Strobe / flickering lights
- ☐ Fast-action movies / video games
- ☐ Certain smells
- ☐ Other (please specify): _____
- ☐ Exercise
- ☐ Caffeine
- ☐ Weather changes
- ☐ Certain foods

Does light make your headache worse? ☐ Yes ☐ No

If Yes, how much worse does it get? ☐ A little ☐ A lot

If Yes, how long does it take for the pain to get worse? ☐ Seconds ☐ Minutes ☐ Hours

Does being in the dark give you any relief? ☐ Yes ☐ No

If Yes, how much better does it get? ☐ A little ☐ A lot

If Yes, how long does it take for the pain to get better? ☐ Seconds ☐ Minutes ☐ Hours

Are your headaches associated with your menstrual cycle? ☐ Yes ☐ No ☐ N/A

If No or N/A, skip to next section, "**Headache Treatment**." ***If Yes*:**

Do you get a headache with every menstrual cycle? ☐ Yes ☐ No

When does your headache begin in relation to your first day of bleeding?

☐ 2 days before ☐ 1 day before ☐ Day of ☐ 1 day after ☐ 2 days after

At what age did you first begin menstruating? _____

Are your periods regular? ☐ Yes ☐ No

Have you ever been pregnant? ☐ Yes ☐ No

Did your headaches change with pregnancy? ☐ Yes ☐ No

Have you ever taken birth control pills or any other female hormones? ☐ Yes ☐ No

If Yes, which ones(s) and for how long? _____

Headache Treatment:

If untreated by medications, how long do your headaches last? _____

Have you ever been treated by a doctor or other healthcare provider for your headaches? ☐ Yes ☐ No

If Yes, by whom? _____

Have you ever seen a neurologist for your headaches? ☐ Yes ☐ No

If Yes, whom did you see? _____ When? _____

Have you ever had: ☐ CT scan of the head ☐ MRI of the head

If Yes, where? _____ When? _____

Have you ever been to a pain clinic? ☐ Yes ☐ No

If Yes, where? _____ When? _____

Have you ever been to the emergency room for your headache? ☐ Yes ☐ No

If Yes, how many times? _____

Do you take pain or headache medication on a daily basis? ☐ Yes ☐ No

If Yes, please list: _____

_____

_____

List all over-the-counter pills you have taken in the past two weeks (pain pills, herbs, vitamins, etc.)

_____

_____

_____

_____

Please complete this chart below as follows:

1. For any medication or treatment you have used or tried, place an **X** in the **I Have Used** column.
2. Place an **X** in the **Helped** column if the medication or treatment helped for some period of time, or an **X** in the **Didn't Help** column if it did not help.
3. Then Indicate **How Long** you took the medication or treatment (in days, weeks, months, or years).

Medication	**I Have Used**	**Helped**	**Didn't Help**	**How Long I took it**
Propranolol (Inderal®)				
Nadolol (Corgard®)				
Atenolol (Tenormin®)				
Amitriptyline (Elavil®)				
Nortiptyline (Pamelor®)				
Imipramine (Tofranil®)				
Verapamil (Calan® / Verelan®)				
Valproic acid (Depakote®)				
Topiramate (Topamax®)				
Gabapentin (Neurontin®)				
Methysergide (Sansert®)				
Other medication to prevent headache:				
Aspirin				
Acetaminophen (Tylenol®)				
Vicodin® / Percocet®				
Ibuprofen (Motrin® / Advil®)				
Naproxen (Anaprox® / Aleve®)				
Cafergot® / Ergostat™ / Wigraine®				
Prochlorperazine (Compazine®)				
Isometheptene / dichloralphenazone / APAP (Midrin®)				
Butorphanol (Stadol® nasal spray)				
Meperidine (Demerol®) / Tylenol® with codeine				
Excedrin® / Anacin® / Vanquish				
Imitrex® injection / nasal spray				
Sumatriptan (Imitrex® tablets) / Almotriptan (Axert® tablets) / Naratriptan (Amerge® tablets)				
Rizatriptan (Maxalt® tablets) / Zolmitriptan (Zomig® tablets) / Frovatriptan (Frova® tablets)				
Fiorinal® / Fioricet® / Esgic				
Dihydroergotamine mesylate (Migrainal® nasal spray)				
Metoclopramide (Reglan®)				
Other treatment to stop headache:				
Acupuncture / Acupressure				
Physical therapy				
Stress reduction				
Ice / cold compresses				
Riboflavin (vitamin B-2) / Magnesium / Herbs (feverfew, etc.)				
Prednisone				
Oxygen				
Yoga / Meditation				
Massage Therapy				
Chiropractic Therapy				
Biofeedback				
Nerve blocks				
Botulinum toxin (Botox®)				
Other: _____				

Are you allergic to any medications? ☐ Yes ☐ No

If Yes, please list: _____

What are your specific goals for treatment? (What do you hope to get out of your treatment here?)

_____

_____

_____

X_____ **or** **X**_____ **and** _____

Patient's Signature | Person authorized to sign for patient | Relationship to patient

Date: ____/____/____ Time: ___ ___ : ___ ___ ◯ a.m. ◯ p.m.

Please bring any previous records / CT scan / MRI / X-rays to your visit if possible.

Thank you for taking the time to fill out this form before your visit.

X_____ M.D. _____ M.D. ____/____/____ ___ ___ ___ ___

Signature | Print Name | Date | Time (24 hour)

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) for injection, for intramuscular, intradetrusor, or intradermal use
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 an underlying condition that would predispose them to these symptoms. (5.2)

RECENT MAJOR CHANGES

- Warnings and Precautions (5.5, 5.7, 5.13, 5.14) 4/2017

INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) (1.2)
- Treatment of spasticity in adult patients (1.3)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.6)
- Treatment of strabismus in patients ≥12 years of age (1.6)

Important Limitations: Safety and effectiveness of BOTOX have not been established for:

- Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.2)
- Treatment of upper or lower limb spasticity in pediatric patients (1.3)
- Treatment of hyperhidrosis in body areas other than axillary (1.5)

DOSAGE AND ADMINISTRATION

- Follow indication-specific dosage and administration recommendations; Do not exceed a total dose of 400 Units administered in a 3 month interval (2.1)
- See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection (2.2)
- Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor (2.3)
- Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor (2.3)
- Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.4)
- Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.5)
- Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.5)
- 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 (2.6)
- Axillary Hyperhidrosis: 50 Units per axilla (2.7)
- Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.8)
- Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX (2.9)

DOSAGE FORMS AND STRENGTHS

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 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, 5.4, 6)
- Infection at the proposed injection site (4.2)
- Intradetrusor Injections: Urinary Tract Infection or Urinary Retention (4.3)

WARNINGS AND PRECAUTIONS

- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.2, 5.6)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
- Bronchitis and upper respiratory tract infections in patients treated for spasticity (5.10)
- Urinary tract infections in patients treated for OAB (5.12)
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus. (5.13)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and >placebo) are (6.1):

- OAB: urinary tract infection, dysuria, urinary retention
- Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention
- Chronic Migraine: neck pain, headache
- Spasticity: pain in extremity
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

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, treatment of OAB, detrusor overactivity associated with a neurologic condition, spasticity, and axillary hyperhidrosis; in patients under 16 years of age for treatment of cervical dystonia; and in patients under 12 years of age for treatment of blepharospasm and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: 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 an underlying condition 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 spasticity and at lower doses. *[See Warnings and Precautions (5.2)]*

1 INDICATIONS AND USAGE

1.1 Bladder Dysfunction

Overactive Bladder

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Detrusor Overactivity associated with a Neurologic Condition

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

1.2 Chronic Migraine

BOTOX 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.

1.3 Spasticity

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), finger flexors (flexor digitorum profundus and flexor digitorum sublimis), and thumb flexors (adductor pollicis and flexor pollicis longus).

Lower Limb Spasticity

BOTOX is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus).

Important Limitations

Safety and effectiveness of BOTOX have not been established for the treatment of other upper or lower limb muscle groups. 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.

1.4 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.

1.5 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.

1.6 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

2.1 Instructions for Safe Use

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)]*.

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 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. An understanding of standard electromyographic techniques is also required for treatment of strabismus, upper or lower limb spasticity, and may be useful for the treatment of cervical dystonia. Physicians administering BOTOX must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs.

2.2 Preparation and Dilution Technique

Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe (see Table 1, or for specific instructions for detrusor overactivity associated with a neurologic condition see Section 2.3), 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).

Table 1: Dilution Instructions for BOTOX Vials (100 Units and 200 Units)**

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	10 Units	1 mL	20 Units
2 mL	5 Units	2 mL	10 Units
4 mL	2.5 Units	4 mL	5 Units
8 mL	1.25 Units	8 mL	2.5 Units
10 mL	1 Unit	10 mL	2 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only
**For Detrusor Overactivity associated with a Neurologic Condition Dilution see Section 2.3

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.

2.3 Bladder Dysfunction

General

Patients must not have a urinary tract infection (UTI) at the time of treatment. Prophylactic antibiotics, except aminoglycosides, *[see Drug Interactions (7.1)]* should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of procedure-related UTI.

Patients should discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder

An intravesical instillation of diluted local anesthetic with or without sedation may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 100 Units of BOTOX, and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Dispose of any unused saline.

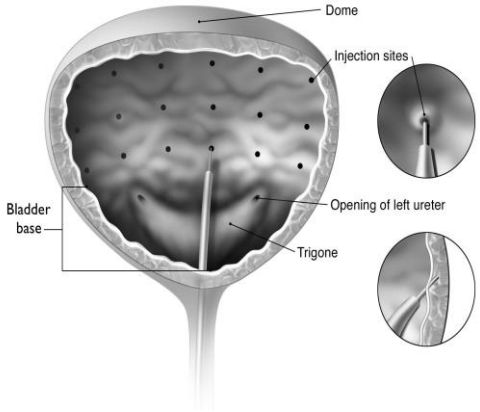
Reconstituted BOTOX (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, patients should demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median time until patients qualified for the second treatment of BOTOX in double-blind, placebo-controlled clinical studies was 169 days [~24 weeks]), but no sooner than 12 weeks from the prior bladder injection.

Figure 1: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Detrusor Overactivity associated with a Neurologic Condition



Detrusor Overactivity associated with a Neurologic Condition

An intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 Units of BOTOX per treatment, and should not be exceeded.

200 Unit Vial of BOTOX

- Reconstitute a 200 Unit vial of BOTOX with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
- Draw 2 mL from the vial into each of three 10 mL syringes.
- Complete the reconstitution by adding 8 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

100 Unit Vial of BOTOX

- Reconstitute two 100 Unit vials of BOTOX, each with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vials gently.
- Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe for a total of 4 mL in each syringe.
- Complete the reconstitution by adding 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstituted BOTOX (200 Units/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, placebo-controlled clinical studies was 295-337 days [42-48 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

2.4 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 Table 1). The recommended dose for treating chronic migraine is 155 Units administered intramuscularly 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 2 below. A one 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 one 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.

Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine

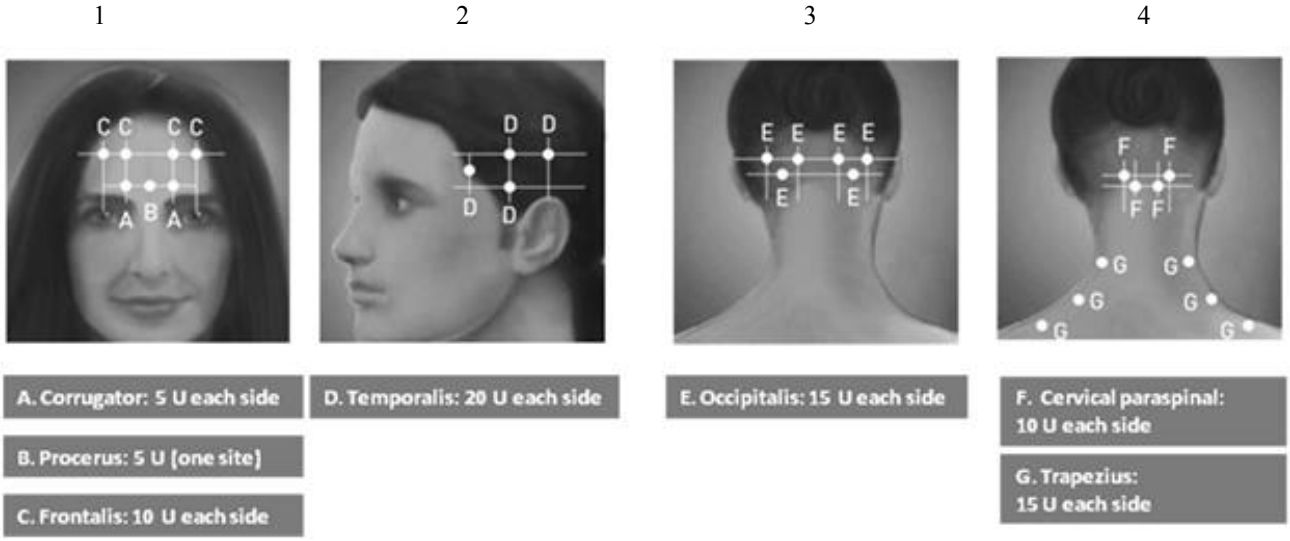


Table 2: BOTOX Dosing by Muscle for Chronic Migraine

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

2.5 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.

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). 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 techniques such as needle electromyographic guidance or nerve stimulation 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.

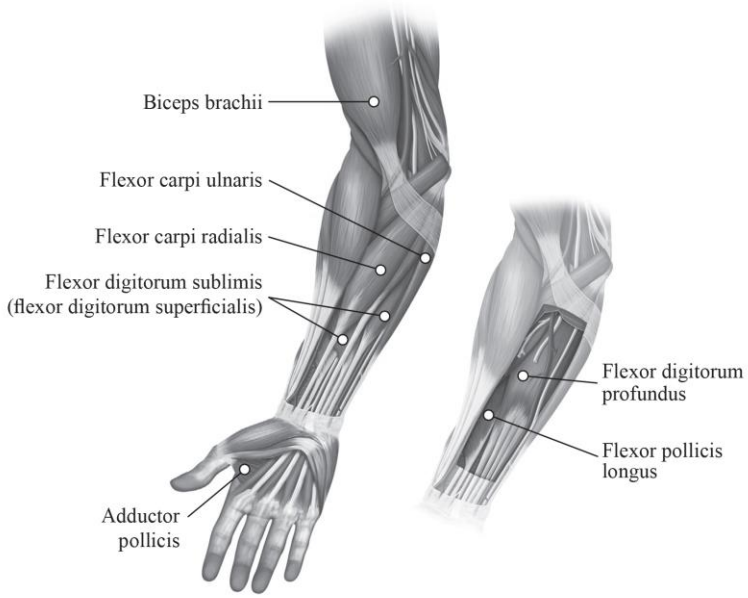
Upper Limb Spasticity

In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 3 and Figure 2) at a given treatment session.

Table 3: 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
Adductor Pollicis	20 Units in 1 site
Flexor Pollicis Longus	20 Units in 1 site

Figure 2: Injection Sites for Upper Limb Spasticity



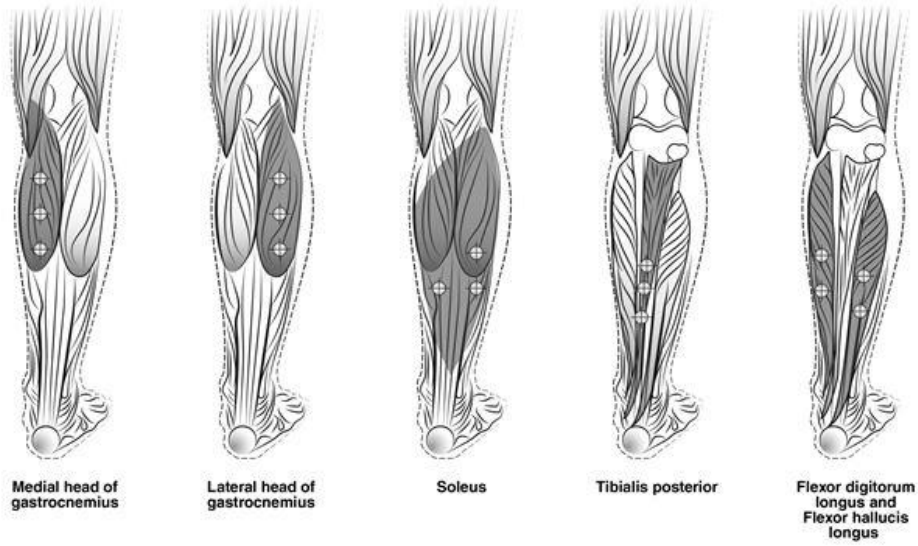
Lower Limb Spasticity

The recommended dose for treating lower limb spasticity is 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus) (see Table 4 and Figure 3).

Table 4: BOTOX Dosing by Muscle for Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	75 Units divided in 3 sites
Gastrocnemius lateral head	75 Units divided in 3 sites
Soleus	75 Units divided in 3 sites
Tibialis Posterior	75 Units divided in 3 sites
Flexor hallucis longus	50 Units divided in 2 sites
Flexor digitorum longus	50 Units divided in 2 sites

Figure 3: Injection Sites for Lower Limb Spasticity



2.6 Cervical Dystonia

A double-blind, placebo-controlled 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 this 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 (14.5)]*.

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, 5.5, 5.6)]*.

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 1). In general, no more than 50 Units per site should be administered using a sterile needle (e.g., 25-30 gauge) of an appropriate length. 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 double-blind, placebo-controlled study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

2.7 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 Table 1). Using a sterile 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.

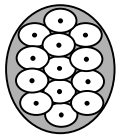
Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

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 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 4.

Figure 4: Injection Pattern for Primary Axillary Hyperhidrosis



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.

2.8 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 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

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.

2.9 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.

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 (2.2)]* 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.

Initial Doses in Units

Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

- For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
- For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

Subsequent Doses for Residual or Recurrent Strabismus

- It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
- Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
- Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
- 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.
- The maximum recommended dose as a single injection for any one muscle is 25 Units.

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

3 DOSAGE FORMS AND STRENGTHS

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection USP prior to injection.

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 (5.4)]*.

4.2 Infection at the Injection Site(s)

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

4.3 Urinary Tract Infection or Urinary Retention

Intradetrusor injection of BOTOX is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection. Intradetrusor injection of BOTOX is also contraindicated in patients with urinary retention and in patients with post-void residual (PVR) urine volume >200 mL, who are not routinely performing clean intermittent self-catheterization (CIC).

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 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 an underlying condition 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 and spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

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), severe primary axillary hyperhidrosis at the recommended dose (100 Units), strabismus, or for chronic migraine at the labeled doses have been reported.

5.3 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

5.4 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.

5.5 Increased Risk of Clinically Significant Effects with 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 when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects

including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX *[see Warnings and Precautions (5.2, 5.6)]*.

5.6 Dysphagia and Breathing Difficulties

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 oropharyngeal muscles that control swallowing or breathing *[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 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.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia 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)]*.

5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients treated for upper limb spasticity 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 (FVC) ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 5).

Table 5: Event Rate Per Patient Treatment Cycle Among Patients with Reduced Lung Function Who Experienced at Least a 15% or 20% Decrease in FVC 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 spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo *[see Warnings and Precautions (5.10)]*.

In a double-blind, placebo-controlled, parallel group study in adult patients with detrusor overactivity associated with a neurologic condition and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 6).

Table 6: Number and Percent of Patients Experiencing at Least a 15% or 20% Decrease in FVC From Baseline at Week 2, 6, 12 Post-injection with BOTOX or Placebo

	BOTOX 200 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%
Week 2	0/15 (0%)	0/15 (0%)	1/11 (9%)	0/11 (0%)
Week 6	2/13 (15%)	1/13 (8%)	0/12 (0%)	0/12 (0%)
Week 12	0/12(0%)	0/12 (0%)	0/7 (0%)	0/7 (0%)

5.8 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.

5.9 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.

5.10 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 251 Units-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%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

5.11 Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition

Autonomic dysreflexia associated with intradetrusor injections of BOTOX could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. In clinical trials, the incidence of autonomic dysreflexia was greater in patients treated with BOTOX 200 Units compared with placebo (1.5% versus 0.4%, respectively).

5.12 Urinary Tract Infections in Patients with Overactive Bladder

BOTOX increases the incidence of urinary tract infection *[see Adverse Reactions (6.1)]*. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

5.13 Urinary Retention in Patients Treated for Bladder Dysfunction

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

The incidence and duration of urinary retention is described below for patients with overactive bladder and detrusor overactivity associated with a neurologic condition who received BOTOX or placebo injections.

Overactive Bladder

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterization (CIC) for urinary retention following treatment with BOTOX or placebo is shown in Table 7. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 7: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB

Timepoint	BOTOX 100 Units (N=552)	Placebo (N=542)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	6.5% (n=36)	0.4% (n=2)
Duration of Catheterization for Urinary Retention (Days)		
Median	63	11
Min, Max	1, 214	3, 18

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 8.

Table 8. Proportion of Patients Experiencing Urinary Retention Following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB According to History of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

Detrusor Overactivity associated with a Neurologic Condition

In two double-blind, placebo-controlled trials in patients with detrusor overactivity associated with a neurologic condition (NDO-1 and NDO-2), the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX 200 Units or placebo is shown in Table 9. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 9: Proportion of Patients Not Using CIC at Baseline and then Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-blind, Placebo-controlled Clinical Trials

Timepoint	BOTOX 200 Units (N=108)	Placebo (N=104)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	30.6% (n=33)	6.7% (n=7)
Duration of Catheterization for Urinary Retention (Days)		
Median	289	358
Min, Max	1, 530	2, 379

Among patients not using CIC at baseline, those with Multiple Sclerosis (MS) were more likely to require CIC post-injection than those with Spinal Cord Injury (SCI) (see Table 10).

Table 10: Proportion of Patients by Etiology (MS and SCI) Not Using CIC at Baseline and then Catheterizing for Urinary Retention Following an Injection in Double-blind, Placebo-controlled Clinical Trials

Timepoint	MS		SCI	
	BOTOX 200 Units (N=86)	Placebo (N=88)	BOTOX 200 Units (N=22)	Placebo (N=16)
At any time during complete treatment cycle	31% (n=27)	5% (n=4)	27% (n=6)	19% (n=3)

A placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) was conducted in non-catheterizing MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. Catheterization for urinary retention was initiated in 15.2% (10/66) of patients following treatment with BOTOX 100 Units versus 2.6% (2/78) on placebo at any time during the complete treatment cycle. The median duration of post-injection catheterization for those who developed urinary retention was 64 days for BOTOX 100 Units and 2 days for placebo.

5.14 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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

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)]*
- Serious Adverse Reactions with Unapproved Use *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Contraindications (4.1) and Warnings and Precautions (5.4)]*
- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders *[see Warnings and Precautions (5.5)]*
- Dysphagia and Breathing Difficulties *[see Warnings and Precautions (5.6)]*
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition *[see Warnings and Precautions (5.7)]*
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm *[see Warnings and Precautions (5.8)]*
- Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus *[see Warnings and Precautions (5.9)]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions (5.10)]*
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition *[see Warnings and Precautions (5.11)]*
- Urinary Tract Infections in Patients with Overactive Bladder *[see Warnings and Precautions (5.12)]*
- Urinary Retention in Patients Treated for Bladder Dysfunction *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug 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 reactions observed with the use of BOTOX Cosmetic also have the potential to be observed with the use of BOTOX.

In general, adverse reactions 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. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment. Needle-related pain and/or anxiety may result in vasovagal responses (including 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)]*.

Overactive Bladder

Table 11 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 11: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Often than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection, in Double-blind, Placebo-controlled Clinical Trials in Patients with OAB

Adverse Reactions	BOTOX 100 Units (N=552)	Placebo (N=542)
Urinary tract infection	99 (18%)	30 (6%)
Dysuria	50 (9%)	36 (7%)
Urinary retention	31 (6%)	2 (0%)
Bacteriuria	24 (4%)	11 (2%)
Residual urine volume*	17 (3%)	1 (0%)

*Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥350 mL regardless of symptoms, and for PVR ≥200 mL to <350 mL with symptoms (e.g., voiding difficulty).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 12.

Table 12: Proportion of Patients Experiencing Urinary Tract Infection following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB according to history of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary tract infection (UTI)	25 (31%)	8 (12%)	135 (26%)	51 (10%)

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

Detrusor Overactivity associated with a Neurologic Condition
Table 13 presents the most frequently reported adverse reactions in the two Phase 3 double-blind, placebo-controlled studies (NDO-1 and NDO-2) within 12 weeks of injection for patients with detrusor overactivity associated with a neurologic condition treated with BOTOX 200 Units.

Table 13: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection in Double-blind, Placebo-controlled Clinical Trials (NDO-1 and NDO-2)

Adverse Reactions	BOTOX 200 Units (N=262)	Placebo (N=272)
Urinary tract infection	64 (24%)	47 (17%)
Urinary retention	45 (17%)	8 (3%)
Hematuria	10 (4%)	8 (3%)

The following adverse reactions with BOTOX 200 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 44 weeks): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

In the Multiple Sclerosis (MS) patients enrolled in the double-blind, placebo-controlled trials, the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX and 0.20 for placebo.

No change was observed in the overall safety profile with repeat dosing.

Table 14 presents the most frequently reported adverse reactions in a placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) conducted in MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least one anticholinergic agent and not catheterized at baseline. The table below presents the most frequently reported adverse reactions within 12 weeks of injection.

Table 14: Adverse Reactions Reported by >2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection (NDO-3)

Adverse Reactions	BOTOX 100 Unit (N=66)	Placebo (N=78)
Urinary tract infection	17 (26%)	5 (6%)
Bacteriuria	6 (9%)	4 (5%)
Urinary retention	10 (15%)	1 (1%)
Dysuria	3 (5%)	1 (1%)
Residual urine volume*	11 (17%)	1 (1%)

* Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥350 mL regardless of symptoms, and for PVR ≥200 mL to <350 mL with symptoms (e.g., voiding difficulty).

The following adverse events with BOTOX 100 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 51 weeks): urinary tract infections (39%), bacteriuria (18%), urinary retention (17%), residual urine volume* (17%), dysuria (9%), and hematuria (5%).

No difference in the MS exacerbation annualized rate (i.e., number of MS exacerbating events per patient-year) was observed (BOTOX =0, placebo =0.07).

Chronic Migraine
In double-blind, placebo-controlled chronic migraine 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 15.

Table 15: 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 System Organ Class	**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 and 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 reactions 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 upper limb spasticity appear in Table 16.

Table 16: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by System Organ Class	BOTOX 251 Units-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%)
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%)

Twenty two adult patients, enrolled in double-blind placebo controlled studies, received 400 Units or higher of BOTOX for treatment of upper limb spasticity. In addition, 44 adults received 400 Units of BOTOX or higher for four consecutive treatments over approximately one year for treatment of upper limb spasticity. The type and frequency of adverse reactions observed in patients treated with 400 Units of BOTOX were similar to those reported in patients treated for upper limb spasticity with 360 Units of BOTOX.

Lower Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 17. Two hundred thirty one patients enrolled in a double-blind placebo controlled study (Study 6) received 300 Units to 400 Units of BOTOX, and were compared with 233 patients who received placebo. Patients were followed for an average of 91 days after injection.

Table 17: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 6)

Adverse Reactions	BOTOX (N=231)	Placebo (N=233)
Musculoskeletal and connective tissue disorders		
Arthralgia	8 (3%)	2 (1%)
Back pain	6 (3%)	4 (2%)
Myalgia	4 (2%)	3 (1%)
Infections and infestations		
Upper respiratory tract infection	4 (2%)	2 (1%)
General disorders and administration site conditions		
Injection site pain	5 (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, 5.6)]*.

The most common severe adverse reaction 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, 5.6)]*. 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 (5.6)]*.

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 reactions (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 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 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to onabotulinumtoxinA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

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 developed the presence of neutralizing antibodies.

In overactive bladder patients with analyzed specimens from the two phase 3 studies and the open-label extension study, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. Response to subsequent BOTOX treatment was not different following seroconversion in these three patients.

In detrusor overactivity associated with neurologic condition patients with analyzed specimens in the drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Following development of neutralizing

antibodies in these 8 patients, 4 continued to experience clinical benefit, 2 did not experience clinical benefit, and the effect on the response to BOTOX in the remaining 2 patients is not known.

The data reflect the patients whose test results were considered positive for neutralizing activity to BOTOX in a mouse protection assay or negative based on a screening ELISA assay or mouse protection assay.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. 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.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions 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 drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy; denervation/muscle atrophy; diarrhea; hyperhidrosis; hypoacusis; hypoaesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

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 (5.4, 5.6)]*.

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.

7 DRUG INTERACTIONS

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

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.

7.2 Anticholinergic Drugs

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

7.3 Other Botulinum Neurotoxin Products

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.

7.4 Muscle Relaxants

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

Risk Summary

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX in pregnant women. In animal studies, administration of BOTOX during pregnancy resulted in adverse effects on fetal growth (decreased fetal weight and skeletal ossification) at clinically relevant doses, which were associated with maternal toxicity *[see Data)]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated populations is unknown.

Data

Animal Data

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 equal to the human dose of 400 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 human dose of 400 Units, 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 2 times the human dose of 400 Units, based on Units/kg.

8.2 Lactation

Risk Summary

There are no data on the presence of BOTOX in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BOTOX and any potential adverse effects on the breastfed infant from BOTOX or from the underlying maternal conditions.

8.4 Pediatric Use

Bladder Dysfunction

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

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.

Axillary Hyperhidrosis

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.

8.5 Geriatric Use

Of the 2145 patients in placebo-controlled clinical studies of BOTOX for the treatment of spasticity, 33.5% were 65 or older, and 7.7% were 75 years of age or older. No overall differences in safety were observed between elderly patients and younger patients.

In clinical studies of BOTOX across other indications, no overall differences in safety were observed between elderly patients and younger patients, with the exception of Overactive Bladder (see below). Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Overactive Bladder

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% were 65 years of age or older, and 14.7% were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 18). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

Table 18: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

	<65 Years		65 to 74 Years		≥75 Years	
Adverse Reactions	**BOTOX 100 Units (N=344)**	**Placebo (N=348)**	**BOTOX 100 Units (N=169)**	**Placebo (N=151)**	**BOTOX 100 Units (N=94)**	**Placebo (N=86)**
Urinary tract infection	73 (21%)	23 (7%)	51 (30%)	20 (13%)	36 (38%)	16 (19%)
Urinary retention	21 (6%)	2 (0.6%)	14 (8%)	0 (0%)	8 (9%)	1 (1%)

Observed effectiveness was comparable between these age groups in placebo-controlled clinical studies.

10 OVERDOSAGE

Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection *[see Boxed Warning and Warnings and Precautions (5.2, 5.6)]*. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

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, intradetrusor 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.

The primary release procedure for BOTOX uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products BOTOX and BOTOX Cosmetic. One Unit of BOTOX corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, 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. The specific activity of BOTOX is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of BOTOX contains either 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 autonomic 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.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

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 toxicology 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 human dose of 400 Units, on a body weight basis (Units/kg).

13.2 Animal Toxicology and/or Pharmacology

In a study to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 Units/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 Units/kg (~12X the highest human bladder dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injections up to 100 Units/kg (~33X the highest human bladder dose [200 Units], based on Units/kg).

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

Two double-blind, placebo-controlled, randomized, multi-center, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency (Studies OAB-1 and OAB-2). Patients needed to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days to enter the studies. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 Units of BOTOX (n=557), or placebo (n=548). Patients received 20 injections of study drug (5 units of BOTOX or placebo) spaced approximately 1 cm apart into the detrusor muscle.

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 19 and 20, and Figures 5 and 6.

Table 19: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

	BOTOX 100 Units (N=278)	Placebo (N=272)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean Baseline	5.5	5.1		
Mean Change[*] at Week 2	-2.6	-1.0	-1.6	
Mean Change[*] at Week 6	-2.8	-1.0	-1.8	
Mean Change[*] at Week 12[**]	-2.5	-0.9	-1.6 (-2.1, -1.2)	<0.001
Daily Frequency of Micturition Episodes[b]				
Mean Baseline	12.0	11.2		
Mean Change[†] at Week 12[**]	-1.9	-0.9	-1.0 (-1.5, -0.6)	<0.001
Volume Voided per Micturition[b] (mL)				
Mean Baseline	156	161		
Mean Change[†] at Week 12[**]	38	8	30 (17, 43)	<0.001

[*] Least squares (LS) mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. Last observation carried forward (LOCF) values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

[**] Primary timepoint

[a] Primary variable

[b] Secondary variable

Table 20: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

	BOTOX 100 Units (N=275)	Placebo (N=269)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean Baseline	5.5	5.7		
Mean Change[*] at Week 2	-2.7	-1.1	-1.6	
Mean Change[*] at Week 6	-3.1	-1.3	-1.8	
Mean Change[*] at Week 12[**]	-3.0	-1.1	-1.9 (-2.5, -1.4)	<0.001
Daily Frequency of Micturition Episodes[b]				
Mean Baseline	12.0	11.8		
Mean Change[†] at Week 12[**]	-2.3	-0.6	-1.7 (-2.2, -1.3)	<0.001
Volume Voided per Micturition[b] (mL)				
Mean Baseline	144	153		
Mean Change[†] at Week 12[**]	40	10	31 (20, 41)	<0.001

[*] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

[**] Primary timepoint

[a] Primary variable

[b] Secondary variable

Figure 5: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-1

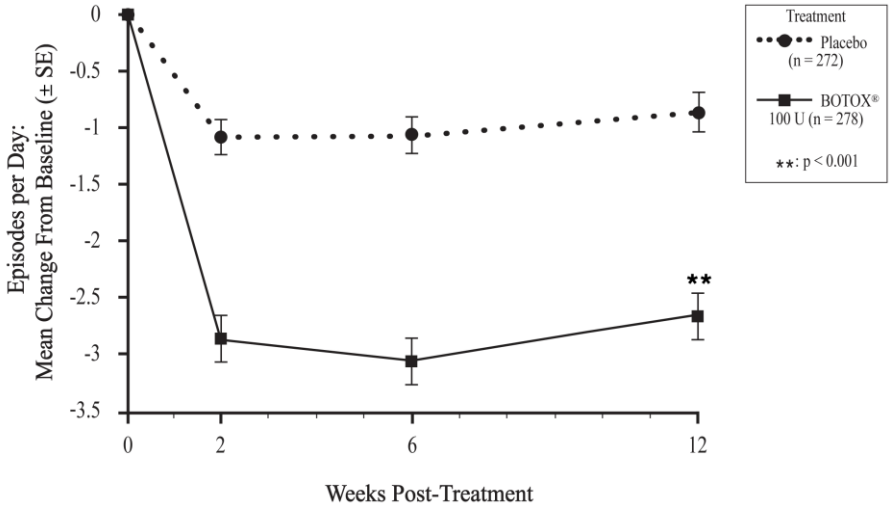
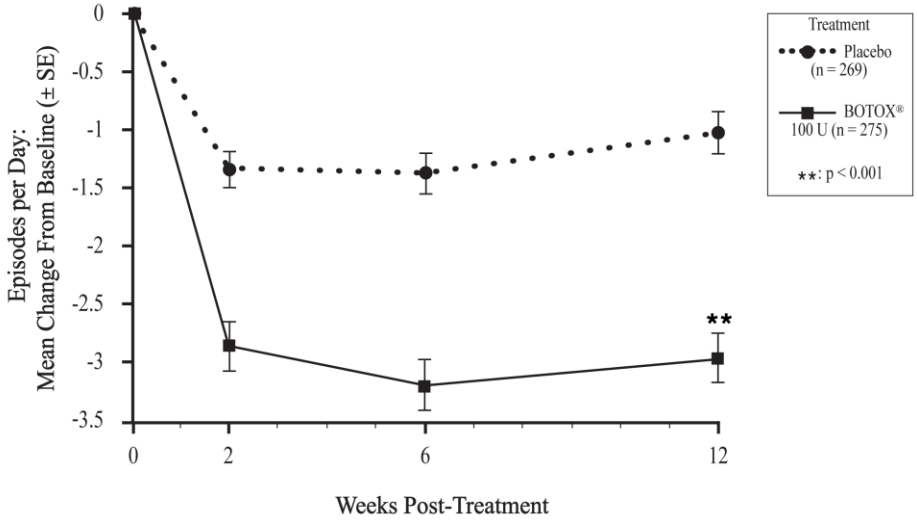


Figure 6: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-2



The median duration of response in Study OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19-24 weeks for the BOTOX 100 Unit dose group compared to 13 weeks for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days.

14.2 Detrusor Overactivity associated with a Neurologic Condition

Two double-blind, placebo-controlled, randomized, multi-center clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (Studies NDO-1 and NDO-2). A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 21 and 22, and Figures 7 and 8.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.

Table 21: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) Study NDO-1

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	134	146		
Mean Baseline	32.3	28.3		
Mean Change* at Week 2	-15.3	-10.0	-5.3	—
Mean Change* at Week 6**	-19.9	-10.6	-9.2 (-13.1, -5.3)	p<0.001
Mean Change* at Week 12	-19.8	-8.8	-11.0	—
Maximum Cystometric Capacity[b] (mL)				
N	123	129		
Mean Baseline	253.8	259.1		
Mean Change* at Week 6**	135.9	12.1	123.9 (89.1, 158.7)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	41	103		
Mean Baseline	63.1	57.4		
Mean Change* at Week 6**	-28.1	-3.7	-24.4	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

** Primary timepoint

[a] Primary endpoint

[b] Secondary endpoint

Table 22: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) in Study NDO-2

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	91	91		
Mean Baseline	32.7	36.8		
Mean Change* at Week 2	-18.0	-7.9	-10.1	—
Mean Change* at Week 6**	-19.6	-10.8	-8.8 (-14.5, -3.0)	p=0.003
Mean Change* at Week 12	-19.6	-10.7	-8.9	—
Maximum Cystometric Capacity[b] (mL)				
N	88	85		
Mean Baseline	239.6	253.8		
Mean Change* at Week 6**	150.8	2.8	148.0 (101.8, 194.2)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	29	68		
Mean Baseline	65.6	43.7		
Mean Change* at Week 6**	-28.7	2.1	-30.7	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

** Primary timepoint

[a] Primary endpoint

[b] Secondary endpoint

Figure 7: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-1

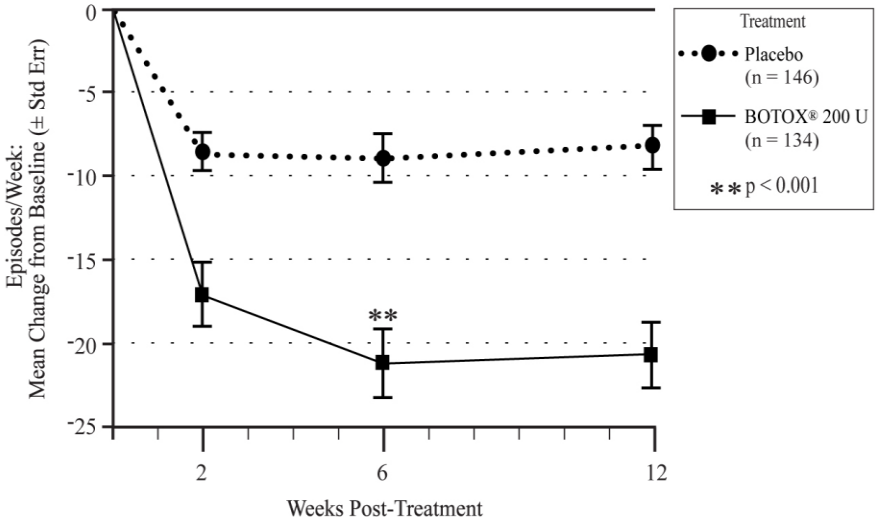
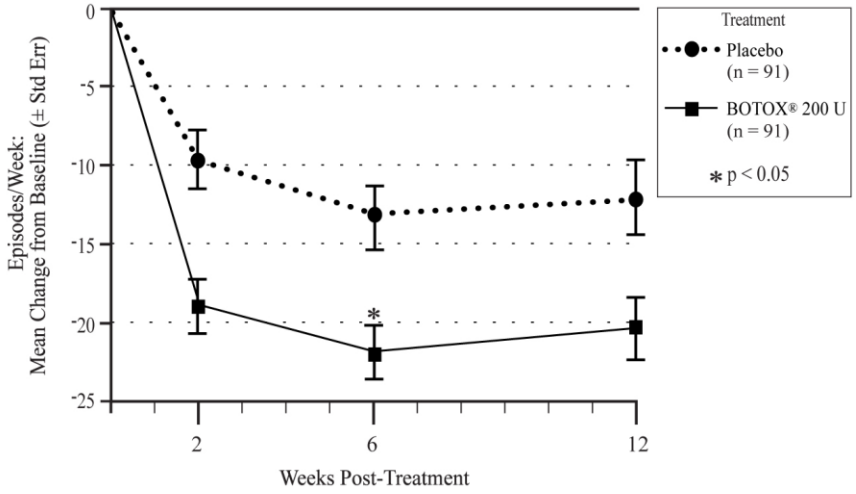


Figure 8: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-2



The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295-337 days (42-48 weeks) for the 200 Units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2).

A placebo-controlled, double-blind randomized post-approval 52 week study (Study NDO-3) was conducted in MS patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. These patients were randomized to receive either 100 Units of BOTOX (n=66) or placebo (n=78).

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for BOTOX® (100 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Table 23.

Table 23: Baseline and Change from Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) in Study NDO-3

	BOTOX 100 Units	Placebo	Treatment Difference*	p-value*
Daily Frequency of Urinary Incontinence Episodes[a]				
N	66	78		
Mean Baseline	4.2	4.3		
Mean Change* at Week 2	-2.9	-1.2	-1.7	—
Mean Change* at Week 6**	-3.4	-1.1	-2.3 (-3.0, -1.7)	p<0.001
Mean Change* at Week 12	-2.7	-1.0	-1.8	—
Maximum Cystometric Capacity[b] (mL)				
N	62	72		
Mean Baseline	248.9	245.5		
Mean Change* at Week 6**	134.4	3.5	130.9 (94.8, 167.0)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	25	51		
Mean Baseline	42.4	39.0		
Mean Change* at Week 6**	-19.2	2.7	-21.9 (-37.5, -6.3)	

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline daily endpoint as covariate and treatment group and propensity score stratification as factors. LOCF values were used to analyze the primary efficacy variable.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

The median duration of response in study NDO-3, based on patient qualification for re-treatment was 362 days (52 weeks) for the BOTOX 100 Units dose group compared to 88 days (13 weeks) for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days with no more than 1 incontinence-free day.

14.3 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 24).

Table 24: 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≤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 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.

Figure 9: Mean Change from Baseline in Number of Headache Days for Study 1

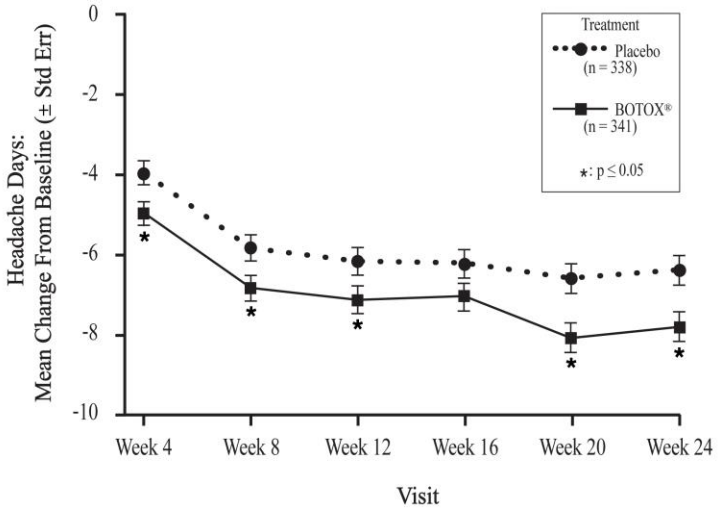
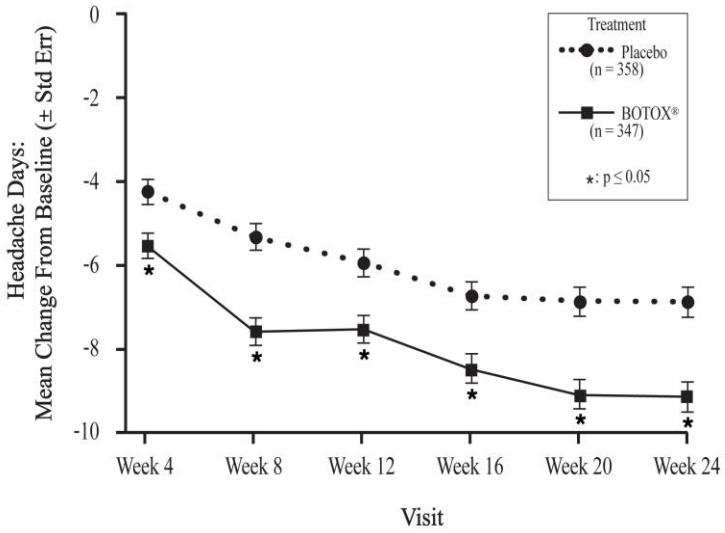


Figure 10: Mean Change from Baseline in Number of Headache Days for Study 2



14.4 Spasticity

Upper Limb Spasticity

The efficacy of BOTOX for the treatment of upper limb spasticity was evaluated in three randomized, multi-center, double-blind, placebo-controlled studies (Studies 1, 2, and 3). Two additional randomized, multi-center, double-blind, placebo-controlled studies for upper limb spasticity in adults also included the evaluation of the efficacy of BOTOX for the treatment of thumb spasticity (Studies 4 and 5).

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 25). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 25: 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 5-point scale with grades of 0 [no increase in muscle tone] to 4 [limb rigid in flexion or extension]. It 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).

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 26.

Table 26: 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 27).

Table 27: 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 28.

Table 28: 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 27).

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 29.

Table 29: 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

Study 4 included 170 patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose =40 Units in thumb muscles) or placebo (see Table 30). Study 5 included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, patients received 15 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus under EMG guidance (total BOTOX low dose =30 Units, total BOTOX high dose =40 Units), or placebo (see Table 30). The duration of follow-up in Study 4 and Study 5 was 12 weeks.

Table 30: Study Medication Dose and Injection Sites in Studies 4 and 5

Muscles Injected	Study 4		Study 5				Number of Injection Sites for Studies 4 and 5
	BOTOX (Units)	Volume (mL)	BOTOX low dose (Units)	BOTOX high dose (Units)	Volume low dose (mL)	Volume high dose (mL)	
Thumb Adductor Pollicis	20	0.4	15	20	0.3	0.4	1
Flexor Pollicis Longus	20	0.4	15	20	0.3	0.4	1

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 31. The MAS uses a similar scoring system as the Ashworth Scale.

Table 31: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

	BOTOX (N=66)	Placebo (N=57)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale[††a]	-1.0[*]	0.0
Median Physician Global Assessment of Response to Treatment[††]	2.0[*]	0.0

[††] Secondary endpoints at Week 6
[*] Significantly different from placebo ($p \leq 0.001$)
[a] BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function]) are presented in Table 32.

Table 32: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

	BOTOX low dose (30 Units) (N=14)	Placebo low dose (N=9)	BOTOX high dose (40 Units) (N=43)	Placebo high dose (N=23)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale†††[a]	-1.0	-1.0	-0.5*	0.0
Median Change from Baseline in Clinical Global Impression Score by Physician ††	1.0	0.0	2.0*	0.0

†† Secondary endpoint at Week 6
††† Other endpoint at Week 6
* Significantly different from placebo ($p \leq 0.010$)
[a] BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Lower Limb Spasticity
The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 33) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.

Table 33: Study Medication Dose and Injection Sites in Study 6

Muscles Injected	BOTOX (Units)	Number of Injection Sites
Mandatory Ankle Muscles Gastrocnemius (medial head)	75	3
Gastrocnemius (lateral head)	75	3
Soleus	75	3
Tibialis Posterior	75	3
Optional Muscles Flexor Hallucis Longus	50	2
Flexor Digitorum Longus	50	2
Flexor Digitorum Brevis	25	1
Extensor Hallucis	25	1
Rectus Femoris	100	4

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement).

Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 34).

Table 34: Co-Primary Efficacy Endpoints Results in Study 6 (Intent-to-treat Population)

	BOTOX 300 to 400 Units (N=233)	Placebo (N=235)
Mean Change from Baseline in Ankle Plantar Flexors on the modified Ashworth Scale		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7

* Significantly different from placebo ($p<0.05$)

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 11) and CGI (see Figure 12) were observed at Week 2, Week 4, and Week 6 for patients treated with BOTOX.

Figure 11: Modified Ashworth Scale Ankle Score for Study 6 – Mean Change from Baseline by Visit

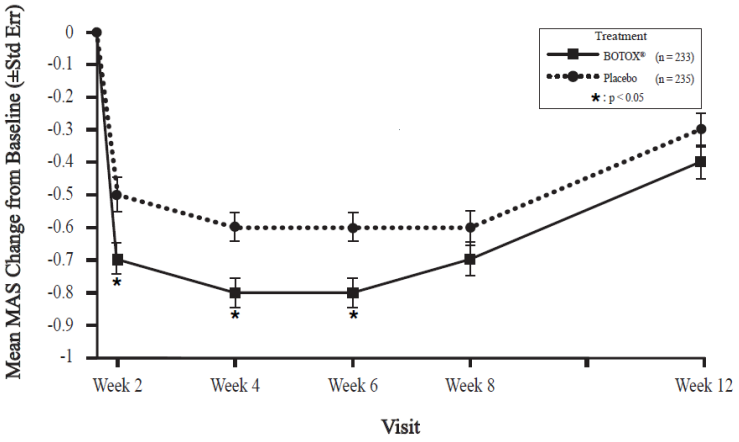
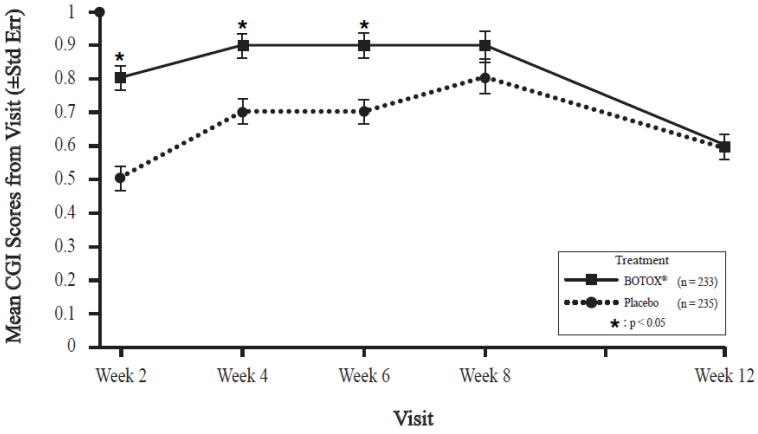


Figure 12: Clinical Global Impression by Physician for Study 6 – Mean Scores by Visit



14.5 Cervical Dystonia

A 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 35.

Table 35: 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.

In this 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 36. The total dose and muscles selected were tailored to meet individual patient needs.

Table 36: 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.

There were several randomized studies conducted prior to the double-blind, placebo-controlled study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of BOTOX.

14.6 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 37).

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 37: 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.

14.7 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.

14.8 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:
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. 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

Advise patients 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, 5.6)]*.

Ability to Operate Machinery or Vehicles

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

Voiding Symptoms after Bladder Injections

After bladder injections for urinary incontinence, advise patients to contact their physician if they experience difficulties in voiding or burning sensation upon voiding.

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

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, including:

- **Problems breathing or swallowing**
- **Spread of toxin effects**

These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. 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, days, 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 people 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, days, 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, crow's feet lines, and/or forehead lines.

What are BOTOX and BOTOX Cosmetic?

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

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- 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 increased muscle stiffness in ankle and toe muscles in adults with lower 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 for adults that is injected into muscles and used for a short period of time (temporary) to improve the look of:

- moderate to severe frown lines between the eyebrows (glabellar lines)
- moderate to severe crow's feet lines
- moderate to severe forehead lines

You may receive treatment for frown lines, crow's feet lines, and forehead lines at the same time.

It is not known whether **BOTOX** is safe or effective in people younger than:

- 18 years of age for treatment of urinary incontinence
- 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 people 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.

It is not known if **BOTOX Cosmetic** is safe and effective for use more than 1 time every 3 months.

Who should not receive BOTOX or BOTOX Cosmetic?

Do not receive **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
- are being treated for urinary incontinence and have a urinary tract infection (UTI)
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing)

What should I tell my doctor before receiving 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**?"

- have allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- have or have had a breathing problem, such as asthma or emphysema
- have or have had swallowing problems
- have or have had bleeding problems
- have plans to have surgery
- had surgery on your face
- have weakness of your forehead muscles, such as trouble raising your eyebrows
- have drooping eyelids
- have any other change in the way your face normally looks
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breastfeeding 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 over-the-counter medicines, vitamins and herbal supplements. 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
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners)

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 will I receive BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **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 receiving BOTOX or BOTOX Cosmetic?

BOTOX and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, vision problems, or dizziness 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.
- drooping eyebrows
- urinary tract infection in people being treated for urinary incontinence
- painful urination in people being treated for urinary incontinence
- inability to empty your bladder on your own and are being treated for urinary incontinence. If you have difficulty fully emptying your bladder after getting **BOTOX**, you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.
- 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.

What are the ingredients in BOTOX and BOTOX Cosmetic?

Active ingredient: onabotulinumtoxin A

Inactive ingredients: human albumin and sodium chloride

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. **Revised: 10/2017**

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PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

This is a joint research project:

Dr. William Gerald Austen Jr. is the PI at Partners.

Dr. Rami Burstein is the Principal Investigator at BIDMC

PROTOCOL TITLE

Novel concepts for OnabotulinumtoxinA (Botox) mechanisms of action: role in altering the molecular environment in which pain fibers exist

FUNDING

Allergan Inc.

VERSION DATE

11/13/18

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

To compare Botox-treated and Botox-untreated symptomatic tissues (defined as areas where the head hurts and the pain is felt) of chronic migraine (CM) patients using targeted transcriptome and genome-wide epigenome analysis. This aim will test the hypothesis that Botox reverses the abnormal expression of inflammatory genes in headache-affected regions and pericranial muscles, fascia, and perineurium of nerves supplying them.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

The broad objective of this proposal is to understand better how Botox works and determine whether it can attenuate inflammation. Based on our preliminary findings, we expect the proposed research to vastly expand the understanding of Botox MOA, both in migraine prophylaxis and somatic pain conditions associated with inflammation. Scientifically, we expect to gain new insight into the role played by Botox in environments that surround relevant peripheral nociceptors – potentially by attenuating local expression of pro-inflammatory molecules (mRNA) and their post-transcriptional regulators (non-coding RNA). In the context of migraine, such tissues include the calvarial periosteum, galea aponeurotica, pericranial muscles and fascia surrounding extracranial nerves (e.g., occipital, supraorbital, auriculotemporal nerves). In the context of other somatic

pains, such tissues include muscles, fascia, and the perineurium. The potential impacts of the proposed research is that if successful, it will broaden the clinical use of Botox. Equally important, it will define a novel framework for conceptualizing about Botox MOA and consequently, why and how it may be used to treat other pains and possibly conditions associated with abnormal inflammatory and immune responses.

The goals of the proposed research will be achieved by studying tissues commonly discarded during nerve decompression surgeries performed to alleviate neck and head pain in chronic migraineurs. These goals were formulated on the basis of two sets of preliminary clinical findings. The first showed that gene transcripts (mRNA) that promote immune and inflammatory responses are significantly upregulated in calvarial periosteum of CM patients (as compared to control subjects) and that gene transcripts (mRNA) that reduce immune and inflammatory responses are significantly down-regulated in calvarial periosteum of CM patients (as compared to control subjects).

In more detail, there is new evidence of extracranial origins of migraine headache. Clinically, there is data that describes an imploding headache (extracranial) versus exploding headache (intracranial) [1]. There is evidence that expression of proinflammatory genes (eg, CCL8, TLR2) in the calvarial periosteum is significantly increased in CM patients, whereas expression of genes that suppress inflammation and immune cell differentiation (eg, IL10RA, CSF1R) is decreased. It is well known that anti- inflammatory drugs improve migraine attacks. It has further been shown that extracranial administration of OnabotulinumtoxinA is effective in reducing the number of migraine days per month in patients who testified to having 'imploding', but not in those who testified to having 'exploding' headache [2]. The identification of extracranial pathophysiologies in chronic migraine patients whose headaches are most commonly perceived as imploding, and the finding that imploding migraine patients are those who benefit most from prophylactic treatment with OnabotulinumtoxinA [1], gave rise to a theory that Botox may help patients with imploding headache due to anti- inflammatory properties.

1. Jakubowski M, McAllister PJ, Bajwa ZH, Ward TN, Smith P, Burstein R (2006) Exploding vs. imploding headache in migraine prophylaxis with Botulinum Toxin A. Pain 125 (3):286-295. doi:10.1016/j.pain.2006.09.012
2. Burstein R, Dodick D, Silberstein S (2009) Migraine prophylaxis with botulinum toxin A is associated with perception of headache. Toxicon 54 (5):624-627. doi:10.1016/j.toxicon.2009.01.009

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Patients diagnosed with chronic migraine (fulfill criteria for CM as defined in the ICHD-3 beta), especially those complaining about chronic muscle tenderness, are routinely considered good candidate to benefit from a surgery in which trapped nerves are decompressed. In routine clinical care, such patients are referred to Dr. Perry to determine whether or not they fit to undergo the nerve decompression procedure. Of great importance to the evaluation of the proposed study is the fact that the decision on whether or not to operate is unrelated to and independent of any academic study. Those deemed good candidate for the surgery would be

presented with an option to hear about the study from Dr. Austen, the plastic surgeon responsible for their well-being during the surgery and the one handling the discarded tissues. Those interested in hearing about the study will be presented with all the necessary details required by the IRB and then given the option to sign (or not to sign).

Accordingly, up to ~~50~~ 65 chronic migraine patients will be recruited to the study (if they are found fit to undergo the surgery) by Dr. Austen, a certified plastic surgeon with enormous experience in performing these procedures.

Inclusion Criteria:

- Age 18-65 years
- Diagnosis of Chronic Migraine consistent with International Classification of Headache Disorders (ICHD-III) criteria, with a history of bilateral headache pain and chronic tenderness in neck muscles
- Patient is capable and willing to provide informed consent
- Female subjects of child bearing potential must have a negative pregnancy test at enrollment and agree to remain abstinent or use acceptable methods of birth control (i.e., hormonal contraceptives, inrauterindevce, diaphragm with spermicide, cervidal cap or spong, condoms or partner has had a vasectomy) for three months following injections of Botox
- Patients referred by their primary Neurologist to the study surgeon and who are determined to be candidates for surgical decompression of extracranial sensory nerves.
- Patient agrees to abstain from protocol-specific excluded medications (see Appendix A) beginning 14 days prior to the decompression surgery.

Exclusion Criteria:

- Patient has hypersensitivity reactions or other intolerance to Botox
- Patient is pregnant or trying to become pregnant with the timeframe of the study.

Infection at proposed injection sites

Those who agree to participate in the study, will be asked to fill out a 15min headache questionnaire that contains questions about their headaches. Subjects will also be asked to complete a headache diary 3 months prior to botox injections.

The headache diary will be filled out every day for 3 months prospectively prior to botox injection. Subjects will indicate whether they had migraines that day (check date box), what severity the migraines were (on a scale of 0-10), what the duration was (hours), what the location was, which other symptoms they experienced, which medications they took, how often they went to the ED, saw doctors or missed work and how much the total cost was. The total time spent every day filling out the diary should not exceed 5min.

Study subjects will be injected with Botox on one side of the back of the head. The FDA-approved injection paradigm includes 7 muscles (Frontalis, Corugator, Procerus, Occipitalis, temporalis, Trapezius, and the Cervical Paraspinal muscle group), 31 sites and 155 units divided as follows: Frontalis – 4 sites, 5 units in each; Corrugator – 2 sites, 5 units in each; Procerus – 1 site, 5 units; Occipitalis – 6 sites, 5 units at each; Temporalis – 8 sites, 5 units in each; Trapezius – 6 sites, 5 units at each; Cervical Paraspinal – 4 sites, 5 units in each.

Of these muscles, sites and doses, patients will be injected (from a 100 Unit vial of OnabotulinumtoxinA reconstituted per product manufacturer label instructions) as follows:

(A)	2 sites in the Occipitalis muscle (5 units each)
(B)	4 sites in the Cervical Paraspinal muscle group (5 units each)
(C)	2 sites in the Trapezius muscle (5 units each)

These injections will be given into one side only. This deviates from the standard of care, as Botox is usually injected on both sides if pain is experienced on both sides. The selection will be random based on subject number. Odd numbers will be injected on the right and even numbers on the left.

Because the standard surgical procedure involves removal of equal amount of corresponding tissues from both sides of the head, an opportunity is created here to analyze identical Botox-treated and Botox-untreated tissues. Importantly, all analyzed tissues are discarded as a part of the surgery and none is collected for the sake of the study.

Note that one of the standard clinical criteria that these patients must fulfill in order to qualify for the surgical decompression procedure (which is unrelated to the study) is to demonstrate that they have failed at least 3 attempts to treat their chronic migraine with (not necessarily Botox). Thus, all those who qualify for the study would have been treated with Botox at least twice before as per the FDA approved protocol.

Thirty days later, patients will undergo a study-unrelated nerve decompression surgery. This procedure involves the removal of different tissues surrounding trapped branches of the occipital nerve. These tissues include muscles, fascia, and periosteum (discarded tissue). The amount of tissue removed at each area is many folds larger than the amount of tissue needed for sampling (less than the size of 1 grain of rice.

There will be two visits:
Screening visit: Patients will be screened for eligibility. This will be performed during the regular clinical assessment for surgery. The study visit will take 30min. The subject will be asked to complete a 15 min questionnaire and will be asked to fill out a 3m headache diary which may take up to 5min a day.
Preoperative visit: will be injected with Botulinum Toxin. This will take 30 minutes.

There will be further routine clinical visits postoperatively (one week, 3 months and 12 months). However, these visits are not related to the study but are part of regular follow up. No study materials for this study will be collected as part of this visit.

Analysis to be Done at BIDMC

(A) Tissue processing, RNA isolation, genetic processing and mRNA counting will occur in Dr. Burstein's lab at Beth Israel Deaconess Medical Center, Harvard Medical School. Bioinformatics and biostatistics analyses will be conducted at Dr. Bhasin's lab at Beth Israel Deaconess Medical Center, Harvard Medical School.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Subjects enrolled at partners will participate in all portions of the study.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Since the surgery, itself is unrelated to the proposed study, all patients (those who sign the informed consent and those who chose not take part in the study) are booked for the surgery. Usual waiting time is 3-6 month. Those who signed the informed consent will be booked for another visit to Dr. Austens clinic 30 days prior to their planned surgery. In this visit, they will be injected with 40 units of Botox in one side of their head/neck as detailed below.

During surgery, calvarial periosteum, pericranial muscles and fascia surrounding nerves that are routinely removed and discarded, will be collected by Dr. Austen, stored in in RNAlater Solution, Ambion, CA, de-identified, frozen, and shipped overnight to Dr. Burstein's lab at BIDMC, where each sample will be recorded, verified, prepared for processing, and analyzed for targeted transcriptome and epigenome involved in inflammatory and immune responses.

The current standard of care for screening for migraine surgery includes injection of Botox to identify nerve triggers. In the occipital region, botox is either injected unilaterally or bilaterally depending on where pain occurs. When pain occurs bilaterally, Botox is injected on both sides. Subjects included in this study have bilateral occipital pain and would therefore as part of routine standard care be injected on both sides. As per this protocol, subjects will only be injected on one side. The risks of unilateral injection of botox (in addition to the risk of Botox in general outlined by the FDA) include continued pain on the uninjected side and/or injected side and one- sided muscle weakness, one- sided bruising, one sided infection on the injected side. . More generally, botox injections may cause the formation of anti-botox antibodies, which may decrease the effectiveness of botox treatment in other areas.

Subjects will be informed that they have the option to be injected with Botox on the uninjected side if any unwanted symptoms are experienced on the uninjected side. The cost of injection on the other side will be covered by the study funds.

A separate IRB protocol has already been approved for the use of discarded tissues, therefore this is also standard procedure.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

All proposed procedures are part of standard care for chronic migraine patients except for unilateral injection of Botox for which the risks are explained above.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

From the time of informed consent and for 3 months following injection, all self-reported adverse events will be reviewed by the study physician at each patient contact (patients are followed every 4 weeks after botox injection and one week, one month, three months, one year and after that yearly after surgery). All serious adverse events will be reported to the IRB and designated

safety monitor within 24 hours of awareness of the event. All unanticipated problems involving risks to subjects or others including adverse events will be presorted to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines.

Patients will not be included in the study if they are deemed poor candidates for surgery (screening occurs independent of this study).

Only subjects who have been selected as a surgical candidate for sensory nerve decompression of chronic headache would have their tissue tested. The taking of the periosteal sample would add no additional risk to the operation, as we are obtaining tissue discarded during surgery.

Botox therapy is currently approved by the FDA for preventive treatment of migraines. Possible side effects of Botox therapy include bruising, pain during injection, twitching, itching, and numbness.

Overall, we believe the risks of this study are sufficiently low and that the benefits of information to be gained and the potential benefit of improved migraine treatment outweigh the risks in this study.

Patients can elect to withdraw from the study at any time.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Only subjects who have been selected as a surgical candidate for sensory nerve decompression of chronic headache would have their tissue tested. The taking of the tissue samples would add no additional risk to the operation, as we are obtaining tissue discarded during surgery.

Botox therapy is currently approved by the FDA for preventive treatment of migraines.

All the potential risks of Botox injections as issued by the FDA are as follows. As we are only injecting the back of the occiput, symptoms occurring around the eyes, the oropharynx or generalized symptoms are very unlikely.

A. General:

- There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, after treatment with botulinum toxin.

- There have also been rare 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.

- The following events have been reported since the drug has been marketed and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction.

- In general, adverse events occur within the first week following injection of **BOTOX®** and while generally transient may have a duration of several months. Localized pain, tenderness and/or bruising may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin.

- Extraocular muscles adjacent to the injection site can be affected, causing ptosis or 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 are 15.7% and 16.9%, respectively.

- The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection.

B. Side effects and discomforts associated with study treatment that subjects may experience include the following and some of these effects may last as long as 3 to 4 months:

  - Drooping of the upper lid
  - Swelling of the eyelid
  - Dryness of the eye
  - Irritation/tearing of the eye
  - Difficulty in closing the upper lid
  - Sensitivity to light
  - Double vision
  - Soreness and/or bruising at the injection sites
  - Skin rash
  - Loss of facial wrinkling
  - Localized muscle weakness in the muscles which have been injected
  - Slight weakness in other muscles in the neck
  - Difficulty swallowing
  - Generalized weakness and fatigue

C. If the subject experiences any illness or discomfort during the study, they should notify Dr. *Austen.* Dr. Austen will then evaluate the subject to determine if the subject should continue in the study.

D. There may be side effects or discomforts from the study treatment which are not yet known. The subject could have an allergic reaction to BOTOX. A severe allergic reaction could be life-threatening.

E. Women who are pregnant, nursing a child, or planning a pregnancy during this study period may not participate in this study. The subject must confirm that, to the best of their knowledge, they are not now pregnant, and that they do not intend to become pregnant during the study. Prior to entering the study, the subject and the study doctor must agree on the method of birth control that they will use during the study. If the subject suspects that they have become pregnant during the study, they must notify the study doctor immediately. The sponsor of the study may need access to the subject's medical records regarding their pregnancy and the outcome of their pregnancy. In

addition, if they are pregnant or become pregnant during the study, there may be a risk of miscarriage or fetal malformation.

F. Treatment with BOTOX for the treatment of migraine headaches may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments with BOTOX for other purposes.

G. Botox injections are associated with pain from the needle prick with pain from the needle prick. A bruise may develop at the site, and there is a small chance the subject might get an infection.

Overall, we believe the risks of this study are sufficiently low and that the benefits of information to be gained and the potential benefit of improved migraine treatment outweigh the risks in this study.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

It is not possible to predict whether participants will benefit directly from participation in this study. However, their participation may help others in the future as a result of knowledge gained from the research

It is important to note that the clinical outcome of the procedure is unrelated to the proposed study. While improvement (or lack of improvement) in headache days per month after the procedure is followed by Dr. Austen, it is outside the scope of the proposed study and as such will not be collected or reported.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Currently, migraine surgery is only standard of care for adult patients who have failed multiple drugs. Pregnant women are not candidates for surgery due to anesthesia risks and cannot be included in this study. Further, Botox is not recommended in pregnancy. Children are not candidates for the same reasons. All other adults can be included in the study if they able to sign surgical consent and are English speakers.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied

participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

The headache questionnaire provided has been validated in English speaking populations only.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Recruitment

Patient screening, recruitment and consent will occur at Dr. Austen's clinic (MGH plastic surgery clinic) during a visit that determines their candidacy to undergo the surgery. As migraine prevalence is high in females we do not feel the need to enhance recruitment for women.

Patients are referred to the investigator or schedule an appointment independently for migraine surgery routinely. Subjects will be selected from among the patients that are referred to the investigator. A research nurse will initially explain participation in the study prior to the visit with the investigator. The patient will be given the consent forms and can take us much time as needed to consent for the study. The patient can also take the consent form home and call if interested. At the scheduled visit with the investigator he will reinforce that participation is voluntary and with their patients that participation is voluntary, that they do not have to participate, and the decision not to participate will not affect their care, now or in the future. The investigator can answer any questions the subject may have.

Subject Protection

Study subjects will not be employees of the study team.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

There is no subject remuneration.

For guidance, refer to the following Partners policies:
Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects

http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Speaking with and consenting participants will be conducted by Dr Austen. Sufficient time will be provided for eligible participants to review the consent form and ask any questions. The PI or designated co-investigator will provide a full description of the consent form and ensure subjects' understanding of the study before the consent is signed. Subjects will receive the same treatment, whether or not they participate in the study.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The principal investigator (Dr. Austen) will be responsible for monitoring outcomes. No independent monitoring will occur. The principal investigator (Dr. Austen) will report adverse events to the IRB in accordance with the IRB adverse event reporting procedures.

The information collected during this study will be placed in a research folder, and not added to the patient's medical record unless deliberately requested by the patient. All research folders will be filed in locked cabinets, independent of clinical charts or any other medical record in electronic format. Any magnetic or electronic information will be saved in password-protected computers to which only study staff will have access.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems reporting guidelines.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The principal investigator (Dr. Austen) will be responsible for monitoring outcomes. No independent monitoring will occur. The principal investigator (Dr. Austen) will report adverse events to the IRB in accordance with the IRB adverse event reporting procedures.

The principal investigator is responsible for adherence to all IRB rules and guidelines and for the accuracy and completeness of all forms, entries, and informed consent.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/datasafe.htm

Adverse Event Reporting Guidelines

http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All participants are given a participation number/ code at the time of enrollment. This code is kept on all data sheets instead of the patient's name. Subject information is only accessible by Partners authorized investigators and will not be shared with outside entities. The final results after statistical analysis will not be shared with any institution.

All clinical study records will be stored in a secure location in the office of Dr. Austen, as all research activities involving patient data will take place at MGH.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

De-identified discarded tissue will be transferred to Dr. Burstein's lab at Beth Israel Deaconess Medical Center for processing and analysis. No personally identifiable data (including name, date of birth, age, and gender) will be shared between the clinical site (MGH) and the processing site (BIDMC).

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Specimens will only be used for this research study. Subjects can withdraw their specimens at any time.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Collaborators will not collect specimens or data