CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 103000-S5232

Trade Name: Botox

Generic Name: onabotulinumtoxinA

Sponsor: Allergan Inc.

Approval Date: August 24th 2011

Indications: Treatment of urinary incontinence due to detrusor overactivity associated with neurological 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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000-5232

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000-5232

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	**sBLA**
Application Number(s)	**103000**
Priority or Standard	**Standard**
Submit Date(s)	**October 26, 2010**
Received Date(s)	**October 27, 2010**
PDUFA Goal Date	**August 27, 2011**
Division / Office	**DRUP/ODE III/OND**
Reviewer Name(s)	**Olivia J. Easley**
Review Completion Date	
Established Name	**onabotulinumtoxinA**
(Proposed) Trade Name	**BOTOX®**
Therapeutic Class	**neuromuscular blocking agent**
Applicant	**Allergan**
Formulation(s)	**Single-use, 200 Units vacuum-dried powder for reconstitution with sterile, non-preserved 0.9% sodium chloride injection USP prior to injection**
Dosing Regimen	**200 Units as 1 mL (6.7 units) injections across 30 sites into the urinary bladder detrusor**
Indication(s)	**Urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g. spinal cord injury, multiple sclerosis)**
Intended Population(s)	**Patients aged ≥18 years who are inadequately managed by or intolerant of anticholinergic medication**

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends, from a clinical perspective, that Botox 200 Units (U) for the treatment (b) (4) receive an **approval action**. However, because (b) (4) is a vague term, the labeled indication should be 'urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g. spinal cord injury, multiple sclerosis).' The population studied in the clinical trials consisted of adults who had been inadequately managed by or were intolerant of anticholinergic medication. Given that, along with the risks associated with Botox, the indication should be restricted to patients refractory to or intolerant of anticholinergic therapy. Therefore, the labeled indication should state, ***"for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g. spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication."***

1.2 Risk Benefit Assessment

In both pivotal phase 3 trials, Botox 200 U led to a statistically significant reduction in weekly urinary incontinence episode frequency (IEF) from baseline to week 6, the primary endpoint, when compared to placebo. The placebo-corrected mean change from baseline to week 6 in weekly IEF for Botox 200 U was -10.8 episodes. Botox 200 U also achieved efficacy when assessed by the two pre-specified secondary endpoints – change from baseline to week 6 in the urodynamic parameters maximum cystometric capacity (MCC) and maximum detrusor pressure (MDP).

The most common adverse events associated with injection of Botox into the bladder detrusor (i.e. intradetrusor injection) are development of urinary retention requiring self-catheterization, and urinary tract infection. Significant adverse events, such as dyspnea and worsened respiratory function, related to spread of toxin to sites remote to the bladder may rarely occur following intradetrusor Botox administration. Such events appear to occur in an idiosyncratic manner, but may be more likely in patients with underlying respiratory compromise (e.g., restrictive lung disease secondary to neuromuscular disorders).

The overall risk benefit profile for Botox in the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition is favorable, particularly as no approved alternative medical therapy exists for this condition. Because of the risks inherent to Botox injection, however, the indication should be limited to patients who have failed or are intolerant of anticholinergic therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) for Botox, approved by FDA on July 31, 2009, has already been implemented. The REMS includes a Medication Guide (MedGuide) for patients and a Communication Plan for Healthcare Providers. The current MedGuide and Dear Healthcare Provider Letter (DHCPL) already contain information regarding risk of significant and potentially life-threatening adverse events (e.g. dysphagia, dyspnea) related to distant spread of toxin. Both documents should be updated to include the most common risks associated with intradetrusor injection – urinary retention requiring self-catheterization, and urinary tract infection.

1.4 Recommendations for Postmarket Requirements and Commitments

A study of Botox in pediatric patients ages 10-17 years with urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g. spina bifida) should be conducted.

Reviewer's comment: For brevity, 'detrusor overactivity associated with a neurologic condition" will be referred to as neurogenic detrusor overactivity (NDO) in the remainder of this review.

2 Introduction and Regulatory Background

2.1 Product Information

BOTOX® (onabotulinumtoxinA) Purified Neurotoxin Complex is sterile, vacuum-dried purified botulinum toxin type A that is produced from the fermentation of Hall strain Clostridium botulinum type A. The United States' adopted name for the product is onabotulinumtoxinA.

Botox is supplied in single-use vials containing 50, 100 or 200 Units of the toxin. Prior to administration, the toxin is to be reconstituted with sterile, non- preserved 0.9% saline solution. The resulting solution is intended solely for intramuscular or intradetrusor injection.

2.2 Tables of Currently Available Treatments for Proposed Indications

Standard therapy for NDO involves clean intermittent catheterization (CIC) to regularly empty the bladder, along with muscarinic antagonist drugs (i.e. anticholinergics), such as tolterodine, which are indicated for overactive bladder (OAB). Ditropan XL (oxybutynin), an anticholinergic medication, is approved for the treatment of pediatric patients (≥6 years) with symptoms of detrusor overactivity associated with a neurologic condition (e.g., spina bifida).

2.3 Availability of Proposed Active Ingredient in the United States

Onabotulinum toxin type A was first approved in the US in 1989, and is currently indicated for chronic migraine headache prophylaxis, and for the treatment of upper limb spasticity, cervical dystonia, axillary hyperhidrosis, blepharospasm, glabellar lines, and strabismus.

Additional commercial preparations of botulinum toxin serotypes A or B are

- abobotulinumtoxinA (Dysport™), indicated for the treatment of cervical dystonia and glabellar lines
- incobotulinumtoxinA (Xeomin), approved for the treatment of cervical dystonia and blepharospasm
- rimabotulinumtoxinB (Myobloc®), indicated for the treatment of cervical dystonia.

These different formulations of botulinum toxin are not interchangeable.

2.4 Important Safety Issues with Consideration to Related Drugs

The most significant safety concern related to the use of Botox is the possibility of distant spread of toxin to areas remote to the injection site, particularly to the respiratory muscles. The current package insert contains a black box warning regarding this risk, which states, "*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 report of death.*"

2.5 Summary of Pre-submission Regulatory Activity

Interactions between FDA and the sponsor occurring prior to sBLA submission are summarized in Table 1.

Table 1 Regulatory Activity prior to submission of sBLA 103000

Date/Date range	Activity	Agreements Reached/Advice given
March 17, 2005	End-of-Phase 2 meeting	Recommendation from FDA to study effect of Botox in subjects with underlying respiratory compromise (b) (4)
May 3, 2005	IND 12430 for NDO indication opened in DRUP	
April 28, 2006	Type A meeting	Discussion of design of pivotal phase 3 studies, 191622-515 and 516
May 31, 2006	Type C meeting	Agreement reached on design of study 191622-082 in patients with respiratory impairment
July 18, 2006	Response to special protocol assessment	Review of phase 3 study 191622-516 Agreement that studies 515 and 516 could serve as pivotal trials in support of efficacy and safety of Botox in NDO
December 12, 2006	Type C meeting	Additional discussion of design of phase 3 studies, 515 and 516: • Labeling claims based on (b) (4) would not be considered. • Urodynamic endpoints of MCC and MDP are considered exploratory and descriptive information may be included in the label (b) (4)
May 24, 2007	Protocol amendment	(b) (4)
May 25, 2007	FDA communication	
April 28, 2008	Type C meeting	Discussion of alignment of pivotal studies and addition of a long-term follow-up study (094) to provide safety data regarding multiple treatments with Botox.
June 30, 2009	FDA communication	Agreement that sBLA could be submitted with an interim dataset from study 191622-082 (patients with respiratory impairment) and that these data would be supplemented with the data from completed study 191622-057 (patients with upper limb spasticity and respiratory impairment).
February 19, 2010	Pre-sBLA meeting	Contents of sBLA submission were discussed

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

An audit of the datasets and case report forms from the U.S. Phase 2/3 uncontrolled and controlled studies confirms that verbatim terms were correctly coded and categorized to the preferred terms and "system, organ, class" (SOC) using the standard MedDRA dictionary. There do not appear to be problems with data quality or integrity.

3.2 Compliance with Good Clinical Practices
All trials submitted to the NDA were conducted in accordance with good clinical practices.

3.3 Financial Disclosures
Financial disclosure was made for all required studies submitted to the NDA. There is no evidence to suggest that a financial relationship had any impact on the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls
According to the DRUP CMC reviewer, "no manufacturing process, facilities or equipment changes are proposed for drug substance and drug product used in this efficacy supplement. The CMC information is the same as the original approved BLA. Therefore, there are no concerns in regard to the CMC."

On June 24, 2011, CMC approved the sponsor's request to use the cell-based potency assay as an alternate method for Botox stability section. The product description section of the label was revised accordingly.

4.2 Clinical Microbiology
A clinical microbiology consult was not required for this application.

4.3 Preclinical Pharmacology/Toxicology
Notable findings from the DRUP pharmacology/toxicology review were

- Nonclinical studies established the maximum dose with no adverse effect for a single injection of onabotulinumtoxinA in the rat and monkey to be 15X and ~7X the clinical dose of 200 U.
- In the monkey, there were minimal long-term effects to the bladder following repeat dosing.
- The most significant toxicological finding was the occurrence of bladder stones in the monkey following peribladder (but not bladder) injection.

The DRUP pharmacology/toxicology reviewer concludes that there are no new non-clinical safety concerns for the new route of administration (i.e. intradetrusor) for Botox, and recommends approval for the new indication.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were conducted for this indication

4.4.1 Mechanism of Action

Botox is an acetylcholine release inhibitor and a neuromuscular blocking agent. Botox binds to receptors on motor nerve terminals and enters the nerve terminals by endocytosis. Once inside

the nerve terminal, Botox cleaves the SNAP-25 protein that is essential for fusion of the synaptic vesicles with the pre-synaptic membrane, and thereby prevents release of acetylcholine at the neuromuscular junction. The end result is a chemical denervation (i.e. loss of synaptic input) of the injected muscle and a reduction in muscle activity.

The mechanism of action of Botox in the treatment of NDO is believed to involve direct inhibition of detrusor muscle contraction. The sponsor also suggests that modulation of various sensory pathways which are thought to be upregulated in patients with detrusor overactivity may contribute to the clinical activity of Botox.

According to the DRUP pharmacology/toxicology review, the duration of Botox toxicity depends on the amount of time needed to replace functional SNAP-25 proteins and to re-establish innervation to the target cell.

4.4.2 Pharmacodynamics

No pharmacodynamic studies were performed for the NDO indication.

4.4.3 Pharmacokinetics

According to the sponsor, using currently available analytical technology, it is not possible to detect Botox in the peripheral blood following intradetrusor injection at the recommended doses. Therefore, no human pharmacokinetic studies have been performed for this or any indication.

The DRUP clinical pharmacology reviewer concludes that the application is "acceptable" from a clinical pharmacology standpoint and no post-marketing commitments are needed.

4.5 Biostatistics

The DRUP biostatistics reviewer concluded that the two submitted phase 3 pivotal trials demonstrated the efficacy of Botox 200 U and Botox 300 U for the treatment of urinary incontinence resulting from neurogenic detrusor overactivity in adult patients who were inadequately managed by or intolerant of anticholinergic therapy.

4.6 Consults from Other Divisions

4.6.1 Division of Scientific Investigations (DSI)

Two domestic clinical sites were selected for inspection by DSI because they had the largest subject enrollment. DSI determined that the data generated by these sites appeared to be acceptable in support of the proposed indication.

4.6.2 Division of Drug Marketing, Advertising, and Communications (DDMAC)

DDMAC reviewed the proposed package insert (PI) for Botox for possible promotional statements and consistency with labels for other similar products. DDMAC recommended the following changes to the NDO portion of the label:

(b) (4)

(b) (4)

4.6.3 Division of Risk Management (DRISK)

The DRISK reviewer edited the MedGuide (MG) to ensure its consistency with the package insert (PI), the regulations specified in 21 CFR 208.20 and the FDA Guidance for Useful Written Consumer Medication Information.

4.6.4 Pediatric Review Committee (PERC)

The sponsor requested a waiver of studies of Botox for urinary incontinence due to detrusor overactivity associated with a neurologic condition for patients aged 0-3 years, and a deferral for patients aged 3-17 years. The sponsor's proposal was discussed at a meeting of the PERC on July 13, 2011.

PERC agreed to grant a waiver for study of the proposed indication in subjects aged 0-3 years, and further agreed to extend the waiver to subjects <10 years to avoid enrollment of patients affected by maturational delay of micturition control rather than a true pathologic condition (in this case, neurogenic detrusor overactivity). PERC also approved a deferral for study of Botox in pediatric patients aged 10-17 years with incontinence due to detrusor overactivity associated with a neurologic condition (e.g. spina bifida, spinal cord injury). DRUP and PERC considered that studying patients aged 10-17 years with NDO was important for dose-finding.

The sponsor expressed understanding and agreement of PERCs recommendations in a teleconference with DRUP on July 18, 2011.

5 Sources of Clinical Data

The clinical development program to support the proposed indication comprises the following

six clinical studies involving 858 patients, all of which have evaluated the efficacy and safety of intradetrusor injection of Botox in patients with urinary incontinence due to NDO:

- 191622-515: phase 3 pivotal study (completed)
- 191622-516: phase 3 pivotal study (completed)
- 191622-094: phase 3 long-term extension of the pivotal studies (ongoing, interim analysis included in this submission)
- 191622-082: phase 3 special population study in patients with neurological respiratory impairment in addition to NDO (ongoing, interim analysis included in this submission)
- 191622-511: phase 2 study (completed)
- 191622-518: phase 2 dose-exploration study (ongoing, primary analysis included in this submission)

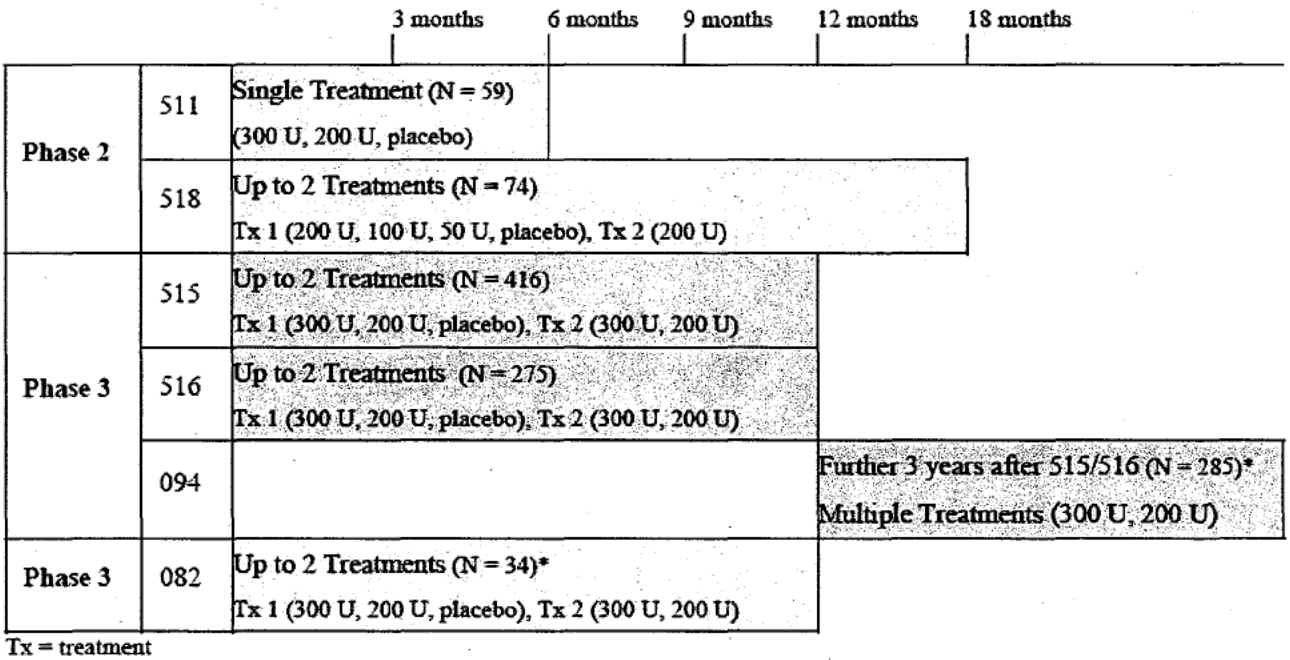
The etiology of NDO in the study population in all trials was spinal cord injury (SCI) (at level T1 or lower) or multiple sclerosis (MS).

Reviewer's comment: The sponsor selected patients with SCI and MS because these disease etiologies were considered representative of the NDO population.

As study 082 was still ongoing at the time of NDA submission, the sponsor also included results from a seventh study, phase 2 trial 191622-057, conducted in patients with reduced lung function and focal upper limb spasticity, to provide additional information on the use of Botox in patients with underlying respiratory compromise.

A summary of the clinical program for the NDO indication is shown in Figure 1.

Figure 1 Clinical Program for the NDO indication



Tx = treatment

* Number enrolled at time of data cut-offs for submission

Source: sBLA 103000 submission 0123, date of submission 10/27/10, Figure

Reviewer's comment: Hereafter, studies will be referred to by their three digit suffix – e.g. study 515 or 082.

5.1 Tables of Studies/Clinical Trials

Design features of the seven clinical trials submitted with the application are shown in Table 2.

Table 2 Design Features of Clinical Trials of Botox submitted to sNDA 103000

Study ID#/ phase/region	N at time of submission	Etiology	No. treatments	Dose	Duration of follow-up (analysis provided in submission)
NDO population					
511 Phase 2 EU	N=59	SCI + MS	Single	Placebo, Botox 200 or 300 U	6 months (final analysis)
518 Phase 2 EAME/AP	N=74	SCI	Up to 2	**Treatment 1:** Placebo, Botox 50, 100 or 200 U **Treatment 2:** Botox 200 U	Up to 1.5 years (primary analysis)
515 Phase 3 US/CAN EAME/AP	N=416	SCI + MS	Up to 2	**Treatment 1:** Placebo, Botox 200 or 300 U **Treatment 2:** Botox 200 or 300 U	at least 1 year (final analysis)
516 Phase 3 US/CAN/EAME/ AP/Brazil	N=275	SCI + MS	Up to 2	**Treatment 1**: Placebo, Botox 200 or 300 U **Treatment 2**: Botox 200 or 300 U	At least 1 year (final analysis)
094 Phase 3 extension to studies 515/516 US/CAN/ EAME/ AP/BRA	N=285 (155 treated in study as of cut-off)	SCI+MS	Multiple	**All treatments**: Botox 200 or 300 U	3 years (interim analysis)
082 Phase 3 (US/CAN/AP)	N=32	SCI+MS+ respiratory impairment	Up to 2	**Treatment 1**: Placebo, Botox 200 or 300 U **Treatment 2**: Botox 200 or 300 U	At least 1 year (interim analysis)
Post-stroke spasticity and reduced lung function					
057 Phase 2	N=155	patients with reduced lung function and focal upper limb spasticity	Up to 2	**Treatment 1**: Placebo, Botox 240 or 360 U	30 weeks (final analysis)

Source: BLA 103000 submission 0123, Clinical Overview, Table 2.5-1, p. 14. and Summary of Clinical Efficacy (SCE), Table 2.7.3-1, p. 10; and BLA 103000 submission 0118 module 5.3.5.4.3.

5.2 Review Strategy

5.2.1 Efficacy Review

The efficacy review focused on results of the two phase 3 pivotal studies, 515 and 516, which the sponsor integrated into the clinical summary of efficacy. The primary analysis of efficacy focused on the week 6 timepoint following the initial placebo-controlled injection of study drug. Efficacy data obtained after subsequent Botox injections (which were not placebo-controlled) were examined to determine whether efficacy was maintained with repeated treatment. The primary analysis population was the intent-to-treat (ITT) population which consisted of all randomized patients.

The phase 2 studies, 511 and 518, provided supportive efficacy data and informed selection of the therapeutic dose.

5.2.2 Safety Review

The sponsor pooled data from five of the NDO clinical studies (515, 516, 094, 511 and 518) into 2 analysis populations:

1) **Placebo-controlled safety population** (all patients who received at least one treatment during a double-blind, placebo-controlled study; includes data from studies 515, 516, 511, and 518).
2) **Botox-exposed safety population** (all patients who received at least one Botox treatment in studies 515, 516, 511, 518, and 094).

Study 082 was not pooled because the study population (patients with NDO and respiratory impairment) differed significantly from that of the other five trials.

The safety review focuses primarily on data obtained during the 12 weeks immediately following the first injection of study drug in the placebo-controlled safety population (includes studies 515, 516, 511, and 518). Data from the Botox-exposed population and from study 082 (patients with NDO and respiratory impairment) were reviewed for deaths and any safety signals identified in the placebo-controlled database. The Botox-exposed population was also analyzed for the safety of repeated Botox injection.

To determine the safety of Botox in patients with respiratory impairment, results of study 082 were reviewed, with a focus on respiratory-related adverse events and pulmonary function test results. Additional safety data in patients with underlying respiratory compromise were obtained from study 057, conducted in patients with focal upper limb spasticity and reduced lung function.

Safety data from approximately 40 patients, all from study 518, treated with Botox doses <200 U were reviewed only for deaths.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Pivotal phase 3 trials (191622-515 and 191622-516)

Studies 515 and 516 were multicenter, double-blind, randomized, placebo-controlled, parallel group phase 3 trials which compared the safety and efficacy of intradetrusor injection of 200 or 300 U BOTOX® to placebo for the treatment of urinary incontinence due to NDO in patients who were not adequately managed with anticholinergic therapy. Eligible patients had urinary incontinence (i.e., ≥ 14 episodes/week) due to NDO resulting from a spinal cord injury (SCI, T1 level or lower and occurring ≥ 6 months prior to screening) or multiple sclerosis (MS, clinically stable for ≥ 3 months prior to screening and an EDSS ≤ 6.5) for ≥ 3 months prior to screening.

Patients were randomized on day 1 to receive one of 2 doses of BOTOX® (200 or 300 U) or placebo in a 1:1:1 ratio. Study drug was injected under cystoscopic guidance as 30 injections of 1 mL each into the bladder detrusor. Injections were distributed evenly across the detrusor, approximately 1 cm apart and to a depth of approximately 2 mm, avoiding the trigone

Patients were eligible to receive a second treatment with study drug if all of the following pre-defined qualification criteria were met:

- Patient request for re-treatment
- At least 12 weeks elapsed since previous treatment
- Demonstrated loss of efficacy with respect to incontinence episode frequency (<50% reduction from baseline for study 515; <30% reduction from baseline for study 516 – i.e. patients had to reach a higher level of incontinence compared to baseline in study 516 than in study 515 to qualify for re-treatment).

Patients qualifying for re-treatment and who received BOTOX® for the first treatment continued to be treated with the same dose. Patients who received placebo for the first treatment received either 200 or 300 U BOTOX® according to a randomization schedule assigned at study enrollment.

Follow-up clinic visits occurred at weeks 2, 6 and 12 after study treatment, and every 12 weeks thereafter until study exit or qualification for re-treatment (see Table 30 for schedule of assessments at each clinic visit). Study exit occurred when subjects had had completed at least 52 weeks post-randomization, or 12 weeks following the last Botox injection (in those receiving two or more treatments), whichever occurred later.

The **primary efficacy endpoint in both pivotal studies** was **change from baseline in the weekly incontinence episode frequency at week 6 after the first treatment** as recorded by the patient in a 7-day bladder diary. Additional data documented in the bladder diary were voluntary voids and volume of each void over 24 hours. **Predefined secondary efficacy endpoints** were **changes from baseline to week 6 in the urodynamic measures of maximum cystometric capacity (MCC) and maximum detrusor pressure (MDP) during first involuntary detrusor contraction (IDC).**

5.3.2 Phase 3 Open-label safety extension (191622-094)

Study 191622-094 is an ongoing multicenter, long-term, follow-up phase 3 clinical trial that is an extension of the pivotal studies 191622-515 and -516. In study 094, additional treatments of BOTOX® (300 or 200 U) are administered if patients qualify (criteria were patient request for re-treatment; ≥1 incontinence episode recorded in the 3-day voiding diary; and at least 12 weeks since the last treatment). Follow-up visits occur at post-treatment weeks 2, 6 and 12, and every 12 weeks thereafter until request for re-treatment or study exit.

5.3.3 Phase 2 studies

Study 191622-511 was a 24-week, multicenter, double-blind, randomized, placebo-controlled, parallel group trial evaluating the safety and efficacy of a single treatment of 200 or 300 U BOTOX® in patients with urinary incontinence due to detrusor hyperreflexia (terminology in place at time of study) secondary to SCI or MS. Eligible patients had a ≥ 6 week history of urinary incontinence refractory to oral anticholinergics, and were regularly using CIC to empty the bladder and manage urinary incontinence. Post-injection follow-up visits occurred at weeks 2, 6, 12, 18 and 24. The primary efficacy endpoint was change from baseline to post-injection week 6 in mean daily urinary incontinence episode frequency.

Study 191622-518 is an ongoing multicenter, double-blind, randomized, placebo-controlled, parallel-group trial designed to explore the dose-response of intradetrusor injection of BOTOX® (50, 100, and 200 U) for the treatment of urinary incontinence due to NDO in patients not adequately managed with anticholinergic therapy. Eligible patients have urinary incontinence (≥ 14 episodes/week) due to NDO resulting from a SCI (T1 level or lower and occurring ≥ 6 months prior to screening) for ≥ 3 months prior to screening

Patients are randomly assigned to receive treatment with 50, 100 or 200 U BOTOX®, or placebo in a 1:1:1:1 ratio. Patients are eligible to receive a second, open-label treatment with 200 U BOTOX® if they fulfill all re-treatment criteria (patient request for re-treatment, a < 30% reduction in the weekly incontinence episode frequency compared to study baseline, and ≥12 weeks since treatment 1). Post-injection follow-up occurs at week 2 and every 6 weeks thereafter until qualification for re-treatment or study exit. Patients exit the study 78 weeks after randomization/day 1, or 12 weeks after the second treatment, whichever is later.

Patient enrollment was stopped prematurely because the sponsor judged it infeasible to recruit the planned 40 patients per group in a reasonable time frame. Data from a total of 73 subjects were included in the primary analysis submitted with the application. Subjects were eligible for inclusion in the primary analysis when they had qualified for re-treatment, completed 52 weeks since randomization/day 1, or prematurely exited.

5.3.4 Phase 3 study in patients with respiratory impairment (Study 191622-082)

Study 191622-082 is an ongoing placebo-controlled, randomized phase 3 clinical trial designed to assess the safety of intradetrusor injection of Botox in subjects with both urinary incontinence secondary to NDO not adequately managed with anticholinergic therapy and neurological respiratory impairment. To qualify for study participation, subjects had to have cervical (C) SCI at levels C5-C8, or MS with an Expanded Disability Status Scale (EDSS) score of 7.0-8.0, and evidence of restrictive lung disease [defined as Forced Vital Capacity (FVC) 50-80% of predicted value on baseline pulmonary function tests (PFTs)].

Reviewer's comment: The EDSS is a widely utilized instrument that measures MS disease severity. The scale ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments.[1] A score of 7.0-8.0 indicates severe disease.

Subjects were randomized in equal numbers to receive intradetrusor injection of saline placebo, 200 U or 300 U Botox. Patients completed 52 weeks of post-treatment follow-up and were eligible for up to 2 treatments during the study, with a minimum of 12 weeks between injections. Pulmonary function testing, including measurement of FVC, Forced Expiratory Volume in 1 second (FEV_1), and maximum inspiratory and expiratory pressures, was performed at baseline and at weeks 2, 6, and 12 weeks post-treatment, and again at study exit (week 52).

As of March 15, 2010, the interim analysis cut-off date, a total of 34 patients had been enrolled and were included in the interim analysis submitted with the application.

6 Review of Efficacy

6.1 Indication

The sponsor seeks an indication of '[redacted] (b) (4)

6.1.1 Methods

Efficacy in support of the NDO indication is based primarily on data from the first treatment cycle of two double-blind, placebo-controlled phase 3 trials, 515 and 516, which the sponsor combined into the summary of clinical efficacy. Data from phase 2 studies 511 and 518 were used to determine the lowest therapeutic dose.

Reviewer's comment: The first treatment cycle represents the time between study drug injection and study exit or qualification for re-treatment, whichever comes first.

[1] From http://www.nationalmssociety.org on June 22, 2011.

6.1.1.1 Design of Pivotal Phase 3 trials (studies 515 and 516)

Both studies were multicenter, randomized, double-blind, placebo-controlled, parallel group trials conducted in adult patients (aged 18-80 years) with neurogenic detrusor overactivity and urinary incontinence resulting from either SCI or MS. Only patients who had not been adequately managed by anticholinergic therapy (i.e. inadequate response or intolerable side effects) were eligible. The duration of both studies was 52 weeks, plus an additional 12 weeks (total 64 weeks) for patients who received re-treatment.

Qualification criteria included ≥14 urinary incontinence episodes per week and urodynamically confirmed detrusor overactivity at screening. Patients with SCI had to have a stable neurological injury at thoracic level 1 (T1) or lower that occurred ≥ 6 months prior to screening. Patients with MS were required to have an EDSS score of ≤ 6.5. Patients taking anticholinergic medication at screening were allowed to continue these products at a stable dose throughout study participation.

Eligible subjects were randomized in a 1:1:1 ratio to receive placebo, Botox 200 U or 300 U injected under cystoscopic guidance as 30 injections of 1 mL each into the bladder detrusor. Injections were evenly distributed across the detrusor approximately 1 cm apart and to a depth of approximately 2 mm, avoiding the trigone.

After treatment 1, subjects were eligible to receive a second injection (Treatment 2) with either Botox 200 U or 300 U if the following pre-specified criteria were fulfilled:

- Patient request for re-treatment
- At least 12 weeks elapsed since previous treatment
- Demonstrated loss of efficacy (<50% reduction from baseline for study 515; <30% reduction from baseline for study 516 – i.e. patients had to reach a higher level of incontinence compared to baseline in study 516 than in study 515 to qualify for re-treatment).

The **primary efficacy endpoint in both pivotal studies was change from baseline in the weekly incontinence episode frequency at week 6 after the first treatment** as recorded in a 7-day bladder diary. Additional data documented in the bladder diary were voluntary voids and volume of each void over 24 hours.

Predefined secondary efficacy endpoints were **changes from baseline to week 6 in the urodynamic measures of MCC and MDP during first involuntary detrusor contraction,** (b) (4)

Reviewer's comment: In a December 12, 2006, industry meeting, DRUP provided the following comments regarding the pre-specified secondary endpoints:

- (b) (4)

(b) (4)

- **We will consider including descriptive information in the label regarding the effect of BOTOX® on the exploratory urodynamic endpoints of MCC and MDP.**

(b) (4)

This review will therefore only address the urodynamic secondary endpoints of MCC and MDP.

6.1.2 Demographics

Demographic characteristics of the pooled placebo-controlled intent-to-treat (ITT) population from the pivotal phase 3 studies were similar across dose groups except for a significantly lower proportion of males in both Botox dose groups compared with placebo (p=0.043) (data shown in Table 3).

Reviewer's comment: The ITT population included all randomized patients.

Table 3 Baseline Demographics, Treatment Cycle 1 (Placebo-controlled Pivotal Study ITT Population)

Characteristic	Botox 300 U	Botox 200 U	*Placebo*
Total N (%)	223 (100)	227 (100)	241 (100)
Age			
Median (years)	46	45	47
>65 years	14 (6.2)	20 (8.8)	15 (6.2)
Sex			
Male	82 (37)	93 (41)	116 (48)
Female	141 (63)	134 (59)	125 (52)
Race			
Caucasian	185 (83)	193 (85)	215 (89)
Non-caucasian	38 (17)	34 (15)	26 (11)
Weight			
Median (kg)	72	73	75

Source: sBLA 103000 submission 0123, Integrated Summary of Efficacy (ISE), table 1-3.1, p. 8

Reviewer's comment: The effect of male gender on Botox efficacy and safety is discussed further in sections 6.1.7.3 and 7.5.3.1, respectively. The smaller proportion of males in the Botox treatment groups does not appear to have skewed efficacy in favor of Botox (see section 6.1.7.3).

Baseline disease characteristics were similar across the three treatment groups (Table 4).

Table 4 Baseline NDO Disease Characteristics, Treatment Cycle 1
(Placebo-controlled Pivotal Study ITT Population)

	Botox 300 U N (%)	Botox 200 U N (%)	Placebo N (%)
Etiology			
MS	120 (54)	130 (57)	131 (54)
SCI	103 (46)	97 (43)	110 (46)
Use of anticholinergic (AT) at screening			
Yes	119 (53)	120 (53)	140 (58)
No	104 (47)	107 (47)	101 (42)
Weekly Incontinence Episode Frequency			
Median	27	25	23
Void pattern			
CIC	83 (37)	79 (35)	92 (38)
Mixed	25 (11)	36 (16)	38 (16)
Spontaneous void only	96 (43)	97 (43)	92 (38)
Urodynamic Parameters			
Median MCC (mL)	237	225	238
Median MDP (cmH20) at 1rst ICD	36	42	39

Source: sBLA 103000 submission 0123, ISE, table 1-4.1, pp 26-30.

6.1.3 Subject Disposition

A total of 691 patients enrolled in the pivotal studies (-515 and -516) and constituted the pooled ITT population for analyzing efficacy data. Subject disposition is shown in Table 5. Premature discontinuation rates were similar across treatment groups.

Table 5 Patient Disposition and Exit Status
(Placebo-controlled Pivotal Study ITT Population)

Disposition	*Botox 300 U N (%)*	*Botox 200 U N (%)*	Placebo N (%)
Enrolled	223 (100)	227 (100)	**241 (100)**
Completed	174 (78.0)	188 (82.8)	**197 (81.7)**
Discontinued	49 (22.0)	39 (17.2)	**44 (18.3)**
Adverse Event	7 (3.1)	5 (2.2)	**5 (2.1)**
Lack of Efficacy	3 (1.3)	0	**3 (1.2)**
Pregnancy	1 (0.4)	2 (0.9)	**1 (0.4)**
Lost to Follow-Up	7 (3.1)	11 (4.8)	**7 (2.9)**
Personal Reasons	11 (4.9)	8 (3.5)	**10 (4.1)**
Protocol Violation	**3 (1.3)**	**6 (2.6)**	**3 (1.2)**

Source: sBLA 103000 submission 0123, ISE, table 1-2.1, p. 4.

6.1.4 Analysis of Primary Endpoint(s)

The **primary efficacy endpoint was the change from baseline in the weekly frequency of urinary incontinence episodes, recorded in patient bladder diaries, at Week 6 after Treatment 1.** The primary analysis was performed using the ITT population. An analysis of covariance (ANCOVA) model was used, with baseline value as covariate, and treatment group, etiology at entry into the study (either SCI or MS), concurrent anticholinergic therapy at screening (use or non-use), and investigator, as factors. Adjustment for multiplicity (200 U vs. placebo, 300 U vs. placebo) was performed using the Hochberg procedure.

Imputation of missing values was performed using the last observation carried forward (LOCF) method. For patients who discontinued from the study prior to the primary week 6 time point, the LOCF was applied only up to week 6; for drop-outs after week 6, the LOCF was applied up to the patient's last visit in treatment cycle 1.

For patients who did not discontinue from the study prematurely, missing data were imputed during treatment cycle 1 only. Missing baseline values were imputed with the mean value from the non-missing baseline data for all patients regardless of dose group. Data were also analyzed without imputation.

In the pooled analysis, statistically significant reductions over placebo in IEF were achieved for both Botox dose groups at the primary time point (week 6) and at weeks 2 and 12 post-injection (see Table 6). Efficacy of Botox was also demonstrated in each individual phase 3 study (Table 7).

Table 6 Change from Baseline in Weekly Incontinence Episode Frequency with LOCF imputation, Treatment Cycle 1 (ITT Population), pivotal Phase 3 trials (pooled data)

Timepoint	Attribute	Botox 300 U N=223	Botox 200 U N=227	Placebo N=241
Baseline	Mean	31.1	32.4	31.5
Week 2	Mean change (SD)	-17.4 (22)	-17.7 (21)	-9.0 (16)
	p-value	<0.001	<0.001	
Week 6	Mean change (SD)	-21.3 (21)	-21.3 (22)	-10.5 (18)
	Placebo-corrected mean change	**-10.8**	**-10.8**	
	p-value	<0.001	<0.001	
Week 12	Mean change (SD)	-21.9 (19)	-20.6 (21)	-9.9 (18)
	p-value	<0.001	<0.001	

Source: sBLA 103000 submission 0123, summary of clinical efficacy (SCE), Table 2.7.3-12, p. 62

Table 7 Baseline and Change from Baseline to Week 6 in Weekly Incontinence Episode Frequency for Treatment Cycle 1 (ITT Population), pivotal Phase 3 trials (individual study data)

Timepoint	Attribute	Botox 300 U	Botox 200 U	Placebo
		Study 515		
Baseline	N	132	135	149
	Mean	31.1	32.3	28.3
Week 6	Mean (SD) change	-22.7 (17)	-21.0 (24)	-8.8 (16)
	Placebo-corrected mean change	**-13.9**	**-12.2**	
	p-value	<0.001	<0.001	
		Study 516		
Baseline	**N**	**91**	**92**	92
	Mean	31.2	32.5	36.7
Week 6	Mean (SD) change	-19.4 (26)	-21.8 (18)	-13.2 (20)
	Placebo-corrected mean change	**-6.2**	**-8.6**	
	p-value	0.002	0.002	

Source: sBLA 103000 submission 0123, summary of clinical efficacy (SCE), Table 2.7.3-12, p. 62

Efficacy analysis of the primary endpoint was analyzed without LOCF imputation, and the results continue to show a statistically significant improvement in weekly IEF for both doses of Botox compared to placebo (see Table 8).

Table 8 Change from Baseline to Week 6 in Weekly IEF for Treatment Cycle 1 (ITT Population) without LOCF, pivotal Phase 3 trials

Timepoint	Attribute	Botox 300 U N=223	Botox 200 U N=227	Placebo N=241
Baseline	Mean	31	32	32
Week 6	Mean change (SD)	-22.5	-21.7	-10.9
	Placebo-corrected mean change	**-11.6**	**-10.8**	
	p-value	<0.001	<0.001	

Source: sBLA 103000, submission 0123, ISE, Table 2-3.2, p. 80.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Mean Cystometric Capacity (MCC)

Urodynamic assessments were performed baseline and at week 6 during treatment cycle 1. In the pooled data analysis and in each pivotal phase 3 study, both Botox doses resulted in a statistically significant increase in mean MCC from baseline when compared to placebo (see Table 9 and Table 10).

Table 9 Maximum Cystometric Capacity (mL) – Baseline and Change from baseline at Week 6 for Treatment Cycle 1 (ITT Population), pivotal Phase 3 trials (pooled data)

Timepoint	Attribute	Botox 300 U N=223	Botox 200 U N=227	Placebo N=241
baseline	Mean (SD)	252 (146)	250 (151)	254 (142)
Week 6	Mean (SD) change from baseline	163(176)	154 (168)	12 (134)
	p-value	<0.001	<0.001	

Source: sBLA 103000 submission 0123, SCE, Table 2.7.3-15, page 69

Table 10 Maximum Cystometric Capacity (mL) – Baseline and Change from baseline at Week 6 in Treatment Cycle 1 (ITT Population), pivotal Phase 3 trials (individual study data)

Timepoint	Attribute	Botox 300 U	Botox 200 U	Placebo
		Study 515		
Baseline	N	132	135	149
	Mean (SD)	255.8 (145)	252.3 (154)	256.0 (144)
Week 6	Mean (SD) change from baseline	167.7 (170)	151.2 (171)	15.5 (127)
	p-value	<0.001	<0.001	
		Study 516		
Baseline	N	91	92	92
	Mean (SD)	246.8 (149)	247.3 (148)	249.4 (139)
Week 6	Mean change from baseline (SD)	157.2 (185)	157.0 (165)	6.5 (145)
	p-value	<0.001	<0.001	

Source: sBLA 103000 submission 0123, SCE, Table 2.7.3-15, p. 69

6.1.5.2 Maximum Detrusor Pressure during First Involuntary Detrusor Contraction

When compared with placebo, significantly greater decreases in mean MDP during first IDC were observed in both Botox treatment groups ($p < 0.001$) (Table 11) in the pooled analysis population and in the individual phase 3 trials (Table 12). The sample size at week 6 in the Botox treatment groups is small because MDP during first IDC could not be evaluated if no IDC occurred. Therefore, this parameter was measured only in those subjects who had an IDC.

Table 11 Maximum Detrusor Pressure (cm H20) during First Involuntary Detrusor Contraction (IDC) – Baseline and Change from baseline at Week 6 in Treatment Cycle 1 (ITT Population), pivotal Phase 3 trials (pooled data)

Timepoint	Attribute	Botox 300 U	Botox 200 U	Placebo
Baseline	N Mean (SD)	223 45.0 (35)	227 51.5 (37)	241 47.3 (36)
Week 6	N Mean (SD) change from baseline p-value	62 -30.1 (35) <0.001	70 -32.4 (41) <0.001	171 1.1 (43)

Source: sBLA 103000, submission 0123, SCE, Table 2.7.3-16, page 71.

Table 12 Maximum Detrusor Pressure (cm H20) during First Involuntary Detrusor Contraction (IDC) Baseline and Change from baseline at Week 6 in Treatment Cycle 1 (ITT Population), pivotal Phase 3 trials (individual study data)

Timepoint	Attribute	Botox 300 U	Botox 200 U	Placebo
		Study 515		
Baseline	N Mean (SD)	132 47.1 (36)	135 51.3 (35)	149 50.9 (38)
Week 6	N Mean (SD) change from baseline p-value	31 -33.3 (38) <0.001	41 -35.1 (36) <0.001	103 -2.4 (43)
		Study 516		
Baseline	N Mean (SD)	91 42.1 (33)	92 51.7 (41)	92 41.5 (31)
Week 6	N Mean change from baseline (SD) p-value	31 -26.9 (33) <0.001	29 -28.5 (48) <0.001	68 6.4 (41)

Source: sBLA 103000, submission 0123 SCE, Table 2.7.3-16, p. 71.

6.1.7 Subpopulations

6.1.7.1 Analysis by Etiology of NDO

6.1.7.1.1 Primary Endpoint

Both doses of Botox resulted in statistically significant reductions in IEF compared to placebo when efficacy was analyzed according to underlying etiology of NDO (i.e. SCI vs. MS) (see Table 13).

Table 13 Baseline and Change from baseline in weekly IEF for Treatment Cycle 1 by NDO Etiology, pivotal Phase 3 trials (pooled ITT population)

		MS patients			SCI patients		
Timepoint	Attribute	Botox 300 U N=120	Botox 200 U N=130	Placebo N=131	Botox 300 U N=103	Botox 200 U N=97	Placebo N=110
Baseline	Mean (SD)	32.1 (19)	33.4 (21)	32.4 (24)	30.1 (15)	30.9 (22)	30.4 (22)
Week 6	Mean change (SD)	-24.0 (21)	-22.6 (23)	-14.0 (21)	-18.2 (22)	-19.6 (19)	-6.4 (12)
	Placebo-corrected mean change	-7.2	-7.1		-9.9	-10.4	
	p-value	<0.001	0.012		<0.001	<0.001	

Source: sBLA 103000, SCE, Table 2.7.3-25, p. 90

Reviewer's comment: The greater placebo response in MS patients may be due to female preponderance in this subgroup (see section 6.1.7.3).

6.1.7.1.2 Secondary Urodynamic Endpoints

A statistically significant increase in MCC and decrease in MDP during first IDC were observed in both disease subpopulations treated with Botox as compared with placebo (see Table 14).

Table 14 Baseline and Change from Baseline in Urodynamic Parameters by Etiology at Week 6, Treatment Cycle 1, pivotal Phase 3 trials (pooled, ITT population)

		MS patients			SCI patients		
Timepoint	Attribute	Botox 300 U	Botox 200 U	Placebo	Botox 300 U	Botox 200 U	Placebo
MCC (ml)							
	N	108	122	121	82	89	93
Week 6	Mean change (SD)	165.1 (174)	149.3 (169)	6.8 (120)	160.6 (180)	159.5 (167)	18.6 (151)
	p-value	<0.001	<0.001		<0.001	<0.001	
MDP							
Week 6	N	29	35	95	33	35	76
	Mean change from baseline (SD)	-24.1 (28)	-22.1 (34)	10.7 (42)	-35.3 (41)	-42.7 (45)	-10.9 (41)
	p-value	<0.001	<0.001		0.020	0.034	

Source: sBLA 103000, SCE, Table 2.7.3-26, p. 92.

6.1.7.2 Analysis by Age Group

Efficacy data were analyzed by age group (< 65 years or ≥ 65 years to <75 years). Placebo-corrected mean change in IEF was similar in the two age groups (Table 15).

Table 15 Baseline and placebo-corrected mean change from Baseline at Week 6 in Weekly IEF by Age Group, Treatment Cycle 1, pivotal Phase 3 trials (pooled ITT population)

		Age <65 years			Age ≥65 years to <75 years		
Timepoint	Attribute	300 U N=209	200 U N=207	Placebo N=226	300 U N=13	200 U N=19	Placebo N=14
Baseline	Mean (SD)	31.1 (18)	31.5 (21)	30.3 (21)	31.5 (18)	40.9 (25)	51.3 (41)
Week 6	mean (SD)change	-21.2 (21)	-21.1 (21)	-10.3 (18)	-24.2 (18)	-22.8 (24)	-14.4 (16)
	Placebo-corrected mean change	-10.9	-10.8		-9.8	-8.4	
	p-value	<0.001	<0.001		0.649	0.025	

Source: sBLA 103000, submission 0123, SCE, Table 2.7.3-32, p. 102

Reviewer's comment: Although the sample size for the >65 year subgroup was too small to allow for a meaningful statistical comparison, the magnitude of treatment response was similar in the two age groups.

6.1.7.3 Analysis by Gender

When efficacy was analyzed by gender, statistically significant reductions from baseline in the weekly IEF were observed in both male and female patients treated with Botox compared to placebo. The magnitude of reduction was higher in females than in males within each treatment group (including placebo) (see Table 16).

Table 16 Change from Baseline to Week 6 in Weekly IEF, Treatment Cycle 1, pivotal Phase 3 trials (pooled ITT population) by Gender

Timepoint	Attribute	Male			Female		
		Botox		Placebo N=116	Botox		Placebo N=125
		300 U N=82	200 U N=93		300 U N=141	200 U N=134	
Baseline	Mean (SD)	28.1 (14)	29.5 (19)	30.3 (23)	32.9 (19)	34.3 (22)	32.7 (23)
Week 6	Mean change from baseline (SD)	-17.6 (22)	-16.7 (21)	-9.6 (16)	-23.5 (20)	-24.6 (21)	-11.3 (19)
	p-value	0.002	0.047		<0.001	<0.001	

Source: sBLA 103000, submission 0123, SCE, Table 2.7.3-33, p. 104

Reviewer's comment: Female subjects exhibited a greater placebo response.

6.1.7.4 Analysis by Race

The majority of patients in the pooled dataset was Caucasian. Both Botox doses resulted in a statistically significant reduction in IEF in Caucasians. In non-Caucasians, only the 200 U dose led to statistically significant reductions in mean IEF at week 6 compared to placebo (see

Table 17).

Table 17 Change from Baseline to Week 6 in weekly IEF, Treatment Cycle 1, pivotal Phase 3 trials (pooled ITT population) according to race

Timepoint	Attribute	Caucasian			Non-Caucasian		
		Botox		Placebo	Botox		Placebo
		300 U N=185	200 U N=193	N=215	300 U N=38	200 U N=34	N=26
Baseline	Mean (SD)	31.5 (18)	32.1 (22)	30.8 (22)	29.5 (17)	33.7 (18)	37.0 (32)
Week 6	Mean change (SD) from baseline	-22.5 (19)	-21.3 (22)	-10.6 (17)	-15.3 (29)	-21.5 (17)	-9.5 (21)
	Placebo-corrected mean change	-11.9	--10.7		-5.8	-11.5	
	p-value	<0.001	<0.001		0.093	0.024	

Source: sBLA 103000, submission 0123, SCE, Table 2.7.3-34, p.105.

Reviewer's comment: Botox 200 U and 300 U reduced mean IEF compared to placebo in both Caucasians and non-Caucasians. The reason for the absence of statistical significance in the non-Caucasian 300 U dose group may be related to the small sample size.

6.1.7.5 Analysis by Botulinum Toxin Naïve Status

A small number of patients were enrolled who had been previously exposed to Botox (site of exposure was not specified). Among Botox-non-naïve subjects, the change from baseline in weekly IEF was greater in Botox-treated subjects than placebo, but the difference was not significant. (Table 18).

Table 18 Change from Baseline to Week 6 in weekly IEF, Treatment Cycle 1, pivotal Phase 3 trials (pooled ITT population) according to Botox-naïve status

Timepoint	Attribute	Botox-Naïve			Botox Non-Naive		
		Botox		Placebo	Botox		Placebo
		300 U N=212	200 U N=218	N=223	300 U N=10	200 U N=8	N=7
Baseline	Mean (SD)	31.5 (18)	32.1 (21)	31.4 (23)	24.1 (8)	26.0 (8)	37.3 (14)
Week 6	Mean change from baseline (SD)	-21.4 (22)	-21.5 (22)	-10.6 (18)	-19.9 (9)	-16.5 (17)	-9.6 (21)
	Placebo-corrected mean change	-10.8	-10.9	[redacted]	-10.3	-6.9	[redacted]
	p-value	<0.001	<0.001	[redacted]	0.425	0.059	[redacted]

Source: sBLA 103000, submission 0123, SCE, Table 2.7.3-35, p.106.

Reviewer's comment: The small sample size of Botox non-naïve subjects prevents a meaningful statistical analysis of the data.

6.1.7.6 Analysis by use of Anticholinergic Therapy at Study Entry

Subjects taking anticholinergic therapy at baseline were allowed to continue on a stable dose during the study. Treatment with Botox resulted in a statistically significant improvement in weekly IEF over placebo in both users and non-users of anticholinergic therapy (see Table 19).

Table 19 Change from Baseline to Week 6 in weekly IEF, Treatment Cycle 1 by Anticholinergic Therapy, pivotal Phase 3 trials, pooled ITT population

Timepoint	Attribute	User of Anticholinergic Therapy			Non-user of Anticholinergic Therapy		
		Botox		Placebo	Botox		Placebo
		300 U N=119	200 U N=120	N=140	300 U N=104	200 U N=107	N=101
Baseline	Mean (SD)	29.8 (17)	28.7 (18)	29.9 (22)	32.6 (18)	36.5 (23)	33.7 (24)
Week 6	Mean change from	-21.0 (17)	-20.3 (18)	-9.0 (14)	-21.7 (25)	-22.5 (25)	-12.5 (22)

	baseline (SD)						
	p-value	<0.001	<0.001		<0.001	0.018	

Source: sBLA 103000, submission 0123, SCE, Table 2.7.3-36, p.107

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor proposes Botox 200 U as the therapeutic dose for treatment of urinary incontinence secondary to NDO. Doses evaluated in Phase 2 and 3 trials ranged from 50 to 300 U.

6.1.8.1 Determining the minimum effective dose

In the initial phase 2 trial, 191622-511, in patients with urinary incontinence secondary to NDO, both 200 U and 300 U Botox led to statistically significantly greater decreases in IEF than placebo. However, no difference in efficacy was noted between the two Botox doses.

To further explore dose-response, an additional placebo-controlled phase 2 study (191622-518) using 50, 100 and 200 U Botox was conducted. Results of that trial demonstrated a dose-response relationship for IEF reduction and for most urodynamic parameters (except MCC). The greatest improvement was observed in the 200 U dose group (data displayed in Table 20).

Table 20 Change from Baseline to Week 6 in selected Efficacy Measures: phase 2 study 518 (mITT population)

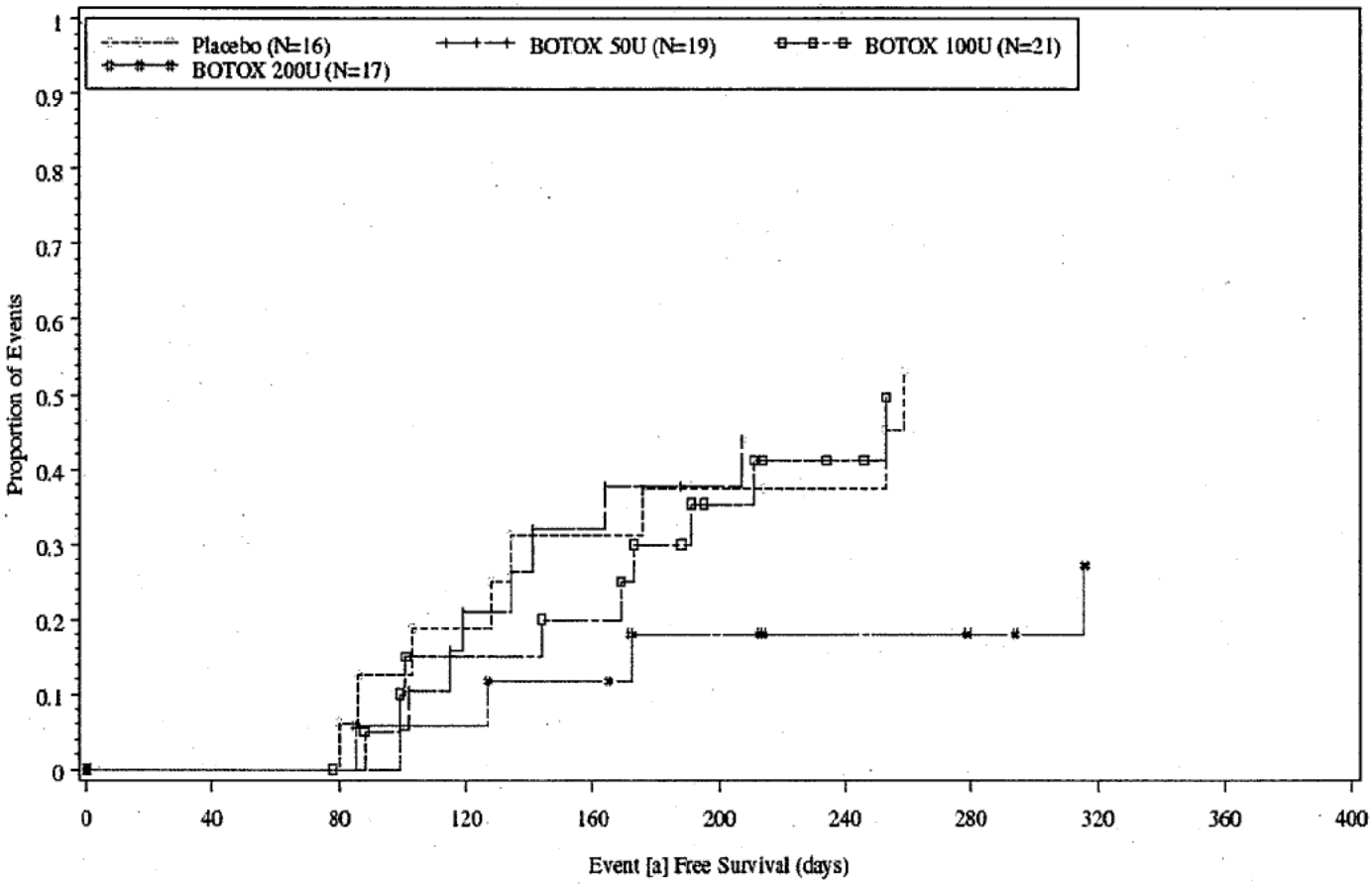
Parameter	Botox 200 U	Botox 100 U	Botox 50 U	Placebo
Weekly IEF				
N	17	21	19	16
Mean (SD)	-15.8 (18)	-14.1 (24)	0-7.7 (11	-8.5 (8)
MCC (mL)				
N	12	17	16	13
Mean (SD)	183.7 (198)	220.1 (183)	136.8 (189)	117.4 (173)
MDP during first IDC (cm H20)				
N	9	11	10	10
Mean (SD)	-33.0* (58)	-29.4* (40)	-20.1 (22)	-2.1 (28)
Volume per void (mL)				
N	14	18	16	14
Mean (SD)	91.8*(188)	44.8 (135)	14.4 (39)	-47.1 (109)
Responder rate				
Percentage	61.5%	50.0%	50.0%	42.9%

*p<0.05
source: sBLA 103000, submission 0123, SCE, Table 2.7.3-37, p. 109.

Reviewer's comment: Although none of the Botox doses resulted in a statistically significant improvement in weekly IEF over placebo, 200 U led to the greatest absolute reduction.

In study 518, durability of response to treatment was also assessed. Following the first injection, subjects were eligible to receive a second open-label treatment (treatment 2) with 200 U Botox if more than 12 weeks had elapsed since the initial injection and subjects reported <30% reduction from baseline IEF. As shown in Figure 2, the interval between treatment 1 and qualification for re-treatment was longest in the 200 U dose group.

Figure 2. Time between Randomization Day and Qualification for Treatment 2 – Kaplan-Meier Curve on Duration of Effect: Study 191622-518 (mITT population: responders)



Source: sBLA 103000 submission 0123, SCE, Figure 2.7.3-9, p. 111.

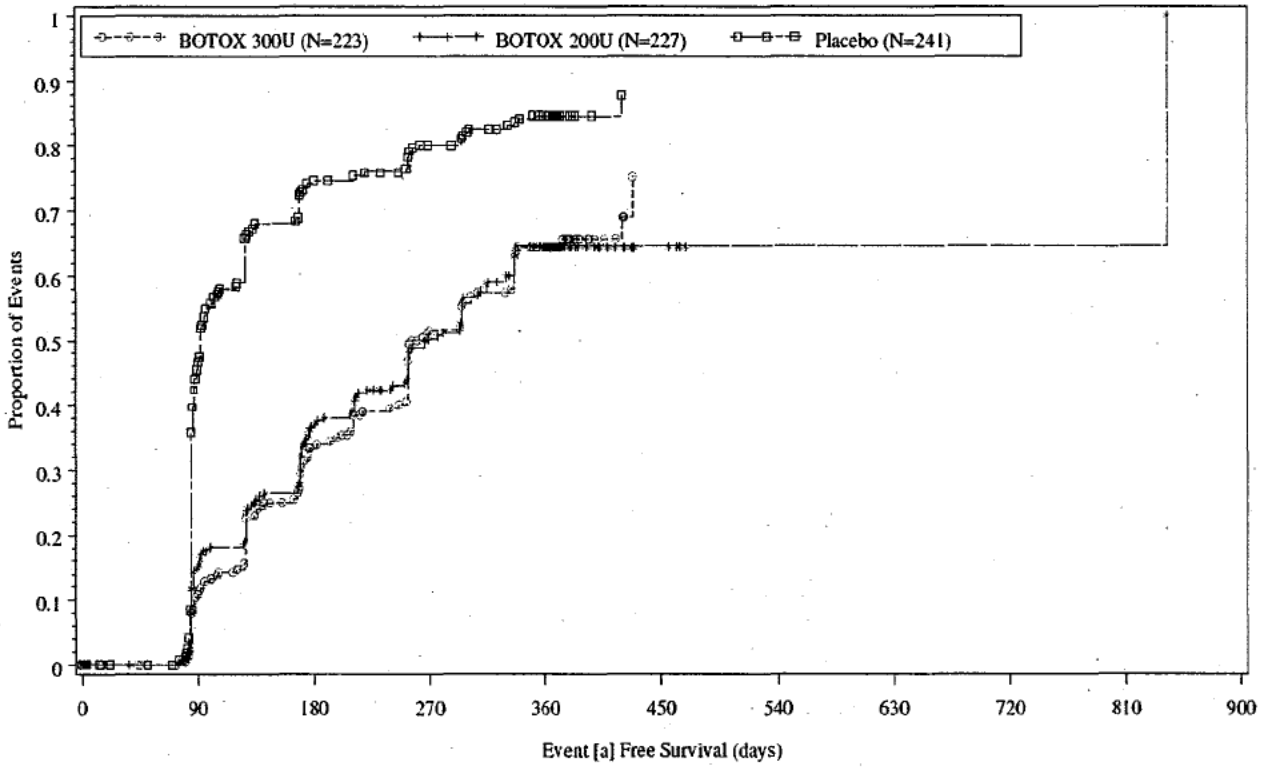
Based on results from study 518, the sponsor concluded that 200 U was the minimum effective dose.

Reviewer's comment: The reviewer concurs that 200 U appears to be the minimum effective dose.

6.1.8.1 Determining the therapeutic dose

As shown in Table 6.2, both 200 and 300 U Botox resulted in statistically significant reductions in weekly IEF from baseline. In phase 3 trials, there was no significant difference between the 200 U and 300 U Botox doses with regards to duration of effect as assessed by time to patient's request for re-treatment – median duration was 265 days and 269 days in the 300 U and 200 U Botox groups, respectively, versus 92 days in the placebo group. These data are displayed in the Kaplan Meier survival analysis curve shown in Figure 3.

Figure 3 Kaplan-Meier Curve for Duration of Effect: Time to Request for Re-treatment (Studies 515 and 516 pooled ITT population)



source: : sBLA 103000 submission 0123, SCE, Figure 2.7.3-11, p. 121.

Based on the similar effect on weekly IEF and duration of effect, the sponsor concluded that Botox 300 U provides no additional efficacy over the 200 U dose, and recommends 200 U as the therapeutic dose.

Reviewer's comment: The reviewer agrees with selection of Botox 200 U as the therapeutic dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As Botox injection is invasive, information regarding durability of response is important in assessing the risk/benefit of this treatment modality. Information on persistence of effect was based primarily on the placebo-controlled Treatment cycle 1 of the pivotal phase 3 trials. In these trials, patients were eligible to receive up to 2 treatments, with the second treatment dependent on fulfillment of the following re-treatment criteria:

- Patient request for re-treatment
- a minimum of 12 weeks has elapsed since previous treatment
- patient has recorded in the voiding diary less than a 50% reduction (in study 515, or <30% reduction in study 516) in weekly IEF as compared to baseline.

Reviewer's comment: In other words, subjects needed to "lose" 50% (or 70% in study 516) of initial efficacy in order to qualify for re-treatment.

Duration of effect was determined for treatment responders and for all patients (regardless of response) in two ways –

- Time to patient request for re-treatment
- Time to qualification for re-treatment.

As shown in Table 21, the median duration of effect was significantly longer in both 200 U and 300 U Botox dose groups compared to placebo in both time-to-event analyses.

Table 21 Median time [days (weeks)] to qualification for re-treatment and to patient request for re-treatment, pivotal phase 3 trials (ITT population)

	300 U Botox	200 U Botox	Placebo
Median time to qualification for re-treatment*			
Study 515	337 (48.1)	295 (42.1)	96 (13.7)
Study 516	421 (60.1)	337 (48.1)	127 (18.1)
Median time to patient request for re-treatment, days			
Study 515	254 (36.3)	256 (36.6)	92 (13.1)
Study 516	295 (42.1)	295 (42.1)	92 (13.1)
515+516 (pooled)	265 (37.8)	269 (38.4)	92 (13.1)

*data for this variable were not pooled because re-treatment criteria differed in studies 515 and 516.
Source: sBLA 103000, submission 0123, SCE, Table 2.7.3-40, p. 118.

Reviewer's comments:

1) **The median duration of effect of both Botox doses was substantially longer than placebo and the suggested 12 week minimum interval between Botox injections.**
2) **Patients request re-treatment somewhat earlier than they met re-treatment criteria.**

In the phase 3 pivotal trials, time to patient request for re-treatment correlated with return of symptoms. As shown in Table 22, at time of request for re-treatment, mean incontinence episode frequency had increased over its 6 week post-injection value in all treatment groups.

Table 22 IEF at baseline, week 6 post-injection and time of patient request for re-treatment, placebo-controlled pivotal study ITT population

Timepoint	Parameter	Botox 300 U	Botox 200 U	Placebo
Study Baseline	N	223	227	241
	Mean IEF	31	32	32
Week 6 post-injection	Mean IEF	10	11	21
Time of patient request for re-treatment	N requesting re-treatment	127	136	192
	Mean (SD) IEF	19	24	28

Source: sBLA 103000 submission 0123, ISE, Table 2-39.1 and 2-39.2

Reviewer's comment: In clinical practice, basing re-treatment on patient request may be reasonable since data suggest that patient request does correlate with return of symptoms and substantial loss of treatment effect.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Repeat Efficacy

The evaluation of repeat efficacy is based on the Botox-treated ITT population for the pooled phase 3 study data (studies 191622-515, -516 and -094). The number of patients per Botox treatment cycle is shown in Table 23. Since few patients received five or more Botox treatments, the analysis of repeat efficacy focuses on the first four treatments.

Table 23 Number (%) of patients per Botox treatment cycle (Botox-treated ITT population)

Treatment Cycle	300 U Botox (N=298)	200 U Botox (N=318)	Total (N=616)
Cycle 1	298 (100%)	318 (100%)	616 (100%)
Cycle 2	147 (49.3%)	172 (54.1%)	319 (51.8%)
Cycle 3	35 (11.7%)	38 (11.9%)	73 (11.9%)
Cycle 4	7 (2.3%)	8 (2.5%)	15 (2.4%)
Cycle 5	1 (0.3%)	1 (0.3%)	2 (0.3%)
Cycle 6	1 (0.3%)	0 (0.0%)	1 (0.2%)

Source: sBLA 103000 submission 0123, ISE, Table 1-1.3

As shown in Table 24, a statistically significant improvement in weekly IEF was observed over repeat treatments in both the 300 and 200 U Botox groups (with the exception of the 300 U dose group in treatment cycle 4). The magnitude of effect remained consistent across treatment cycles. The responder rate at week 6 (i.e. patients with a >50% or 100% decrease in IEF relative to baseline) was also maintained across treatment cycles.

Table 24. Change in IEF from baseline to Week 6 and responder rate at week 6 according to Botox treatment cycle (Botox-treated ITT Population)

	Cycle 1 Botox		Cycle 2 Botox	
	300 U (N=298)	**200 U** (N=318)	**300 U** (N=147)	**200 U** (N=172)
Weekly IEF				
baseline mean	31.4	32.5	31.9	32.4
Week 6 mean (SD) change from baseline	-22.6 (21)	-22.5 (22)	-23.1 (19)	-19.6 (23)
p-value	<0.001	<0.001	<0.001	<0.001
Responder Rate				
50% reduction [n/N (%)]	219/278 (78.8)	239/302 (79.1)	108/130 (83.1)	111/149 (74.5)
100% reduction) – [n/N (%)]	116/278 (42)	114/302 (38)	55/130 (42)	52/149 (35)

	Cycle 3 Botox		Cycle 4 Botox	
	300 U (N=35)	**200 U** (N=38)	**300 U** (N=7)	**200 U** (N=8)
Weekly IEF				
baseline mean	35.0	36.2	35.0	41.4
Week 6 mean (SD) change from baseline	-26.8 (13)	-31.0 (22)	-36.8 (31)	-31.9 (19)
p-value	<0.001	<0.001	0.058	0.004
Responder Rate				
≥50% reduction – n/N (%)	26/28 (93)	22/26 (85)	5/5 (100)	6/7 (86)
100% reduction – n/N (%)	13/28 (46)	13/26 (50)	3/5 (60)	3/7 (43)

Source: sBLA 103000 submission 0123, SCE, Table 2.7.3-42, p. 125.

Reviewer's comment: The data suggest that there is no loss of effect with repeated Botox treatments.

Reviewer's Summary Comments:

- **Intradetrusor injection of Botox 300 U and 200 U results in statistically significant improvements in weekly IEF and the urodynamic parameters of MCC and MDP at first IDC at week 6 over baseline as compared to placebo.**
- **Botox 200 U is the minimum effective dose for treatment of NDO.**
- **Botox 300 U does not provide additional efficacy over 200 U, so 200 U is the recommended therapeutic dose.**

- **Efficacy of Botox 200 U is not significantly impacted by etiology of NDO (SCI or MS), gender, race (Caucasian versus non-Caucasian) or concurrent use of anti-cholinergic therapy.**
- **Botox 200 U resulted in larger absolute reductions in weekly IEF than placebo in patients older than age 65, and in patients previously exposed to Botox. These differences from placebo, however, were not statistically significant which may be a reflection of the small sample size of these sub-populations.**
- **The median duration of effect of Botox 200 U is 38 weeks and substantially longer than the effect of placebo (13 weeks).**
- **Patient request for re-treatment correlates with return of symptoms (i.e. increase in urinary incontinence episode frequency).**
- **Botox efficacy is sustained with repeated treatments.**

7 Review of Safety

7.1 Methods

The assessment of the clinical safety of Botox for the treatment of urinary incontinence secondary to NDO is based on data from 843 subjects who received study drug in the following six clinical trials, all performed in subjects with urinary incontinence secondary to NDO:

- Two completed double-blind, placebo-controlled, pivotal phase 3 clinical studies (191622-515 and 191622-516)
- One ongoing long-term extension study (191622-094) with an interim analysis
- One ongoing phase 3 clinical study in patients with NDO and neurological respiratory impairment (191622-082)
- Two placebo-controlled phase 2 clinical studies (191622-511 [completed] and 191622-518 [ongoing].

Additional safety data on the use of Botox in patients with underlying respiratory impairment was obtained in study 057, a phase 2 trial conducted in patients with reduced lung function and focal upper limb spasticity due to upper motor neuron syndrome.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The design of the studies used in the analysis of safety is shown in Table 2.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were defined as "any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product." AEs were recorded on a standardized case report form (CRF) and coded from the investigator's "verbatim term" to a "preferred term" using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0.

Reviewer's comment: To evaluate the accuracy of adverse event coding, investigator verbatim terms for a select sample of patients was compared to the corresponding preferred term assigned by the applicant.

Events were allocated to a treatment cycle based on their onset date. For example, an adverse event with an onset date during the first treatment cycle that continued through to the second treatment cycle was counted as one event in the first cycle, but was not considered an adverse event in the subsequent treatment cycle.

The sponsor categorized adverse events as treatment-related or unrelated, and further characterized the treatment-related events as study drug-related or procedure related.

The following specific adverse events were defined by protocol:

UTI: a positive urine culture result with a bacteriuria count of $\geq 10^5$ colony forming units/mL conjoint with > 5 WBCs/high power field, or a positive urine culture that, in the investigator's opinion, required antibiotic therapy.

MS Exacerbation: sudden worsening of an MS symptom or symptoms, or the appearance of new symptoms, which lasted at least 24 hours and was separated from a previous exacerbation by at least 1 month.

MS Progression: an increase in the Expanded Disability Symptom Scale (EDSS) score from screening to exit (of 0.5 if baseline score was ≥ 6.0 or 1.0 if baseline score was ≤ 5.5), or sustained worsening of the signs/symptoms of MS for a period of at least 6 months with or without super-imposed exacerbations.

Reviewer's comment: Urinary retention was not defined by study protocol; this was left to investigator's judgment.

7.1.2.1 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor pooled data from five phase 2 and 3 trials (studies 515, 516, 094, 511 and 518) into 2 analysis populations:

1) **Placebo-controlled safety population** -- all patients who received at least one treatment during a double-blind, placebo-controlled study; includes data from studies 515, 516, 511, and 518.
2) **Botox-exposed safety population** -- all patients who received at least one Botox treatment in any phase 2 or 3 trial (includes studies 515, 516, 511, 518, and 094).

Study 082 was not pooled because the study population (patients with NDO and respiratory impairment) differed from those of the other five trials.

This review focuses primarily on data obtained during the 12 weeks following the first study drug injection (treatment cycle 1) in the placebo-controlled safety population (includes studies 515, 516, 511, and 518). Data from the Botox-exposed population and from study 082 (patients with NDO and respiratory impairment) were reviewed for deaths, any safety signals identified in the placebo-controlled safety database, and for the safety of repeated treatment with Botox. An additional focus of the review of study 082 was on respiratory complications and pulmonary function test results. Approximately 40 patients (all from study 518) received Botox doses < 200 U and are excluded from the safety discussion of this review (with the exception of deaths in those dose groups).

7.2 Adequacy of Safety Assessments

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

Botox for the NDO indication has been studied in a total of 843 patients with NDO secondary to either MS or SCI at doses ranging from 50 to 300 Units injected into the bladder detrusor. A total of 707 subjects have received doses of Botox ≥200 U in six clinical trials.

Reviewer's comment: The total number of exposed patients in clinical trials falls below that recommended by ICH guidelines. However, when considering the large number of additional subjects studied in clinical trials reported in the literature, the extent of exposure is sufficient.

7.2.1.1 Placebo-controlled safety population

The placebo-controlled safety population consists of 769 patients who received at least one study treatment (placebo or Botox 200 U or 300 U). Exposure during treatment cycle 1 (interval between first and second treatment or study exit) is presented in Table 25.

Table 25 Cumulative Duration of Study Drug Exposure for Treatment Cycle 1 (Placebo-controlled Study Safety Population)

	300 U Botox	200 U Botox	Placebo
Total N	235	262	272
N(%) exposed for >12 weeks	231 (98.3%)	252 (96.2%)	260 (95.6%)
N(%) exposed for >48 weeks	108 (46.0%)	110 (42.0%)	49 (18.0%)
N(%) exposed for >54 weeks	57 (24.3%)	57 (21.8%)	20 (7.4%)
Median duration (weeks) of treatment cycle 1	43.9	43.7	23.2

Source: sBLA 103000 submission 0123, Summary of Clinical Safety (SCS), Table 2.7.4-2, p. 28.

Reviewer's comment: The median duration of exposure for treatment cycle 1 was nearly twice as long for the Botox groups as for placebo (43 weeks versus 23.2 weeks, respectively). The reason for the difference in cycle lengths is that subjects receiving placebo requested and qualified for Treatment 2 sooner than subjects receiving Botox.

7.2.1.2 Botox-exposed safety population

The Botox-exposed safety population consisted of 680 patients who received at least one dose of Botox 200 U or 300 U. Patient exposure to Botox according to number of treatments received, and to cumulative duration in weeks, is shown in Table 26 and Table 27, respectively.

Table 26 Summary of patient exposure to Botox by number of treatment cycles (Botox-exposed safety population)

Population	300 U BOTOX® (N = 318)	200 U BOTOX® (N = 362)
Received at least 1 treatment	318 (100.0%)	362 (100.0%)
Received at least 2 treatments	147 (46.2%)	175 (48.3%)
Received at least 3 treatments	35 (11.0%)	38 (10.5%)
Received at least 4 treatments	7 (2.2%)	8 (2.2%)
Received at least 5 treatments	1 (0.3%)	1 (0.3%)
Received at least 6 treatments	1 (0.3%)	0 (0.0%)

Note: Treatment group is based on the first BOTOX® dose received. Studies include 191622-511, -515, -516, -518, and -094
Source: Module 5.3.5.3, ISS Table 1-1.2
Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-4, p. 30.

Table 27 Cumulative Duration of Exposure in weeks (Botox-exposed Safety Population)

Duration of Exposure[1]	300 U Botox (N=318)	200 U Botox (N=362)
≥1 week	318 (100.0%)	361 (99.7%)
≥6 weeks	317 (99.7%)	359 (99.2%)
≥12 weeks	312 (98.1%)	354 (97.8%)
≥24 weeks	278 (87.4%)	315 (87.0%)
≥48 weeks	202 (63.5%)	236 (65.2%)
≥54 weeks	139 (43.7%)	161 (44.5%)
≥104 weeks	22 (6.9%)	18 (5.0%)

1 – duration of exposure for each patient was from the first Botox treatment day to the study exit day, regardless of number of injections received
Includes studies 191622-511, 515, 516, 518, and -094
Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-3, p. 29.

Reviewer's comment: The extent of exposure is sufficient.

7.2.1.3 Botox Exposure in Patients with Respiratory Impairment

Botox exposure by dose and number of treatments in patients with underlying respiratory impairment (includes both patients treated for spasticity in study 057 and patients with neurogenic detrusor overactivity in study 082) is shown in Table 28.

Table 28 Botox exposure (N), patients with underlying respiratory impairment

	360 U	300 U	240 U	200 U	Placebo
1 injection	55	12	52	12	58
2 injections	50	3	46	5	48

Reviewer's comment: Safety data in patients with neurogenic detrusor overactivity and respiratory impairment is limited (i.e. only 34 patients to date).

7.2.2 Explorations for Dose Response

As discussed in section 6.1.8, the sponsor investigated doses of Botox up to 300 U for the NDO indication. The 300 U dose provided no additional efficacy with respect to incontinence episode frequency over the 200 U dose (see Table 7). The incidence of the most common adverse events was for the most part greater in the 300 U dose group (see Table 29).

Table 29 Most common adverse events (>3 % in any Botox treatment group and 2x rate of placebo), first 12 weeks of treatment cycle 1, placebo-controlled study safety population

Preferred Term	300 U Botox N=235	200 U Botox N=262	Placebo N=272
Overall	152 (64.7%)	161 (61.5%)	144 (52.9%)
UTI	70 (29.8%)	64 (24.4%)	47 (17.3%)
Urinary retention	49 (20.9%)	45 (17.2%)	8 (2.9%)
Hematuria	15 (6.0%)	10 (3.8%)	8 (2.9%)
Constipation	10 (4.3%)	4 (1.5%)	5 (1.5%)
Bladder pain	8 (3.4%)	2 (0.8%)	2 (0.7%)
Fatigue	5 (2.1%)	10 (3.8%)	3 (1.1%)

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-10, p. 42.

The sponsor concluded that Botox 200 U displayed the most favorable risk/benefit profile.

Reviewer's comment: This reviewer agrees that Botox 200 U should be the recommended dose for treatment of NDO.

7.2.3 N/A

7.2.4 Routine Clinical Testing

In the phase 2 and 3 placebo-controlled trials, safety assessments included medical history and physical examination, and periodic measurement of vital signs, urine and serum laboratory evaluation, urodynamic parameters and renal/bladder ultrasound. Patients were queried for adverse events at each follow-up encounter. Table 30 displays the schedule of safety assessments during the pivotal phase 3 clinical trials (studies 515 and 516).

Table 30 Schedule of Clinical Assessments in Phase 3 Pivotal Trials

	Screening	Treatment visit 1	Qualification for re-treatment	Re-treatment visit	Post-treatment clinic visits (weeks 2, 6, 12 and then q 12 weeks)	Post-treatment telephone visits (q 12 weeks)	Study exit (week 52)
Medical history	X	X					
Physical exam	X						x
Vital signs	X	X	X	x	X		X
Urodynamic parameters	X				X (week 6 only)		
Post-void residual	X	X	X		X (week 2, 6 and then q 12 wks)		X
Bladder/ kidney u/s	X		X		X (q 12 weeks)		X
Urinalysis	X		X		X (wk 2 and then q 12 weeks		X
Urine culture	X		X				X
Urine cytology	X						
Bladder diary		X			X	x	X
Total volume voided		x			x	x	x
EDSS	X						X
Safety blood parameters	X		X		X		X
Toxin neutralizing antibody test	X		X				X
Pregnancy test	X (serum)	X(urine)	X(serum)	X (urine)	X (urine)		X (serum)
PSA	x						
Concurrent medications	X	X	X	X	X	X	X
Concurrent procedures		X	X	X	X	X	X
Adverse events		X	X	X	X	X	x

Source: sBLA 103000 ser 0123, Study 191622-515 protocol, module 5.3.5.1.4, p. 61. and Study 191622-516 protocol, module 5.3.5.1.3., p. 61.

7.2.5 Metabolic, Clearance, and Interaction Workup

According to the sponsor, the extreme potency of Botox and limits to analytical sensitivity limit the opportunity to study the pharmacokinetic (PK) profile of Botox in humans. Therefore, no human PK studies have been performed for any indication.

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

Botox is a neuromuscular blocking agent that inhibits acetylcholine release from the nerve terminal at the neuromuscular junction. Other neuromuscular blocking agents, such as vecuronium and pancuronium, have a different mechanism of action, and are indicated as an adjunct to anesthesia to produce global paralysis during surgery. Botox, because it is injected directly into the target muscle, should theoretically have only a local effect. Still, there is concern for adverse events related to remote spread of the toxin. This issue is discussed in section 7.3.5.1.

7.3 Major Safety Results

7.3.1 Deaths

Through November 15, 2010, the date of the data-lock for the 120 day safety update, seven deaths were reported across all 6 NDO studies included in the submission. No death was considered by the clinical investigators to be study drug or treatment-related. Narratives follow.

***Study 515*:**
Case 1: Patient 10014-1613 (300 U Botox) was a 54 year-old Caucasian female with a 26 year history of MS who was found dead in bed (b) (6) after receiving treatment 1. Concomitant medications at the time of death were trospium 60 mg qd and calcium 800 mg bid.

At a week 24 post-randomization visit on (b) (6), and (b) (6) prior to death, the patient was noted to be in stable condition with no changes. A scheduled kidney/bladder ultrasound at that visit found no abnormalities.

The day prior to death, the patient had a teeth cleaning and had then gone to bed that evening without complaint. The cause of death was undetermined. It was not stated whether an autopsy had been performed.

Reviewer's comment: There is insufficient information for this case to determine causality.

Case 2: Patient 10015-1656 (200 U Botox) was a 28 year old Caucasian female with a past medical history of T-12 SCI, chronic back pain and depression (>1 year) who died (b) (6) after last study drug administration of acute methadone intoxication. Ongoing concomitant medications at the time of death included methadone 10 mg po qid, diazepam (dose and frequency not stated), Flexeril and nordiazepam. The patient also smoked marijuana.

The patient was injected with blinded study drug (placebo) on December 16, 2008, and re-treated (Botox 200 U) on March 24, 2009.

(b) (6) after the last documented dose of study drug, the patient was admitted to the hospital for depressive psychosis and suicidal ideation. The patient had threatened to kill her mother and herself and was

admitted to a psychiatric service for therapy and administration of psychotropic medications. At admission urine toxicology was positive for marijuana. Treatment included IV and oral Ativan and oral Haldol for agitation.

On (b) (6), the patient was found in her room unresponsive. She did not respond to resuscitative measures and was pronounced dead. Autopsy report confirmed cause of death as 'acute intoxication by methadone'.

Reviewer's comment: This death from methadone intoxication was unrelated to study drug or procedures.

***Study 516*:**

Case 3: Patient 10029-6001 (200 U Botox) was a 44 year-old Black male with SCI who died (b) (6) after treatment 1 due to acute renal failure, enterococcal endocarditis, acidosis, and respiratory failure. The patient's medical history included T6 SCI (since 2007), NDO with requirement for CIC (since 2006), spinal stenosis (since 1991) DVT (2007), left heel pressure ulcer (since 2008), UTI (2009), and constipation (2008),

The patient was injected with blinded study drug (Botox 200 U) on September 4, 2008. Concomitant medications were oxybutynin, omeprazole, baclofen, and Levaquin 500 mg daily for UTI (started September 1, 2009).

On (b) (6) the last documented dose of study drug, the patient presented to a medical facility in respiratory failure and was immediately intubated. Diagnostic work up confirmed enterococcal endocarditis. The patient's condition worsened despite intravenous fluids and intravenous antibiotics of *vancomycin, ampicillin* and *ciprofloxacin.* He developed acute renal failure and acidosis. Per request of the patient and family, no other life saving interventions were implemented, and the patient died on (b) (6).

Case 4: Patient 11206-9528 (placebo) was a 46 year-old Caucasian male with MS who died (b) (6) after treatment 1 due to sepsis, pneumonia, and renal impairment. Past medical history was significant for secondary-progressive multiple sclerosis (1988), depression, back pain, and hypertension (2007). Concomitant medication at the time of the adverse event included fluoxetine 20 mg bid, diazepam 5 mg qd, enalapril 20 mg qd, vardenafil 20 mg prn, interferon 44 MU IM thrice weekly, amantadine 100 mg qd, dorflex and carbamazepine 200 mg qd

The patient was injected with blinded study drug (Botox 200) on January 20, 2009. (b) (6) after last dose of study drug, the patient was hospitalized in the intensive care unit with high fever. The patient was transferred to another hospital for further care (b) (6).

Through information obtained from the patient's daughter, the investigator reported that sepsis, pneumonia and renal impairment were the cause of patient's hospitalization and death. No additional information regarding patient's care was available to the investigator.

***Study 518*:**

Case 5: Patient 13009-1114 (100 U Botox) was a 40 year old Asian male who died suddenly from an unknown cause (b) (6) Significant past medical history included L1 spinal cord injury (2006)) and bed sores (2008). Ongoing concomitant medication at the time of death was *solifenacin* 5 mg bid for overactive bladder.

The patient was injected with blinded study drug per protocol (BOTOX 100 U) on January 11, 2009. (b) (6) after the last documented dose of study drug, the patient was found dead in his home by his wife when she returned from work. No autopsy was performed.

The investigator reported that at the scheduled weeks 2 and 6 post-treatment study visits the patient had reported improvement of symptoms and was physically well. The patient had a previous AE of hyperchlorhydria for which he had received *ranitidine* (1/11/2009 to 1/15/2009).

Reviewer's comment: Insufficient information is available to determine causality.

Case 6: Patient 13009-1049 (50 U Botox) was a 35 year old Asian male who [redacted] (b) (6) after treatment 1 due to "undiagnosed respiratory problems." Significant past medical history included spinal cord injury (2008), bed sores (2009), constipation (2008), and NDO with requirement of CIC to void (2008). Concomitant medication at the time of death was tolterodine 2 mg bid.

The patient received Botox 50 U injection on November 12, 2008. At an unscheduled follow-up visit on April 21, 2009, the patient was diagnosed with a sacral decubitus ulcer with purulent drainage. The ulcer was treated with local neomycin and betadine cleaning. In addition, A urinary tract infection was found at laboratory screening on April 25, 2009, and the patient was advised to take nitrofurantoin 100 mg bid for 7 days. The ulcer had improved at the week 24 follow-up visit (.

On June 10, 2009, the patient returned for a week 30 visit. He appeared ill and reported increased frequency of urinary incontinence (between CIC). Vital signs at that visit were BP 90/40 mm Hg, pulse 84 bpm, respirations 28 bpm and temperature of 98.6°F. No laboratory testing was performed at that time.

On June 17, 2009, the investigator was informed that the patient developed mild breathlessness and had not eaten since June 13, 2009. The patient's caretakers did not seek medical attention for the patient and he died [redacted] (b) (6). No autopsy was performed.

Reviewer's comment: Clinical history suggests that the patient may have had urosepsis at the time of death.

Case 7: Patient 14804-1081 (200 U Botox) was a 52-year-old Caucasian male with a history of neurogenic detrusor overactivity secondary to T10 spinal cord injury who died suddenly on [redacted] (b) (6) after study drug administration. Ongoing concomitant medication at the time of the event was tolterodine 2 mg bid for OAB. The patient was found deceased by his mother. No other information is available regarding circumstances of death.

Summary Comment: There were a total of 7 deaths that occurred as of November 15, 2010, in the Botox-treated safety population – one in the 300 U dose group, three in the 200 U group, two in subjects treated with <200 U Botox and one in the placebo group. Of the six deaths in Botox-treated subjects,

- **Cause of death in cases 2 and 3 was methadone intoxication and enterococcal endocarditis/sepsis, respectively, and neither death was related to study drug.**
- **Cause of death in case 6 is not specified but clinical history suggests sepsis – either stemming from the urinary tract or an infected decubitus ulcer. The [redacted] (b) (6) interval between Botox injection and death argues against Botox causality.**
- **In the remaining cases (#1, 5 and 7), cause of death is unknown, but, as in Case 6, the long interval between Botox injection and death in each case is inconsistent with Botox pharmacology.**

Therefore, the evidence does not suggest a relationship between any death and Botox treatment or study procedures.

7.3.2 Nonfatal Serious Adverse Events

The incidence of serious adverse events was highest in the Botox 300 U dose group – both across treatment cycle 1 and during the first 12 weeks (Table 7.7). The most common serious adverse events (those occurring in >1 subject per Botox dose group) are shown in Table 31.

Table 31 Most common Serious Adverse Events (occurring in >1 subject per Botox dose group), placebo-controlled safety population, treatment cycle 1

Category Preferred Term	*Across Treatment Cycle 1*			*First 12 weeks of Treatment Cycle 1*		
	300 U (N=235)	200 U (N=262)	Placebo (N=272)	300 U (N=235)	200 U (N=262)	Placebo (N=272)
Serious adverse events	36 (15.3%)	30 (11.5%)	29 (10.7%)	17 (7.2%)	7 (2.7%)	19 (7.0%)
Urinary tract infection (UTI)	7 (3.0%)	4 (1.5%)	3 (1.1%)	2 (0.9%)	2 (0.8%)	2 (0.7%)
MS relapse	10 (4.3%)	2 (0.8%)	8 (2.9%)	4 (1.7%)	0 (0.0%)	3 (1.1%)

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-19, p. 65-68.

Summary Comment: The incidence of serious UTI was similar between Botox 200 U and placebo dose groups.

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Placebo-controlled treatment cycle 1

Both in the first 12 weeks of and throughout treatment cycle 1, the incidence of premature discontinuation due to adverse events was greatest in the Botox 300 U treatment group. During the first twelve weeks, discontinuation rates due to AEs were similar in the Botox 200 U and placebo groups (see Table 32). No single adverse event led to discontinuation among Botox-treated patients more commonly than in placebo so individual AE preferred terms are not listed.

Table 32 Discontinuations due to Adverse Events, placebo-controlled study safety population*

	Across Treatment Cycle 1			*First 12 weeks of treatment Cycle 1*		
	300 U (N=235)	200 U (N=262)	Placebo (N=272)	300 U (N=235)	200 U (N=262)	Placebo (N=272)
Overall	6 (2.6%)	6 (2.3%)	3 (1.1%)	3 (1.3%)	1 (0.4%)	2 (0.7%)

* (includes studies 511, 515, 516, 518)
Source: sBLA 103000 submission 0123, SCS Table 2.7.4-21, p. 74.

7.3.3.2 Repeat Treatments (Botox treated safety population)

In the Botox-treated safety population, regardless of treatment cycle, the rate of adverse events leading to study discontinuation was equivalent in the two Botox dose groups (see Table 33). Urinary tract infection was the single most commonly reported adverse event leading to early discontinuation, and occurred more often in the Botox 300 U dose group. No other single adverse event was reported in more than one subject per dose group.

Table 33 Adverse Events Leading to Study Discontinuation (Botox-treated Safety population; across all treatment cycles)

Category/Preferred Term	Botox 300 U N=318	Botox 200 U N=362
Overall	9 (2.8%)	10 (2.8%)
Urinary tract infection	3 (0.9%)	0

Source: : sBLA 103000 submission 0123, SCS, Table 2.7.4-23, p. 78 (includes studies 094, 511, 515, 515, 516, 518)

7.3.4 Significant Adverse Events

7.3.4.1 Urinary Retention

Because of the pharmacology of Botox, urinary retention was an expected side effect. A definition of urinary retention was not provided in the study protocols; determination was left to the judgement of the investigator.

During placebo-controlled treatment cycle 1, urinary retention occurred in a dose-proportional manner (see Table 34). Investigators considered the majority of these events to be related to study drug as opposed to the injection procedure. All but one event of urinary retention occurred within the first 12 weeks after treatment.

Table 34 Incidence of Urinary Retention, Treatment Cycle 1 (Placebo-controlled study safety population)

	Across Treatment Cycle 1			*First 12 weeks of treatment Cycle 1*		
	Botox 300 U (N=235)	Botox 200 U (N=262)	Placebo (N=272)	Botox 300 U (N=235)	Botox 200 U (N=262)	Placebo (N=272)
Urinary retention	50 (21.3%)	45 (17.2%)	8 (2.9%)	49 (20.9%)	45 (17.2%)	8 (2.9%)

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-30, pp 98-99.

7.3.4.2 Post-Void Residual (PVR) Urine Volume

PVR urine volume was measured at protocol-specified time points only in patients who had the ability to spontaneously void at that time (i.e. they were not using CIC at that time). At week 2 (the time of first post-baseline measurement), mean PVR urine volume increased significantly in both Botox treatment groups, but not in the placebo group. In addition, the percentage of subjects with a PVR urine volume ≥200 mL at week 2 increased in a dose-proportional manner (see Table 35 Change from baseline to Week 2 in PVR Urine Volume and Proportion).

Reviewer's comment: According to consensus recommendations from the U.S. Department of Health and Human Services Agency for Health Care Policy and Research

(AHCPR), a PVR volume greater than 200 mL is considered indicative of inadequate emptying.[2]

Table 35 Change from baseline to Week 2 in PVR Urine Volume and Proportion Patients with PVR Urine Volume at Various Levels at Week 2 of Treatment Cycle 1 (placebo-controlled study safety population not using CIC at baseline)

Timepoint/statistic	300 U Botox (N=100)	200 U Botox (N=108)	Placebo (N=104)	p-value[2]
Week 2				
Median	105.0	41.5	0	<0.001
Min-max	-140, 1200	-200, 955	-156, 200	
p-value[1]	<0.001	<0.001	0.920	
≥200 mL	38 (44.2%)	29 (29.3%)	3 (3.4%)	
≥300 mL	27 (31.4%)	15 (15.2%)	1 (1.1%)	
≥400 mL	20 (23.3%)	9 (9.1%)	0 (0.0%)	

Source: sBLA 103000 submission 0123, SCS, Tables 2.7.4-35 and 2.7.4-36, p. 116 and 117.
1 – p-value for change in PVR at week 2 compared to baseline
2 – p-value for baseline-corrected change in PVR at week 2 versus placebo

7.3.4.3 Patients Catheterizing for Urinary Retention

The investigator recorded on a specific CRF if a patient were, in their assessment, performing catheterization (CIC or indwelling catheter) for urinary retention. The percentage of patients catheterizing for urinary retention during treatment cycle 1 and who were not catheterizing at baseline increased in a dose-proportional manner (see Table 36).

Table 36 Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization, Treatment Cycle 1 (placebo-controlled study safety population)

Timepoint/Statistic	300 U (N=100)	200 U (N=108)	Placebo (N=104
Proportion of Patients Catheterizing for Urinary Retention			
At any time during treatment cycle 1	44 (44.0%)	33 (30.6%)	7 (6.7%)
Duration of Catheterization for Urinary Retention (Days)			
Median	293	289	358
Min, Max	1, 612	1, 530	2, 379

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-38, p. 119.

Reviewer's comment: No specific protocol guidance was provided for the initiation or cessation of catheterization.

[2] U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. Clinical practice guidelines: urinary incontinence in adults. Washington, D.C.: U.S. Department of Health and Human Services; March 1992.

7.3.4.4 Urinary Tract Infection

UTI (preferred term) was the most frequently reported adverse event among Botox-treated patients, and occurred in a dose-dependent manner during placebo-controlled treatment cycle 1 (both during the first 12 weeks and for the entire treatment cycle) and at a rate greater than placebo. In addition, other preferred terms representing UTI (*Escherichia UTI, UTI bacterial, urosepsis, cystitis, pyelonephritis, pyelonephritis chronic, kidney infection, urethritis, pyuria, culture urine positive)* were more frequent among Botox treated subjects than those receiving placebo (Table 37). Approximately half of UTI adverse events occurred within the first 12 weeks of treatment cycle 1.

Table 37 Incidence of UTI during Treatment Cycle 1, placebo-controlled study safety population

Preferred Term	*Across Treatment Cycle 1*			*First 12 weeks of treatment Cycle 1*		
	300 U (N=235)	200 U (N=262)	Placebo (N=272)	300 U (N=235)	200 U (N=262)	Placebo (N=272)
UTI	125 (53.2%)	129 (49.2%)	97 (35.7%)	70 (29.8%)	64 (24.4%)	47 (17.3%)
Other UTI terms	14 (6.4%)	8 (3.1%)	10 (3.7%)	5	5	5
Total	139 (59.1%)	137 (52.5%)	107 39.3%)	75 (31.9%)	69 (26.3%)	52 (19.1%)

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-12 and 2.7.4-13, p. 47.

7.3.4.5 UTI with Complications

The placebo-controlled safety database was searched for preferred terms consistent with a UTI with complications (search terms were *urosepsis* and *pyelonephritis*). Neither dose of Botox was associated with an increased incidence of such events during placebo-controlled treatment cycle 1 (Table 38).

Table 38 Proportion of Subjects Experiencing UTI with Complications, Treatment Cycle 1 (Placebo-controlled Safety Population)

Preferred Term	Across Treatment Cycle 1			*First 12 weeks of treatment Cycle 1*		
	300 U (N=235)	200 U (N=262)	Placebo (N=272)	300 U (N=235)	200 U (N=262)	Placebo (N=272)
urosepsis	0	0	2 (0.7%)	0	0	1 (0.4%)
pyelonephritis	1 (0.4%)	0	2 (0.7%)	0	0	2 (0.7%)

7.3.4.6 Renal Failure

The placebo-controlled safety database for treatment cycle 1 was searched for adverse event preferred terms that could represent renal impairment (search terms were *renal failure acute, renal failure chronic, renal impairment, blood creatinine increased).* Results, shown in Table 39, did not demonstrate an increased incidence of this adverse event among Botox-treated subjects when compared to placebo.

Table 39 Proportion of subjects experiencing renal impairment, Treatment Cycle 1 (placebo-controlled study safety population)

Adverse Event Category	Across Treatment Cycle 1			*First 12 weeks of treatment Cycle 1*		
	300 U (N=235)	200 U (N=262)	Placebo (N=272)	300 U (N=235)	200 U (N=262)	Placebo (N=272)
Renal impairment	1 (0.4%)	4 (1.5%)	3 (1.1%)	1 (0.4%)	1 (0.4%)	1 (0.4%)

7.3.4.7 Autonomic Dysreflexia

Autonomic dysreflexia, a complication of spinal cord injuries above T6, consists of paroxysmal sympathetic and parasympathetic hyperactivity that is initiated by noxious stimuli, such as bladder overdistension or fecal impaction, below the level of the spinal cord lesion. Symptoms include sweating, flushing, hypertension, bradycardia and piloerection.[3] Autonomic dysreflexia has also been reported in patients with multiple sclerosis.[4] Because intradetrusor injection of Botox is done via cystoscopy, there was a concern that autonomic dysreflexia might occur during the study procedure.

The incidence of autonomic dysreflexia was greater among patients receiving Botox than those treated with placebo (Table 40).

Table 40 Incidence of Autonomic Dysreflexia, Treatment Cycle 1, (Placebo-controlled study safety population

Treatment cycle 1	**Botox 300 U** (N=235)	**Botox 200 U** (N=262)	**Placebo** (N=272)
Autonomic dysreflexia	4 (1.7%)	4 (1.5%)	1 (0.4%)

Source: sBLA 103000 submission 0123, ISS, Table 2-2.1, p. 185.

The majority of cases of autonomic dysreflexia occurred on treatment day 1, either after study drug injection (5/9 cases) or during urodynamic testing (2/9 cases – both on Botox 200 U) performed prior to injection. Five patients required treatment with an anti-hypertensive agent. Two cases occurred >1 day following treatment – one case (Botox 200 U) following urodynamic testing on study day 50, and the second five days after Botox 200 U injection. In the latter case, elevated blood pressure was noted which did not require medical treatment. The patient did not experience a recurrence following treatment 2. Of the nine cases, all but one involved a patient with SCI.

[3] Moro-Sutherland Donna, "Chapter 138. The Child with Special Health Care Needs." Tintinalli JE, Stapczynski JS, Cline DM, Ma OJ, Cydulka RK, Meckler GD: Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 7e: http://www.accessmedicine.com/content.aspx?aID=6383989

[4] Bateman, AM, and GD Goldish. Autonomic dysreflexia in multiple sclerosis. J Spinal Cord Med. 2002 Spring; 25 (1): 40-2.

Reviewer's comment: If the two subjects in the Botox 200 U group who developed autonomic dysreflexia during urodynamic testing are excluded, the incidence of autonomic dysreflexia following Botox 200 U injection drops to 0.7% -- only slightly greater than that observed with placebo. Autonomic dysreflexia appears to stem primarily from the injection procedure itself (i.e. cystoscopy and bladder distension) and no case was severe. The risk of autonomic dysreflexia associated with the procedure itself as well as the slightly increased incidence of autonomic dysreflexia associated with Botox observed in clinical trials should be addressed in labeling.

7.3.4.8 Multiple Sclerosis Exacerbation

The sponsor analyzed the safety database for any signal that Botox treatment increased the risk of an MS exacerbation. In the pivotal study protocols (studies 515 and 516), MS exacerbation was defined as a sudden worsening of an MS symptom or symptoms, or the appearance of new symptoms, which lasted at least 24 hours and was separated from a previous exacerbation by at least 1 month. The MS exacerbation event rate per patient year in treatment cycles 1 and 2 is shown in Table 41 Multiple Sclerosis Exacerbation Event Rates

Table 41 Multiple Sclerosis Exacerbation Event Rates
(Treatment Cycle 1, placebo-controlled study safety population)

	Botox 300 U	Botox 200 U	placebo
Treatment cycle 1			
Total exposure (patient years)	108.0	106.4	73.2
Event rate	0.29	0.23	0.20
Treatment cycle 2			
Total patient years	26.6	36.2	n/a
Event rate	0.38	0.33	n/a

Source: sBLA 103000 submission 0123, ISS, Table 3-45.1-2, p. 2842-3.

Reviewer's comment: Although the MS exacerbation event rate increased during the second treatment cycle, it is difficult to interpret this result without a placebo control. Patients receiving a second treatment may not be representative of all MS patients (i.e. may have more severe disease).

The Division of Neurology Products (DNP) was asked to review the data on MS exacerbation rates and to respond to the following questions:

1) ***Do you believe that the observed 0.03 difference in event rate per patient year between Botox 200 U and placebo is not an unreasonable risk to patients?***
2) ***If so, do you believe that this risk can be adequately managed with labeling?***

DNP provided the following response and additional comments in a memorandum of consultation dated May 5, 2011:

> **"The observed difference of 0.03 in the event rate per patient year between Botox 200U and placebo does not suggest that there is a clinically relevant increased risk of exacerbations in the MS population with the use of this product. There is considerable variability in MS relapse rates for patients with this disorder, with the range lying between 0.2-1.2 per year. The relapse rates for patients using previously approved MS medication is lower and more closely approximates the rates described in this trial. Although the pooled data suggest a dose related increase in MS exacerbation annualized rates per patient year, this dose related relationship does not occur in the individual studies.... In study 515 although the 300U group has a higher exacerbation rate than placebo, the 200 U group has a lower exacerbation rate than placebo. In study 516, the 300U Botox group and the placebo group have comparable MS exacerbation rates and the 200 U group has a higher rate. Therefore, looking individually at the trials, the dose relationship seen in the pooled data is not replicated. In addition, these exacerbation rates are all within the normal variation seen in a treated MS population, and actually closely approximate each other. The evidence presented suggests that the 0.03 increased MS exacerbation event rate in the pooled data from these two trials, when the 200U cohort is compared to the placebo cohort, does not represent a clinically significant difference."**

The opinion of DNP and of this DRUP reviewer is that Botox 200 U is not associated with an increased risk of MS exacerbation over placebo.

7.3.4.9 Multiple Sclerosis Progression

The sponsor also examined the effect of Botox on progression of MS. The sponsor defined MS progression as an increase in the Expanded Disability Status Scale (EDSS) score at exit compared to baseline of 0.5 if the baseline score was $\geq$ 6.0, and of 1.0 if the baseline score was $\leq$ 5.5, or any sustained worsening of signs/symptoms of MS for a period of at least 6 months. EDSS was assessed at entry and at study exit (not at conclusion of a treatment cycle).

The mean change from baseline in EDSS scores was similar among the three treatment groups (Table 42 Summary EDSS Scores, and Change from baseline to study exit in EDSS Score).

Table 42 Summary EDSS Scores, and Change from baseline to study exit in EDSS Score (Placebo-controlled study safety population)

Timepoint	Botox 300 U (N=117)	Botox 200 U (N=129)	Placebo (N=130)
Baseline EDSS			
Median (min, max)	5.5 (1, 8)	5.5 (1, 7)	5.5 (2, 7)
Study exit EDSS			
Median (min, max)	6.0 (1, 9)	5.5 (1, 8)	6.0 (1, 8)
N (%) with change in EDSS			
>2.5	1 (1.0%)	0	1 (0.9%)
1.5-2.5	5 (4.9%)	2 (1.8%)	2 (1.8%)
0.5-1.5	10 (8.5%)	11 (8.5%)	8 (6.1%)

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-28, p. 93

Reviewer's comment: Data are presented by the dose the patient received at treatment 1 regardless of any subsequent treatments administered between enrollment and study exit. As some placebo patients may have received Botox for treatment 2, these data are not truly placebo-controlled.

To control for treatment received, change from in EDSS baseline to one year post-randomization was examined in subjects who received only a single treatment. There was no difference in median change in EDSS from baseline across treatment groups (Table 43).

Table 43 Baseline and Change from Baseline in EDSS for MS Patients during Teatment Cycle 1, (Placebo-controlled study safety population)

	Botox 300 U	Botox 200 U	Placebo
Baseline			
N	117	128	129
Median (min, max)	5.5 (1, 8)	5.5 (1, 6.5)	5.5 (2, 6.5)
1 Y post-randomization			
N	43	31	37
Median Δ (min, max)	0 (-2.5, 1)	0 (-0.5, 1)	0 (-1, 3)

Source: sBLA 103000 submission 0123 ISS, Table 3-49.1, p. 2850.

Reviewer's comment: DNP recommended that the sponsor provide an analysis of MS disease progression rates by treatment group at 52 weeks, 64 weeks, and study exit. The analysis should specify the progression rates for patients based on the doses received for treatment cycle 1 and treatment cycle 2 (if they received two treatments).

The sponsor responded to this request for information in serial submission 0143, dated June 24, 2011. Among patients receiving only a single treatment, EDSS Progression

rates at 52+/-6 weeks were 22.2% for placebo and 15.2% for Botox 200 U. For those receiving two treatments, rates were 28.1% for Botox 200 U/200 U and 32.0% for placebo/Botox 200 U.

The available data do not suggest that Botox accelerates MS disease progression.

Reviewer's Summary Comment Regarding Significant Adverse Events:

1. **Intradetrusor injection of Botox 200 U is associated with an increased risk of urinary retention, increased post-void residual urine volume and catheterization for urinary retention when compared to placebo. These adverse events are consistent with Botox pharmacology and should be labeled, but do not pose an unreasonable risk to patients.**
2. **Botox 200 U also increases the risk of urinary tract infection when compared to placebo. However, Botox 200 U does not appear to confer a greater risk of UTI with complication (i.e. pyelonephritis or urosepsis) over placebo.**
3. **Botox 200 U may slightly increase the risk of autonomic dysreflexia following injection when compared to placebo though the mechanism for this effect is not clear. This risk can be managed adequately in labeling, in this reviewer's opinion.**
4. **Available data do not suggest that Botox 200 U is associated with an increased risk of MS exacerbation or acceleration of disease progression.**

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Distant Spread of Toxin

7.4.5.1.1 Placebo-controlled study safety population

Possible distant spread of toxin was defined as pharmacologic effects of botulinum at sites remote to the injection site. The sponsor searched the placebo-controlled study safety database for 40 MedDRA preferred terms (shown in Table 44) that could signal adverse events caused by distant spread of botulinum toxin.

Table 44 MedDRA Preferred Terms Evaluated for Distant Spread of Toxin

Cardiac Disorders	Hyporeflexia
Bradycardia	Hypotonia
Eye Disorders	Paralysis
Accommodation disorder	Paralysis flaccid
Diplopia	Paresis cranial nerve
Extraocular muscles paresis	Peripheral nerve palsy
Eyelid function disorder	Peripheral paralysis
Eyelid ptosis	Speech disorder
Pupillary reflex impaired	Vocal cord paralysis
Vision blurred	Vocal cord paresis
Gastrointestinal Disorders	**Renal and Urinary Disorders**
Constipation	Urinary retention
Dry mouth	**Respiratory, Thoracic and**
Dysphagia	**Mediastinal Disorders**
Ileus paralytic	Aspiration
Infections and Infestations	Diaphragmatic paralysis
Botulism	Dysphonia
Musculoskeletal and	Dyspnoea
Connective Tissue	Pneumonia aspiration
Disorders	Respiratory arrest
Muscular weakness	Respiratory depression
Nervous System Disorders	Respiratory failure
Bulbar palsy	**Reproductive System and**
Cranial nerve palsies multiple	**Breast Disorders**
Cranial nerve paralysis	Pelvic floor muscle weakness
Dysarthria	
Facial palsy	
Facial paresis	

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-29, p. 95.

Search results for treatment cycle 1 reveal a higher incidence of such adverse events among patients receiving Botox than placebo. However, when the search is confined to the first 12 weeks of treatment cycle 1 (Table 45), only the adverse events of constipation and urinary retention show a dose-response relationship.

Table 45 Patients Reporting Adverse Events Potentially Associated with Effects Remote to the Site of Injection, placebo-controlled study safety population

	Across Treatment Cycle 1			*First 12 weeks of Treatment cycle 1*		
Preferred Term	Botox 300 U N=235	Botox 200 U N=262	Placebo N=272	Botox 300 U N=235	Botox 200 U N=262	Placebo N=272
Urinary retention	50 (21.3%)	45 (17.2%)	8 (2.9%)	49 (20.9%)	45 (17.2%)	8 (2.9%)
Muscular weakness	13 (5.5%)	10 (3.8%)	5 (1.8%)	4 (1.7%)	4 (1.5%)	5 (1.8%)
Constipation	11 (4.7%)	11 (4.2%)	7 (2.6%)	10 (4.3%)	4 (1.5%)	4 (1.5%)
Vision blurred	2 (0.9%)	3 (1.1%)	0	0	0	0
Diplopia	1 (0.4%)	2 (0.8%)	0	0	1 (0.4%)	0
Dyspnea	1 (0.4%)	1 (0.4%)	4 (1.5%)	1 (0.4%)	0	3 (1.1%)
Dysarthria	1 (0.4%)	0	2 (0.7%)	0	0	1 (0.4%)
Dysphonia	0	1 (0.4%)	0	0	0	0
Respiratory failure	0	1 (0.4%)	0	0	0	0
Bradycardia	0	0	1 (0.4%)	0	0	0

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-30

Reviewer's comment: Urinary retention is considered an expected local effect of intradetrusor Botox injection. Constipation may occur secondary to urinary retention.

The single report of respiratory failure occurred (b) (6) after Botox injection and in the setting of hospitalization for enterococcal endocarditis in a 44 year old male patient with SCI. The patient subsequently died (see full narrative in section 7.3.1). This event was not related to study drug.

7.5.4.1.2.2 Individual Case Review

Because of the pharmacology of Botox and its expected 12 week duration of action, only adverse events occurring in Botox-treated patients within the first 12 weeks following injection are considered to be possibly related to distant spread of toxin. Those events are discussed further below.

Muscular weakness

All events of muscular weakness occurred in the MS subpopulation with the exception of a single case in a man with SCI. In MS patients, the incidence of muscular weakness during the first 12 weeks of treatment cycle 1 was not greater in Botox treated subjects than those in the placebo group (Table 46).

Table 46 Incidence of Muscular Weakness according to NDO Etiology, First 12 weeks of Treatment Cycle 1 (Placebo-controlled study safety database)

Preferred term	Botox 300 U N=117	Botox 200 U N=132	Placebo N=133	Botox 300 U N=118	Botox 200 U N=130	Placebo N=139
Muscular weakness	3 (2.6%)	4 (3.0%)	5 (3.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)

Source: sBLA 103000 submission 0123, SCS, Table 2.7.4-42, pp 130-131.

In the SCI sub-population, the single report of muscular weakness involved a patient treated with Botox 300 U:

Patient 11202-9436, a 36-year-old male with T-11 SCI, developed progressive lower limb weakness three days after intradetrusor injection with Botox 300 U. Botox was administered under general anesthesia using propofol, fentanyl, and midazolam. He was hospitalized for lower limb weakness 70 days after injection. The clinical investigator considered the adverse event to be serious and related to study drug. Cerebrospinal fluid analysis did not reveal any clinically significant abnormalities and electromyography was normal. The patient was discharged after 2 days and the event was considered resolved with sequelae since the patient was unable to perform his normal daily activities. The event was ongoing for 356 days. The patient continued in the study and completed as per the protocol. In the final follow-up report, the investigator assessed the event to have caused persistent/significant disability.

Reviewer's comment: Time of onset of symptoms in this case is consistent with Botox pharmacology. Potential distant spread of toxin can not be excluded.

Constipation

During the first 12 weeks of treatment cycle 1, the incidence of constipation was greatest in the Botox 300 U dose group. Of the 14 reports of constipation in the Botox treatment groups, three were in patients taking concomitant medications associated with constipation (hydromorphone, venlafaxine and Inderal, respectively). Five cases involved concomitant report of urinary retention.

Reviewer's comment: Although constipation might occur secondary to urinary retention, only 5 of 14 cases reported concurrent urinary retention. Therefore, a mechanism other than development of urinary retention is needed to explain the increased incidence of constipation in the Botox 300 U dose group. Distant spread of toxin can not be excluded. The incidence of constipation was not increased in the Botox 200 U group relative to placebo.

Diplopia

A single case was reported in a subject administered Botox 200 U –
Patient 13403-7401, a 47 year old male patient with SCI and a history of hypertension developed diplopia 23 days after Botox administration. The diplopia was intermittent, resolved in less than 24 hours, and was not assessed as the result of distant spread of toxin.

Reviewer's comment: The brief duration and intermittent nature of diplopia in this patient are not consistent with Botox toxicity.

7.3.5.1.1.2 Respiratory Impaired population

Safety data from treatment cycle 1 of study 082 was searched for adverse events that might signal distant spread of toxin (search terms shown in Table 44 were used). The rate of such events was not higher in patients receiving either dose Botox than those on placebo (Table 47).

Table 47 Proportion of subjects experiencing Adverse Events Possibly Associated with Distant Spread of Toxin, Treatment Cycle 1, Study 082

Preferred Term	Botox 300 U N=12	Botox 200 U N=12	Placebo N=10
Total	2 (16.6%)	2 (16.6%)	4 (40%)
Constipation	0	1 (8.3%)	0
Diplopia	0	0	1 (10.0%)
Dry mouth	1 (8.3%)	0	0
Dyspnea	0	0	2 (20.0%)
Muscular weakness	1 (8.3%)	0	0
Urinary retention	0	1 (8.3%)	0
Vision blurred	0	0	1 (10.0%)

The single patient (subject #10022-1076) who developed muscular weakness in the Botox 300 U dose group was a 43 year old female who experienced lower extremity muscle weakness 8 days after injection with Botox 300 U. The event lasted for 6 days and was considered to be a symptom of an MS exacerbation by the investigator. It resolved without sequelae.

Summary Comment:
In the first 12 weeks of placebo-controlled treatment cycle 1, the following was noted with regards to adverse events possibly associated with distant spread of toxin:

- **The incidence of constipation was greatest in the Botox 300 U dose group. Only a portion of reports of constipation occurred in the setting of urinary retention or concomitant administration of constipating medications. The remaining cases may be secondary to distant spread of toxin. Botox 200 U, however, was not associated with an increased risk of constipation over placebo.**
- **In the MS subpopulation, muscle weakness was the most commonly reported adverse event but did not occur more often in Botox-treated subjects compared to placebo.**
- **In the SCI subgroup, a single case of muscular weakness occurred in a subject treated with Botox 300 U and is consistent with possible distant spread of toxin.**
- **The single report of diplopia in a subject administered Botox 200 U is inconsistent with Botox toxicity with respect to time of onset or duration of symptoms.**

The current Botox label contains a black box warning regarding "Distant Spread of Toxin Effect." Based on the single report of lower extremity muscular weakness in the SCI patient, this warning should be expanded to include increased vulnerability of patients with underlying neurologic disease (e.g. SCI).

7.3.5.2 Hypersensitivity Reactions

Because Botox is an exogenous protein, it has the potential to elicit hypersensitivity type reactions in humans. To determine the presence of adverse events potentially indicating a hypersensitivity reaction, the safety database was searched for adverse events coded to the one of the following:

- the MedDRA System Organ Class (SOC) of *immune system disorder;*
- the MedDRA high level group term (HLGT) of *angioedema and urticaria*; or
- the high level term (HLT) of *rashes, eruptions and exanthems NEC; purpura and related conditions; erythemas and dermatitis; eczema;* and *pustular conditions.*

Within the immune system disorder SOC, events of seasonal allergy were excluded because these were clearly not drug related.

Results of the search for the first twelve weeks of placebo-controlled treatment cycle 1 are shown in Table 48. The single report of drug hypersensitivity was a reaction to tetracycline. If this event is excluded, the incidence of hypersensitivity reactions in the Botox 300 U dose group is 1.7%.

Table 48 Adverse Events Potentially Indicating Hypersensitivity Reactions (Placebo-controlled Safety Population, First 12 weeks of Treatment Cycle 1)

AE Category/Preferred Term	Botox 300 U N=235	Botox 200 U N=262	Placebo N=272
Hypersensitivity Reaction	5 (2.1%)	1 (0.4%)	4 (1.4%)
Rash	3 (1.3%)	0	4 (1.5%)
Rash generalized	1 (0.4%)	0	0
Erythema	0	1	0
Drug hypersensitivity	1 (0.4%)	0	0

Summary Comment: These data do not suggest an increased risk of hypersensitivity reactions associated with BOTOX injection into the detrusor, particularly at the 200 U dose. There were no reports of anaphylaxis in the NDO clinical trials database.

The current version of the Botox label contains the following warning regarding 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.**

The current labeling is sufficient and does not require expansion, in this reviewer's opinion.

7.3.5.3 Seizures

According to approved BOTOX labeling, new onset or recurrent seizures have been reported in the post-marketing experience. These have occurred typically in patients predisposed to seizures.

The sponsor searched the NDO safety database for adverse events coded to the MedDRA HLT "seizures and seizure disorders NEC." A total of 3 patients reported seizures across the 5 pooled NDO studies (N=1 per treatment group). The events occurred between 60 days and 379 days following injection. Two of three affected subjects had a prior history of seizures. None were considered related to study drug.

Reviewer's comment: Narratives were reviewed. No event appears to have been related to study drug. No change to the label regarding seizures is recommended.

7.3.5.4 Guillain-Barre Syndrome

There were no reports of Guillain Barré syndrome across the 5 pooled NDO studies or in study 191622-082.

7.3.5.5 Cardiovascular Events

According to the most recently approved BOTOX label, "*there have 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.*"

None of the NDO clinical studies prospectively collected electrocardiogram data.

The placebo-controlled safety database for treatment cycle 1 was searched for adverse events coding to the SOC of Cardiac Disorders. Search results, shown in Table 49, show no dose-response relationship to Botox.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000-5232

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	sBLA 103000
Supporting document/s:	BLA 103000 BB-IND 12430 BB-IND 6432
Applicant's letter date:	October 26, 2010
CDER stamp date:	October 26, 2010
Product:	Botulinum Toxin A
Indication:	(b) (4)
Applicant:	Allergan Pharmaceuticals, Inc., Irvine, CA, USA
Review Division:	Reproductive and Urologic Drugs
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Lynnda Reid, PhD
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Project Manager:	Freshnie DeGuia

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1 Executive Summary

1.1 Introduction

Supplementary Biologics Licensing Application (sBLA) 103000, Botulinum Toxin A (BTxA, BOTOX®), has been submitted by Allergan Pharmaceuticals, Inc. (b) (4) The proposed total dose is 200 U (3.33 U/kg) to be administered by injection (b) (4) to the detrusor muscle of the bladder. The dose will be divided into 30 injections distributed over the surface of the muscle (6.66 U in 1 mL per site).

This application represents a new route of administration and indication for this product, and is supported by 6 clinical and 5 nonclinical studies. Both the total clinical dose and the dose per injection site are comparable to those already approved for intramuscular and / or intradermal injection.

1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies that were conducted to support this new indication were designed to address the following questions:

1. What is the limiting safe dose for injection of BTxA into the bladder?
2. What are the long term effects of repeated injections to the bladder?
3. What would be the consequences of a misplaced injection of BTxA?

Single intradetrusor injections studies of up to 2 months duration in rats and cynomolgus monkeys and a repeat-dose study in monkeys of 9 months duration with a 6 month recovery period were conducted to address questions 1 and 2. Studies on the effect of a single BTxA injection into organs adjacent to the bladder (uterus, prostate, urethra, rectum, seminal vesicles) were conducted in the monkey to address question 3.

Results established the limiting safe dose for a single dose injection of BTxA in the rat and monkey to be <50 U/kg and ≤ 24 U/kg, respectively, which is 15X and ~7X the clinical dose of 3.33 U/kg, based on body weight). In the monkey, there were minimal long-term effects to the bladder following repeat dosing. The most significant toxicological finding was the occurrence of bladder stones in the monkey following peribladder (but not bladder) injection. This was discovered in Phase 2/3 and was monitored clinically throughout the Phase 3 trials.

1.3 Recommendations

1.3.1 Approvability

There were no new non-clinical safety concerns for the new route of administration for BTxA. Based on previous approval for BTxA at doses greater than the proposed dose for treatment (b) (4), PharmTox recommends approval for the new indication.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Section 12.1 Mechanism of Action

Sponsor's suggested wording:

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition, BOTOX (b) (4) afferent neurotransmitters and sensory pathways.

Reviewer's suggested wording:

Following intradetrusor injection, BOTOX (b) (4)

Comment: Currently, evidence that BOTOX inhibits afferent neurotransmitters and sensory pathways in the bladder is indirect. (b) (4)

Section 13 Nonclinical Toxicology

Add the following paragraph:

Section 13.2. Animal Toxicology

In a study of peribladder administration, bladder stones were observed in (b) (4) monkeys that were injected with a total of 6.8 U/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 U/kg (~12X the human dose, based on body weight) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injections up to 100 U/kg (33X the human dose, based on body weight).

2 Drug Information

2.1 Drug — Botulinum Type A (BTxA) BOTOX®

CAS Registry Number (Optional)	none
Generic Name	onabotulinum toxin A
Code Name	none
Chemical Name	Clostridium botulinum type A
Molecular Formula/Molecular Weight	For protein sequence, see Thompson et al., 1990. The MW of BTxA is 150 kD. When complexed to accessory proteins, the MW is 900 kD.

Structure or Biochemical Description

BTxA is a 1285 amino acid protein consisting of two subunits, a 100 kD heavy chain (light blue) and 50 kD light chain (dark blue), linked by a loop of the heavy chain that wraps around the light chain as well as critical disulfide bond (Lacy et al., 1998).

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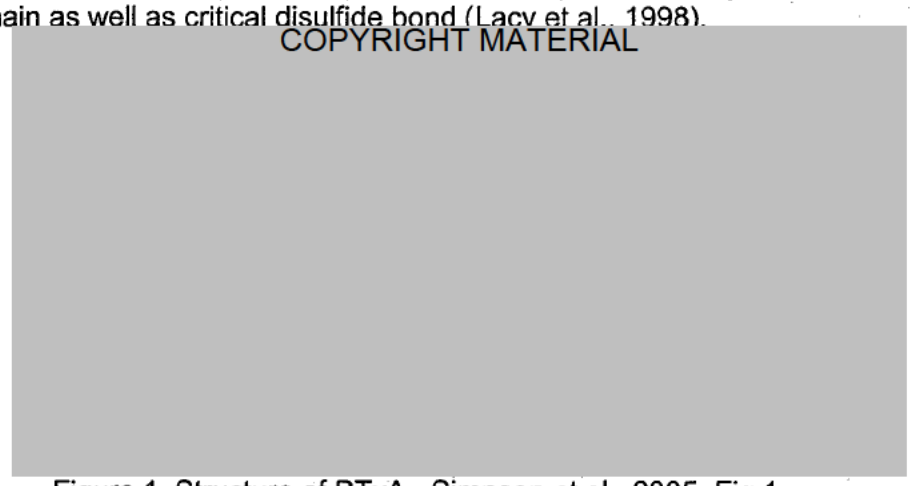

Figure 1. Structure of BTxA. Simpson et al., 2005, Fig 1

There are three functional domains. The heavy chain contains a binding domain (gold) and a translocation domain (green) and is responsible for targeting BTxA to its site of action. The light chain (dark blue) is a Zn^{2+} metalloprotease responsible for its activity in disrupting synaptic transmission.

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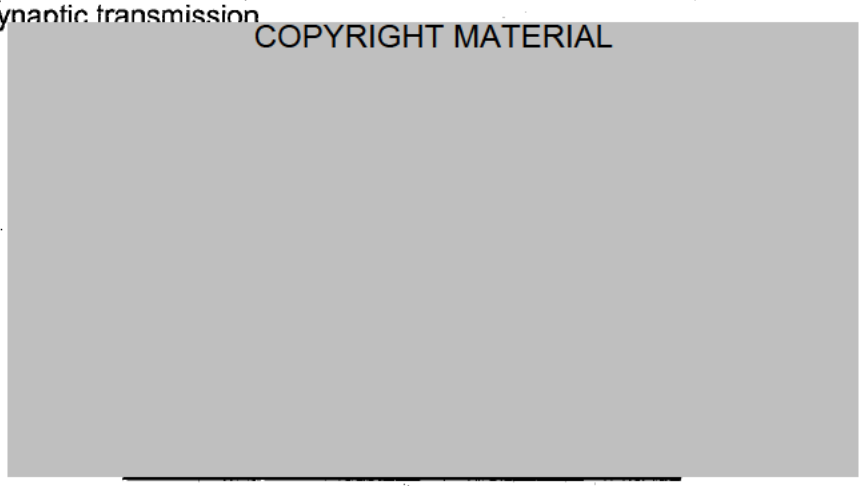

Figure 2. Functional domains of BTxA. Simpson, 2004, Fig.4

Pharmacologic Class	Acetylcholine release inhibitor

2.2 Relevant BB-INDs

Clostridium botulinum type A is approved for cosmetic use under BLA 103000 (Botox®). It is also approved under supplements to BLA 103000 for treatment of hemifacial spasm, cervical dystonia, and axillary hyperhydrosis (excessive sweating). For all nonclinical data submitted prior to this supplementary BLA, BB-INDs 6432 and 12430 have been cross-referenced by the sponsor, as well as the original BLA 103000.

2.3 Drug Formulation

Clinical formulation: sponsor's table submitted to IND 12430

Table 1. Clinical formulation

Name of ingredient(s)	(b) (4)	Amount per vial	Derivation	Reference to standards (USA)	Reference to standards: other
Clostridium botulinum type A		100 U	*Clostridium botulinum* type A	N/A	N/A
Preservative		N/A	N/A	N/A	N/A
Albumin		0.5 mg	Human	USP	PhEur
Sodium chloride		0.9 mg	N/A	USP	BP

Sponsor's product description: BOTOX® is a sterile, vacuum-dried product containing purified botulinum toxin type A complex without a preservative. The neurotoxin complex is produced from fermentation of *Clostridium botulinum* type A grown in a medium containing casein hydrolysate, glucose, and yeast extract. It is purified from culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several other accessory proteins.

Each vial of Botox® contains 100 units (U) (~4-5 nanograms) of *Clostridium botulinum* type A neurotoxin complex 900 kD. Thus, the specific activity of Botox® is approximately 20 U/ng of neurotoxin protein. One Unit (U) corresponds to the calculated median lethal dose (LD_{50}) in mice using reconstituted product injected intraperitoneally.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Proposed clinical population: (b) (4) Two clinical populations were studied in the Phase 3 trials for this BLA: 1) subjects with spinal cord injury and 2) subjects with multiple sclerosis.

Dosing regimen: injection of a total of 200 U of BTxA administered via cystoscopy as 30 intradetrusor injections, each of approximately 1 mL (6-7 U/mL). Subjects can be retreated when symptoms recur, but no sooner than 12 weeks since the previous treatment. According to the sponsor, the median time to patient request for retreatment was (b) (4)

weeks following initial treatment. A list of the clinical studies supporting this application is given in the Appendix.

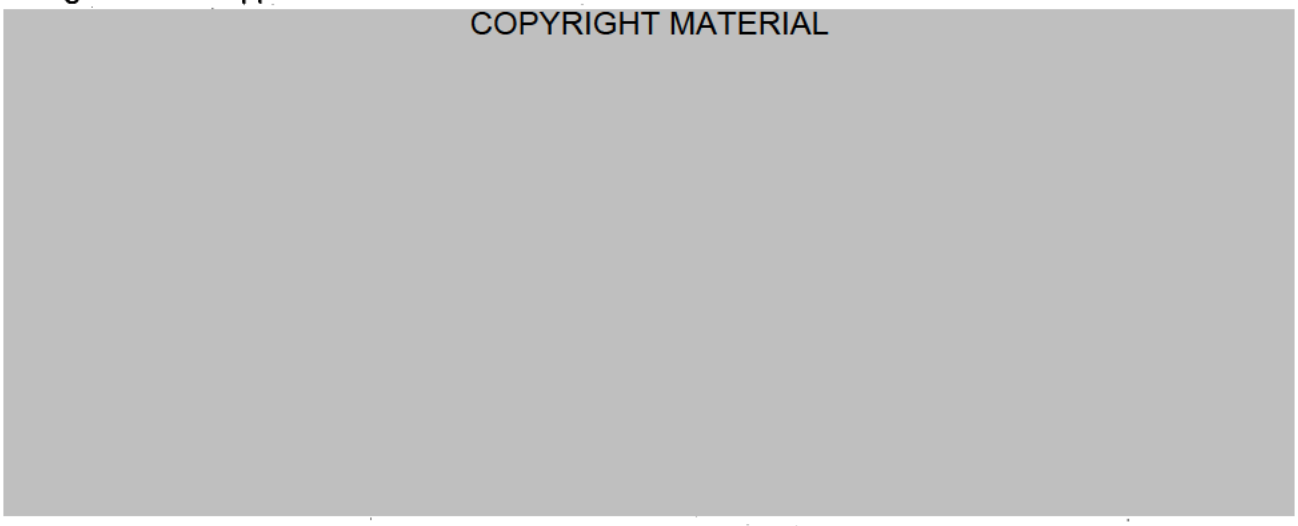

Figure 3A and B. Anatomy of the female and male lower urinary tracts.
http://www.life-tech.com/uro/urolib/urinary_anatomy.shtml accessed May 6, 2011.

2.7 Regulatory Background

IND 12430, which supports this supplement to BLA 103000, was opened on 6/03/2005. An End-of-Phase 2 meeting was held on 2/05/2009, and a preBLA meeting was held one year later on 2/19/2010.

3 Studies Submitted

3.1 Studies Reviewed

Single dose toxicity

TX01064	A single dose intradetrusor single injection toxicity study in female rats
TX02086	A single dose range-finding bladder injection study in the female monkey
TX03052	A single dose toxicity and peribladder injection study in the female monkey with 2-month follow-up
TX02042	A single dose periprostatic injection study in the male monkey with 2 month follow-up

Repeat dose toxicity

TX05046	A repeat-dose bladder injection study in the monkey with 6 month follow-up

3.2 Studies Not Reviewed

Nonclinical studies submitted or cross-referenced to IND 6432 in support of other indications were not reviewed. Two studies, TX-07077-TX and TX05055, single and repeat dose studies respectively for injection of BTxA to the prostate, were submitted as references and are cited but not reviewed.

3.3 Previous Reviews Referenced

Reviews for IND 12,430, BTxA for neurogenic overactive bladder.

4 Pharmacology

4.1 Primary Pharmacology

Mechanism of action:

BTxA blocks chemical synaptic transmission by inhibiting the fusion of synaptic vesicles containing neurotransmitter with the synaptic membrane. It does so by cleaving a protein, SNAP-25 (synaptosomal protein of molecular weight 25 kDa), that is part of the vesicle fusion machinery, the SNARE (Soluble NSF [N-ethylmaleimide-sensitive factor] Attachment protein Receptor) complex (Schiavo et al., 2000).

Figure 4A and B. Synaptic vesicle fusion proteins

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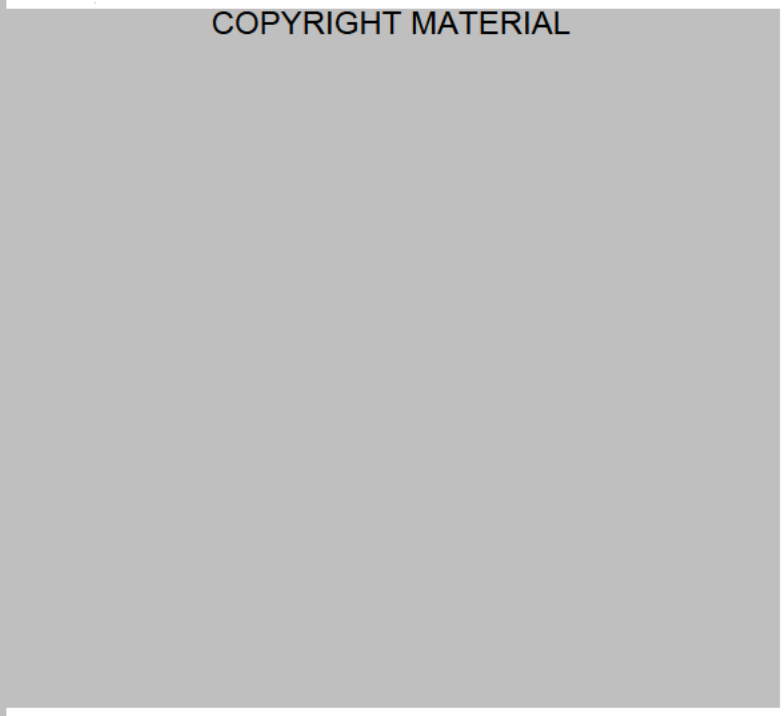


Neuroscience 4th Ed, Purves, et al., Editors. Chapter 5, Synaptic Transmission. Fig. 5.14, A and B.

Because the site of action of BTxA is intracellular, a key step in its mechanism of action is uptake into the synapse, which occurs by endocytosis. Botulinum toxin is taken up by the nerve terminal when it binds to synaptic vesicle protein 2 (SV2), a protein that is localized to the synaptic vesicle membrane and becomes transiently accessible on the exterior surface of the synapse after fusion of the vesicle. An accessory ganglioside binding site is also involved in uptake.

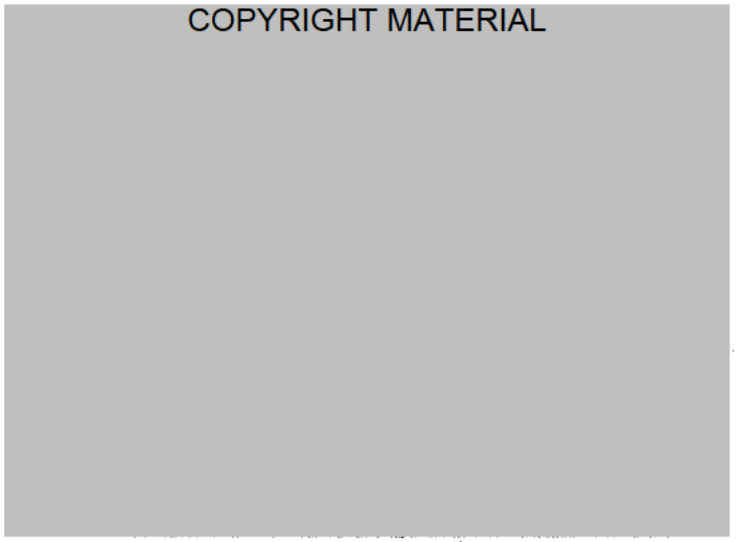
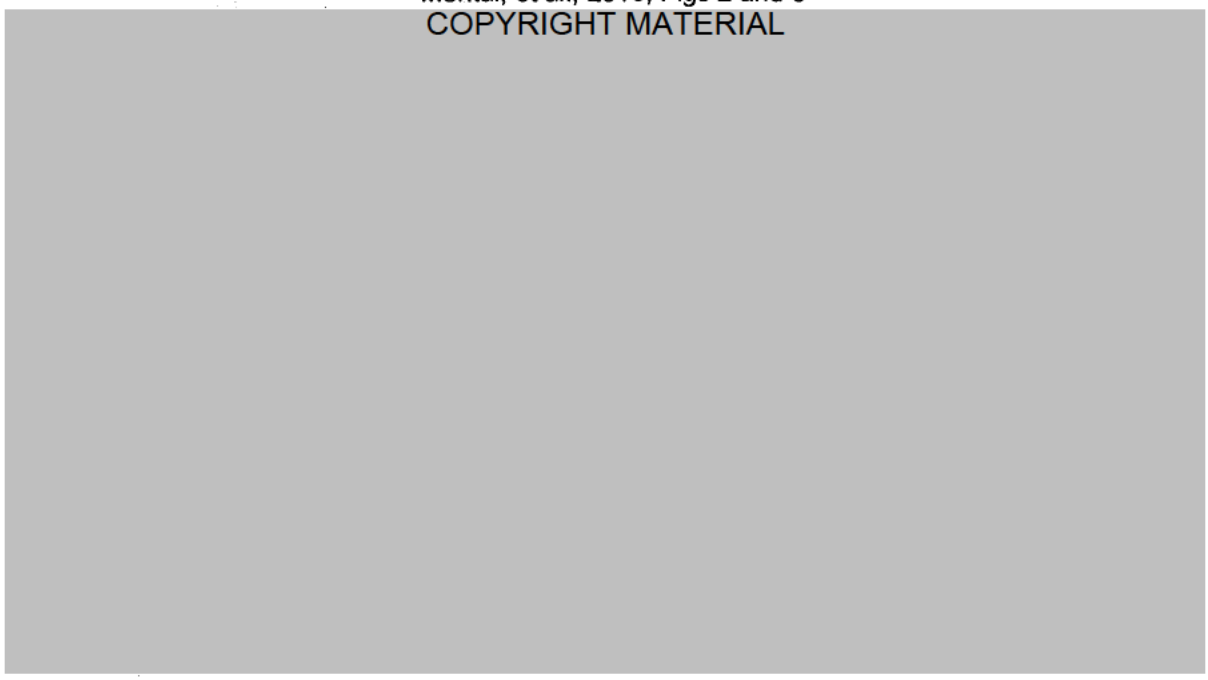


Figure 5. Binding and uptake of BTxA
Verderio et al., 2006, after Montecucco et al., 2004. Fig 1

When the vesicle is recycled, BTxA acquires access to the cytosol. This is thought to be a multistep, pH- and redox-dependent process that involves insertion of the heavy chain into the vesicle membrane, followed by translocation of the (possibly unfolded) light chain through the translocation domain. Reduction of the disulfide bond results in release of the light chain. Once released, the light chain, which is a zinc-dependent protease, can access its target protein, SNAP-25.

Figure 6A and B. Activation of BTxA
Montal, et al., 2010, Figs 2 and 5



The specificity of BTxA action derives from two things: (1) SV-2 receptor mediated uptake of BTxA into the synapse and (2) targeting of the protease to SNAP-25. BTxA thus only affects neurons that express both SV2 and SNAP-25. While BTxA is commonly thought to act

preferentially on cholinergic neurons, it will, in fact, act on all types of SNAP-25 mediated vesicular release, which can include both small molecule and peptide neurotransmitters.

The effect of BTxA is long lasting. Following the loss of synaptic input (chemical denervation), muscle cells undergo atrophy. The persistence of BTxA toxicity depends on how long it takes to replace functional SNAP-25 proteins (see Grumelli et al., 2005, for review) and to reestablish innervation to the target cell (Rogozhin et al., 2008, and Ko, 2008). Although muscle atrophy is reversible, animal studies have shown that full recovery may not always be achieved (Broide et al., 2008).

Drug activity related to proposed indication:

(b) (4)

4.2 Secondary Pharmacology

NA

4.3 Safety Pharmacology

No nonclinical safety pharmacology studies were conducted for this BLA. BTxA is well known to cause death by respiratory arrest, presumably by paralysis of the phrenic nerve. BTxA is not known to cross the blood brain barrier and does not produce CNS toxicity following oral ingestion. LD_{50} values for a number of different species are available from the historical literature (see previous reviews) and demonstrate a steep dose response.

The observed safety of injected botulinum toxin A in humans is due to the fact that (a) there is a low probability of accidental systemic injection when BTxA is administered to superficial musculature in small amounts and (b) diffusion out of the tissue is slow, so pharmacological effects tend to be local.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Brief summary: Because Botox® is intended to act locally, ADME studies for injected BTxA have historically not been carried out. The only relevant toxicokinetic issue for Botox® is whether and how much diffusion occurs from the site of injection, and whether Botox® retains its activity at sites distant from the site of injection. To that end, there have been a number of nonclinical studies utilizing labeled BTxA that have established that diffusion of BTxA from the site of injection can occur at low levels over a time course of hours. In addition to diffusion, BTxA can be actively transported away from the site of injection by retrograde axonal transport after being taken up at the synapse. There is evidence for very low levels of transsynaptic transport, and it has been recently shown that BTxA can retain catalytic activity at those sites. For informational purposes only, these studies are briefly described here.

Diffusion studies:
^{125}I-labeled botulinum toxin A was injected into rat gastroenemius muscle. Injected radioactivity was cleared from the injection site over a time course of 48 hrs. The majority of radioactivity was recovered in the urine, possibly as a degraded form of the protein. A small amount of radioactivity was recovered from the contralateral gastroenemius muscle, indicating trans-spinal transport via nerve pathways. (Tang-Liu et al., 2003).

^{125}I-labeled botulinum toxin A hemagglutinin complex was injected intramuscularly into the rabbit upper eyelid. Little diffusion from the injection site was observed for 6 hrs post-injection. By 24 hrs, uptake/degradation appeared to be complete: radioactivity was present only at trace levels at the injection site and not in adjacent tissues. (Tang-Liu et al., 2003)

Transport studies:
^{125}I-labeled botulinum toxin A was injected into the gastroenemius muscle of the cat. Radioactivity was detected in the ventral roots of the spinal cord at 48 hrs, indicating retrograde transport. (Wiegand et al., 1976)

Unlabeled BTxA was injected into the hippocampus (mouse), superior colliculus (rat), or whisker muscles (rat). Immunostaining demonstrated retrograde transport and transcytosis of the active toxin from the sites of injection (Antonucci et al., 2008). Using antibodies to cleaved SNAP-25, this study also showed that the transported BTxA is catalytically active, raising the potential for activity at sites distant from the site of uptake.

5.2 Toxicokinetics

TK data are not generated for BOTOX®, because (a) the site of action is local and diffusion into the bloodstream is limited and (b) the doses administered are so small that the amount of protein that reaches the bloodstream is below the detection limit of current analytical methods. For example, a 200 U dose of BOTOX® contains 8 ng of protein, (assuming the standard conversion factor of 25 U/ng for the commercial product). If the full 8 ng were distributed into a plasma volume of ~2.75 L, the concentration would be ~3 ng/L or ~3 pg/mL. This is at or below the lower limit of detection for plasma proteins by mass spectrometry (see Fig. 1, Schiess et al, 2009).

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: BOTOX®: A 14-day intradetrusor single injection toxicity study in (female) rats	
Study no.:	TX01064
Study report location:	4.2.3.1.1
Conducting laboratory and location:	Allergan, Irvine, CA
Date of study initiation:	Oct 17, 2001
GLP compliance / QA statement:	no / no
Drug, lot #, and % purity:	Botulinum toxin A, lot # R12665, formulation #9060X, 96 U/vial

Key Study Findings

The objective of this study was to establish the maximum tolerated dose (MTD) in the rat by the bladder injection route. Animals were given a single dose of **0, 10, 50, or 100 U/kg** and observed for 14 days. There was mortality at the high dose (1/4) due to respiratory failure. There were multiple clinical signals of distress at the mid- and/or high-doses, and one low-dose animal showed tachypnea and curling of left hind toes. There was a dose-dependent loss of bodyweight and decreased food consumption. There was a reduction in serum creatine at the mid- and high-doses, attributed to body weight loss and possible reduced muscle mass. The sponsor's MTD was set between 10 and 50 U/kg. Reviewer agrees and notes that there is only a 10-fold difference between the tolerated dose of 10 U/kg and the lethal dose. Although findings at the low dose were minimal, any clinical sign of systemic toxicity must be considered adverse.

Methods	
Doses:	**0, 10, 50, or 100 U/kg**
Frequency of dosing:	single dose
Route of administration:	injection to the detrusor muscle via laparotomy
Dose volume:	0.05 mL/rat
Formulation/Vehicle:	saline with human serum albumin
Species/Strain:	Sprague-Dawley (Crl:CD®(SD)IGS BR
Number/Sex/Group:	4F/group
Age:	11 weeks
Weight:	232-262
Satellite groups:	none
Unique study design:	Two control groups: Sham surgery or placebo. Rats observed for 14 days following injection, necropsied on day 15.
Deviation from study protocol:	none significant

Observations and Results

Mortality: 1 at the high dose on day 5. Cause of death attributed to progressive respiratory failure.
Clinical Signs: taken daily and included bowel function. At the mid- and/or high-dose dyspnea, tachypnea, decreased activity, hunched posture, abnormal gait, piloerection, emaciation, reddish urine, no feces, chromodacryorrhea, chromorhinorrea was observed. One low-dose animal showed tachypnea and curling of left hind toes.
Body Weights: dose-dependent decrease in mean terminal body weight: 4, 18, and 21% respectively compared to controls.
Feed Consumption: decreased (up to 87%) at the mid- and high-doses for the first 6 days post-dosing; food consumption partially recovered in week 2.
Ophthalmoscopy: not done
ECG: not done

Hematology: Samples taken at necropsy. Mild changes observed at the high dose were probably related to systemic toxicity and dehydration: slightly increased RBC counts, Hb, and HCT; increased WBCs in one animal.

Clinical Chemistry: Samples taken at necropsy. Dose-dependent reduction of serum creatine (32 and 44%) seen at the mid- and high-dose respectively, attributed to reduced food consumption and reduced muscle mass.

Urinalysis: Samples collected on day 14/15 by placing animals into a metabolism cage overnight (~16 hrs). No dose-dependent changes in urine volume, specific gravity, color, clarity, pH, glucose, ketones, protein, blood, bilirubin, presence of epithelial cells, WBCs or RBCs, casts, crystals, or bacteria were observed. Study report text incorrectly states that Table 6 contains mean urinalysis values; it does not, but reports bladder weights. Mean urinalysis data were not found; conclusions based on individual values.

Gross Pathology: Macroscopic changes seen in two animals at the high dose. One animal showed flaccid dilatation of the vagina, emaciation and chromodacryorrhea and was apparently athymic. A second animal showed elongation of the trigone and neck of the urinary bladder.

Organ Weights: Only the urinary bladder was assessed. A statistically significant increase in the bladder weight relative to body weight observed at the mid- and high-dose was due to body weight loss and not due to increased bladder weight.

Histopathology: adequate battery / not peer reviewed

Bladder: Incidental findings in the bladder included focal edema and inflammation, likely due to the injection procedure. There were no-dose related findings.

Vagina: Moderate dilatation of the vaginal lumen was seen in two high-dose animals.

Skeletal muscle and diaphragm: Drug-related changes were seen at the mid- and high-dose. Myofiber atrophy (minimal to moderate) and/or necrosis (minimal to mild) were observed in sections of caudal thigh muscle and diaphragmatic muscle. Focal inflammation and minimal regeneration were also seen.

Stress-related tissue changes: thymic atrophy, lymphoid atrophy of the spleen, atrophy of mandibular and mesenteric lymph nodes, increase pigment production in the Harderian gland (correlative to chromodacryorrhea).

Toxicokinetics: NA

Dosing Solution Analysis: not done; COA available in Study Report, Appendix III

Study title: BOTOX®: A single dose range bladder injection toxicity study in (female) cynomolgus monkeys	
Study no.:	TX02086
Study report location:	4.2.3.1.1
Conducting laboratory and location:	Allergan, Irvine, CA
Date of study initiation:	Sept 18, 2002
GLP compliance / QA statement:	no and no
Drug, lot #, and % purity:	Botulinum toxin A, lot #STD008(C330), formulation #9060X, potency: 103 U/vial

Key Study Findings:

The objective of this study was to establish the maximum tolerated dose (MTD) in the monkey by injection to the bladder. Two female monkeys per dose were given a single intradetrusor injection (divided into 3 sites) of **12 or 24 U/kg** transabdominally and observed for 4 weeks. There was no mortality and there were no significant clinical findings. There was an increase in the presence of amorphous crystals in the urine in all control and treated animals, and bilateral, minimal, microlithiasis was noted in the kidney in one low-dose animal. There was an unexplained dose-dependent decrease in creatine kinase attributed to artifactually high baseline values in both groups.

This study established that 24 U/kg was tolerated by the bladder injection route. In comparison, single injections of 24 U/kg intramuscularly were associated with systemic toxicity and mortality in the monkey (data cited from study # 99-3334, summarized in study #3052, p 15).

Methods	
Doses:	**12 or 24 U/kg (no control group)**
Frequency of dosing:	single injection followed by a 4-wk observation period
Route of administration:	injection through the abdominal wall to the urinary bladder visualized by ultrasound under ketamine/isoflurane anesthetic. The dose was divided and placed in 3 sites, the dorsal, and left and right dorsolateral walls of the detrusor.
Dose volume:	0.2 mL/injection,(3 injections totaling 0.6 mL), 60 or 120 U/mL
Formulation/Vehicle:	saline with human serum albumin
Species/Strain:	Cynomolgus monkeys *(Macaca fascicularis)* (b) (4) Original source not stated.
Number/Sex/Group:	2 females/group
Age:	estimated to be 5-6 yrs
Weight:	~3.0 kg
Satellite groups:	none
Study design:	monkeys were observed for 28 days then euthanized
Deviation from study protocol:	none stated

Observations and Results:

Due to the low numbers of animals (2 per dose), there was no statistical analysis of findings.

Mortality: no mortality

Clinical Signs: daily cage side and weekly detailed; full physical exam under anesthesia once before dosing and during week 4; no treatment-related signs reported

Body Weights: prior to dosing and weekly; very slight reduction at the end of study

Feed Consumption: semi-quantitative assessment weekly; very slight reduction in week 4

Ophthalmoscopy: not done

ECG: not done

Hematology, Clinical Chemistry, Coagulation: prior to dosing and at termination

No changes in hematology or coagulation.

Clinical chemistry: prior to dosing and at termination

Creatine kinase decreased 28-38% and 65-90% at 12 and 24 U/kg respectively; other findings included elevated bilirubin (3-fold) and decreased BUN (44%) in one female given 12 U/kg, and decreased glucose (53%) in one female given 24 U/kg.

Urinalysis: 3 hour free catch

Elevated pH relative to baseline and urinary phosphate and amorphous crystals were observed at week 4 in all monkeys.

Gross Pathology: no findings reported

Organ Weights: Adrenal glands, brain, heart, kidneys, liver, lungs, pituitary gland, uterus, ovaries, spleen, thymus, thyroid (with parathyroids), and urinary bladder were examined.

No changes were reported in any organs other than liver. An increased liver weight was observed in one high-dose monkey, which was attributed to glycogenesis (increased hepatocellular glycogen deposition).

Histopathology: Adequate Battery: yes Peer Review: no

Kidney: microlithiasis, papillary, minimal, bilateral, in one low-dose animal

Liver: vacuolation, clear, moderate, diffuse, consistent with glycogenesis (increased glycogen deposition) in one high-dose animal

Toxicokinetics: NA

Dosing Solution Analysis: not done; COA available in Study Report, Appendix III

Study title: BOTOX®: A 2-month single dose bladder toxicity and peribladder injection safety study in (female) cynomolgus monkeys.	
Study no.:	TX03052
Study report location:	4.2.3.1.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Sept 22, 2003
GLP compliance / QA statement:	yes / yes
Drug, lot #, and % purity:	Botulinum toxin A, formulation #9060X, Lot # STD008, 103 U/vial

Key Study Findings

The objective of this study was to evaluate the local toxicity of a single administration of BOTOX® into the female monkey urinary bladder (3 sites of injection) or of a single off target administration of BOTOX® injection into the uterus (1 site of injection) with a 2- and 8-week postdose observation period. Doses were **0, 12, 24, or 36 U/kg** to the bladder, which extended dosing higher than in the previous range finding study, presumably due to the low toxicity observed at 24 U/kg. The off-target dose to the uterus was supposed to be 6 U/kg, but a dosing error led to a lower dose of ~2 U/kg (6 U total) being applied.

There was no mortality or significant adverse clinical findings in this study. There was possible evidence of systemic toxicity in the high-dose animals, shown by a 5-10% mean body weight loss in 4/5 animals during the 2nd week. Weight loss was reversed for the two high-dose animals surviving to 8 weeks. The reviewer's NOAEL for systemic toxicity in this study was therefore set at 24 U/kg.

Methods:	
Doses:	into the bladder: **0, 12, 24, or 36 U/kg** (total dose level: 0, 36, 72, 108 U) into the uterus: 6 U
Frequency of dosing:	single dose
Route of administration:	single constant volume injection (0.2 mL per site, 0.6 mL total) distributed into three sites (dome, right lateral and left lateral walls) of the bladder (groups 1, 3, 4, 5) OR as a single injection into the midbody of the uterus (group 2). All injections were guided by transabdominal ultrasound imaging, under anesthesia.
Dose volume:	0.2 mL per site; dose volume selected to approximate 10% of the volume of the monkey bladder
Formulation/Vehicle:	The control group received injections of 0.2 mL per injection site of saline placebo into the three bladder sites and into the uterus.
Species/Strain:	Cynomolgus monkeys *(Macaca fascicularis)* (b) (4) Experimentally naïve at the start of the study.
Number/Sex/Group:	5 groups of 5 females/group; 4 groups were dosed to the bladder, 1 group was dosed to the uterus
Age:	3.9-9.4 yrs
Weight:	2.7-3.9 kg
Satellite groups:	none
Study design:	Fifteen animals (3 from each group) were euthanized on Day 15. The remaining 10 animals (2 from each group) were maintained over an additional 6-week treatment-free period and terminated on Day 57.
Deviation from study protocol:	Dose of 6 U to the uterus was supposed to be 6 U/kg; dosing error Day 14 body temperature not take for 12 animals

Observations and Results:

Mortality: there was no mortality
Clinical Signs: cageside twice daily
Body Weights: twice prior to dosing and weekly thereafter.
Although not statistically significant, at the high dose, 4/5 animals had a body weight loss of 0.2 to 0.3 kg (5.7 to 9.4%) between Day 8 and Day 15, probably due to some systemic toxicity
Feed Consumption: qualitatively once daily; no adverse changes
Body Temperature: taken rectally 1 week prior to dosing and at week 2 and week 8; no treatment-related changes
Ophthalmoscopy: not done
ECG: not done
Hematology, Clinical Chemistry, and Coagulation Parameters: taken by femoral vein 1 week prior to dosing and at week 2 and week 8; no treatment-related changes
Urinalysis: taken by pan drainage at 1 week prior to dosing and at week 2, 4, and 8
Results: no treatment related findings; urinary crystals present in all groups sporadically
Gross Pathology: complete gross examination at termination
Organ Weights: Adrenals, spleen, kidneys, lungs, pituitary (post fixation) uterus, thyroid with parathyroids, brain, heart, liver, ovaries, urinary bladder, and thymus were examined; there were no significant findings.
Histopathology: Adequate Battery: yes Peer Review no
no significant findings reported
Toxicokinetics: NA
Dosing Solution Analysis: Not done. COA available in Study Report, Appendix C.

Study title: BOTOX®: A 2-month single dose periprostatic injection safety study in (male) cynomolgus monkeys.	
Study no.:	TX02042
Study report location:	4.2.3.1.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 20, 2002
GLP compliance / QA statement::	yes / yes
Drug, lot #, and % purity:	Formulation #9060X, Batch #C398, COA: 98 U/vial

Key Study Findings

The objective of this study was to evaluate the toxicity of a single off-target administration of BOTOX® injection into sites adjacent to the bladder in the male monkey with a 2- and 8-week postdose observation period. The sponsor refers to this study as either a peribladder or a periprostatic injection study. Two groups of male monkeys (4/group) received 'off-target' injections of **3.4 U/kg/site** at 2 sites for a total of **6.8 U/kg**. One treatment group received injections into the prostatic urethra and proximal rectum. The other treatment group received injections into the urinary bladder wall (base) and left seminal vesicle. A control group of 2 males each received saline injections into all four sites.

Results: There was no mortality. The sponsor reported no treatment-related clinical signs or effects on body weight or temperature. Hematology and clinical chemistry were negative. Urinalysis did not show treatment related findings. At the 2 wk necropsy, 1 of 2 monkeys in the group dosed with 6.8

U/kg divided into the prostatic urethra and proximal rectum was found to have bladder stones. No animals were found to have bladder stones at the terminal 8 week necropsy in either group. Other than minor findings of mononuclear cell infiltrates in the injected organs, which were not always associated with sites of injection, there were no significant microscopic findings.

Methods	
Doses:	**0, 3.4 U/kg/site, 6.8 U/kg total**
Frequency of dosing:	single injection
Route of administration:	transabdominal injection into the prostatic urethra and proximal rectum (Group #2) or into the urinary bladder wall (base) and left seminal vesicle (Group #3). Control group was saline injected (Group #1)
Dose volume:	0.4 mL per injection site, 50 U/mL
Formulation/Vehicle:	saline with human serum albumin
Species/Strain:	Cynomolgus monkeys *(Macaca fascicularis)*
Number/Sex/Group:	4 males/treated group; 2 per control group (10 total)
Age:	5.3 yrs, sexually mature, wild caught, obtained from (b) (4)
Weight:	5.3-6.3 kg
Satellite groups:	none
Study design:	Monkeys were necropsied on Day 15 (1 control, 2/treated group) or Day 57 (1 control, 2/treated group).
Deviation from study protocol:	deviations not deemed significant

Observations and Results

Mortality: none
Clinical observations: made twice daily; no treatment-related clinical signs
Body Weights: taken pre-dose and weekly; no treatment related changes
Body temperature: rectal temperature was taken prestudy and at weeks 2 and 8; no treatment related changes were reported
Feed Consumption: measured daily; no treatment related changes were observed
Ophthalmoscopy: not done
ECG: not done
Hematology, clinical chemistry, coagulation parameters: prior to dosing and at termination; no treatment-related changes
Urinalysis: Urinalysis was conducted daily by cage pan drainage. Two high-dose animals were rated as having relatively more bacteria (Table 7 p 111). Oxalate crystals were noted in all groups on day 14 and thus were not deemed treatment related.
Gross Pathology: The only significant finding at gross necropsy was bladder stones (multiple yellow calculi, pinpoint to 3 mm) in one animal sacrificed at the 2 week time point. The pathologist characterized the stones as consisting of mineral fragments and protein. There was no evidence for hydroureter or hydronephrosis, and thus no indication of urinary tract obstruction in the affected animal. As previously noted, there was no abnormal clinical chemistry to indicate compromised kidney function (elevated BUN or creatine). There were no bladder stones found in the remaining animals at the 8 week necropsy.
Organ Weights: no treatment related findings
Histopathology: Adequate Battery – yes Peer Review: no
Mononuclear infiltrates were reported in the injected organs, but were not necessarily associated with the sites of injection. There were no other treatment related histology findings.
Dosing Solution Analysis: not done; COA in Study Report, Appendix B

6.2 Repeat-Dose Toxicity

Study title: A 9-month repeat dose bladder injection safety study in cynomolgus monkeys with a 6-month recovery	
Study no.:	TX05046
Study report location:	4.2.3.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Sept 28, 2005
GLP compliance / QA statement:	yes / yes
Drug, lot #, and % purity:	Botulinum Toxin A, Lot #C1331C1; formulation #9060X; potency 90 U/vial

Key Study Findings

Mortality: 7 of 32 animals (3 of 4 animals/sex in the high-dose group and 1 male in the mid-dose group) died or were euthanized early after the 1st or 2nd injection of Botox® into the bladder wall, indicating significant systemic exposure that did not require accumulation of the drug. Early mortality was unexpected based on tolerability of 36 U/kg in study #03052. All 7 animals had clinical signs that included bilateral ptosis, decreased activity, hunched appearance, shallow or labored breathing, and respiratory distress. Five animals had decreased body temperature. The loss of most of the high-dose animals meant that much of the long-term toxicity data was also lost. Necropsies were conducted, and histology carried out, but those data did not extend past the 2nd dose, and were therefore limited in their usefulness.

The toxicity evaluation for this study is thus primarily based on data from the low- and mid-dose groups. The sponsor focused on evaluation of the bladder, and reported no changes in bladder wall thickness, urine output or urinalysis, and no findings of bladder stones. At the mid- and high-doses, there were inflammatory infiltrates in the bladder thought to be due to the injection process that did not completely resolve in the recovery animals. There was also evidence of skeletal muscle degeneration/regeneration in the diaphragm and thigh consistent with systemic exposure that did not completely resolve. Lastly, there were findings of increased spleen and thyroid weight, and decreased thymus weight, with concomitant microscopic findings in the spleen and thymus, but not thyroid. Significance of these observations was not clear.

On the basis of minimal toxicity in the low-dose group, the sponsor assigned a NOAEL for systemic toxicity of 12 U/kg. Reviewer agrees.

Methods	
Doses:	**0, 12, 24, or 36 U/kg**; sponsor reported actual mean administered doses of 12.3, 26.2, and 40.7 U/kg respectively.
Frequency of dosing:	There were 4 treatment cycles: single injections given on days **1, 92, 183, and 274. Cumulative total doses were 48, 96, or 144 U/kg.**
Route of administration:	transabdominal injection
Dose volume:	A single constant volume (0.6 mL) injection was distributed into three sites in the bladder (dorsolateral walls and near the apex of the bladder, 0.2 mL per injection site) under ultrasound guidance. Injection volume was selected based on earlier investigations showing this to be optimal volume for retention within the detrusor muscle of the cynomolgus monkey without leakage in the bladder lumen (TX03052, data not submitted). Animals were chosen based on body weight to allow administration of total doses (U/kg) that met or approached the targeted systemic dose
Formulation/Vehicle:	sterile saline placebo
Species/Strain:	cynomolgus monkeys

Number/Sex/Group:	4/sex/group; 32 total
Age:	2.9-3.8 yrs (M) 3.3-5.3 yrs (F)
Weight:	2.4-2.9 kg (M) 2.3-3.0 kg (F)
Satellite groups:	1 sex/group for recovery
Unique study design:	Injections were guided by transabdominal ultrasound imaging conducted under sedation. 3 animals/sex/group were euthanized after completion of week 41 (2 weeks post-final administration). 1 animal/sex/group was allowed to recover for 6-months, then euthanized after week 65.
Deviation from study protocol:	Due to early mortalities in the high-dose group, the remaining 1 animal/sex in the high-dose group was necropsied 2 weeks after the 2nd dose. Due to early mortality in the mid-dose group only 2 males in the mid-dose group were euthanized at the week 41 necropsy

Observations and Results

Mortality: There was significant mortality occurring as soon as after the 1st dose.

Dose U/kg	M	F	Comments
0	0/4	0/4	
12	0/4	0/4	
24	1/4	0/4	1 found moribund ~1 wk post 2nd dose
36	3/4	3/4	1 died on day 6, 1 on day 13 after the 1st dose 4 were found moribund and euthanized ~1-2 wks after the 2nd dose

Due to the mortality in the high-dose group, the remaining two animals were euthanized 2 weeks after the 2nd dose. Thus, data do not exist for the high-dose group beyond week 16.

Clinical Signs: cage side twice daily

All seven animals that died or were euthanized had clinical signs beginning 4-6 days after dose administration that included respiratory distress, bilateral ptosis, and decreased activity. 5 animals had decreased body temperature. Ptosis was present even in low-dose animals, appearing ~1 week post dose for varying amounts of time (detailed observations are in sponsor's table below; ptosis not observed in control animals).

-- = no observations
NA = not applicable

Physical Exam: Sedated heart rate and sedated respiratory rates were not changed in the treatment groups compared to control.

Body Weights:

Taken once prior to dosing (day -1) and weekly thereafter through week 15, 41, or 65. Terminal body weight collected at necropsy

Body weight gain was decreased in the mid-dose group.

Dose U/kg	Change in mean group body weight pre-study to week 40
0	+27%
12	+30%
24	+11%
36	similar to control up to week 14

Body temperature (rectal): Recorded once prestudy, on each dosing day prior to administration of anesthesia and near the end of weeks 41 and 65; remaining group 4 animals on the 1st day of week 16, prior to necropsy.

Results: 5/7 animals in moribund condition had decreased body temperature; other animals showed no changes in body temperature

Feed Consumption:

Taken once daily; qualitatively reported; amounts not given; no specific comments

Water consumption: Taken twice prestudy, once in week 1 after the first dose, and once monthly thereafter through the recovery period; no treatment-related effect on water consumption

Ophthalmoscopy: not done

ECG: not done

Hematology, Clinical Chemistry, Coagulation Parameters:

Measured prestudy in the week prior to dosing and weeks 24, 41, and 65 and from remaining group 4 animals on the first day of week 16, prior to necropsy; there were unscheduled blood draws from individual animals as deemed necessary.

Results: No treatment related changes were reported. One animal in the mid-dose group had elevated neutrophils at week 24, thought to be secondary to localized inflammation of skeletal muscle (thigh). Note: due to mortality, there was no summary hematology data, summary data on coagulation parameters, or summary clinical chemistry data from the high-dose group; some data were available from unscheduled blood draws from some individuals.

Serum antibody samples (neutralizing):

Samples taken at weeks 55 and 65 from all available animals; results not reported.

Clinical signs (ptosis, decreased body weight gain) were deemed sufficient to establish activity of BTxA over the duration of the study.

Serum antibody samples (BTxA binding antibodies):

Samples taken at weeks 55 and 65 from all available animals; results not reported.

Urinalysis

24-hour urine volume: collected twice one week prior to dosing, once in week 1 after the first dose, and once monthly thereafter through the recovery period (days -6, -2, 7, 35, 63, 91, 119, 147, 175, 203, 231, 259, 287, 315, 343, 371, 399, 427, 455). Highlighted days are closest to the days of injection, which were 1, 92, 183, and 274.

Results: no effect on urine output, but collection days did not closely follow the injection days.

Urinalysis:

urine sample for urinalysis obtained by drainage from pans twice prestudy in the week prior dosing, in week 1 and monthly thereafter through the recovery period; urine samples also obtained by bladder puncture (cystocentesis) during necropsy (1st day of week 16 for high-dose animals, 41, or 66 for the other groups)

Results: no treatment-related changes

Ultrasound measurement of bladder wall:

Measurement taken prior to each dose (pre-dose in weeks 1, 14, 27, and 40) and near the end of weeks 41 and 65; remaining group 4 animals on the first day of week 16, prior to necropsy; no treatment related effects

Gross Pathology

Findings related to mortality:

The primary finding in the animal in the high-dose group (b) (4) that died (b) (4) after the 1st dose was congestion or hemorrhage associated with cardiovascular collapse and/or shock.

The primary finding in the animal that died (b) (4) after the 1st dose was minimal to moderate necrotizing vasculitis in multiple organs and multifocal degeneration of cardiac myocytes. One animal showed lymphoid depletion of the thymus thought to be stress related.

Other findings: accentuated follicular pattern in the spleen, mottling of the bladder mucosa

Recovery animals: no specific comments by the pathologist

Organ Weights

adrenals, epididymides, kidneys, lungs, pituitary, testes, thyroid with parathyroids, brain, heart, liver, ovaries, spleen, thymus, bladder; weights not recorded for 2 animals found dead

Results: *no data from the high-dose group*

Spleen organ weights (absolute and ratios) were greater (~2-fold) for males at the low-dose, but were not statistically significant. Increased weight ascribed to histologic finding of hypercellularity of follicles of uncertain significance.

Thymic weight variations were ascribed to normal maturity-related involution and were not considered treatment-related.

Thyroid:body weight ratio was increased ~2-fold in the mid-dose females; variations were not associated with any histological alterations, although infiltration and exfoliation were scattered among groups.

Large variations were noted in testes weight; increased at low-dose; reduced at mid-dose.

Recovery animals (N=1/sex for each group): no specific findings by the pathologist; reviewer notes that the control female had a very low weight thymus (possibly a typo) that artificially inflated the thymus:body weight ratios for the treated groups (apparent 10-fold increase)

Histopathology
recorded for all animals, including those found dead or euthanized
Adequate Battery: yes Peer review: yes
Histology Findings: (note data from the high-dose group were taken at week 16):
skeletal muscle: myofiber degeneration was present in the diaphragm (mid- and high-dose) and thigh (low- and mid-dose) accompanied in some cases by regeneration of myofibers and infiltrates of mixed inflammatory cells in the treated groups. The pathologist described this as being similar to segmental myofiber necrosis and considered this secondary to Botox® treatment; it was noted that atrophy was *not* present and there was no clear dose response.
bladder: inflammatory cell infiltrates observed predominantly in the submucosa and occasionally the muscularis; scattered across all groups including control
spleen: increased incidence of hypercellularity of follicles; no dose-dependence
thymus: lymphoid depletion in females, all groups including control
Recovery animals: one mid-dose animal still had myofiber degeneration/regeneration in the diaphragm; bladder inflammation still present in multiple animals across groups, including controls.
Toxicokinetics: NA
Dosing Solution Analysis: not done; COA in Study Report, Appendix 3

7 Genetic Toxicology

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

8 Carcinogenicity

Current labeling: Long term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX®.

9 Reproductive and Developmental Toxicology

Impairment of fertility:

Current labeling: In fertility studies of BOTOX® (4, 8, or 16 U/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 mid- and high-doses and in females at the high-dose. The no-effect doses for reproductive toxicity (4 U/kg in males, 8 U/kg in females) are approximately equal to the average high human dose for upper limb spasticity of 360 U on a body weight basis (U/kg).

Developmental studies:

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

Repeat dose studies:
Current labeling: When BOTOX® (4, 8, or 16 U/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 U/kg) is approximately 1 1/2 times the average high human dose for upper limb spasticity of 360 U on a body weight basis (U/kg).

When BOTOX® was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 U/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 U/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 tat 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 U/kg in rats and 0.25 U/kg in rabbits are less than the average high human dose based on U/kg.

10 Special Toxicology Studies

NA

11 Integrated Summary and Safety Evaluation

Systemic toxicity:

The currently approved maximum single dose for intramuscular administration of BTxA in humans is (b) (4)

The primary safety concern for administration of BTxA by intradetrusor injection is systemic toxicity by the new route of administration. Systemic toxicity could occur if BTxA either diffused from the site of injection or if the injection was misplaced and BTxA was able to access the systemic circulation via another route.

Nonclinical studies established a dose-response for BTxA toxicity by the bladder injection route. Mortality was observed in the rat for a single intradetrusor dose of 100 U/kg, and in the monkey for a single intradetrusor dose of 36 U/kg. Mortality was observed in the monkey following a repeat-dose injection of 24 U/kg. The dose at which mortality was observed was only 1-2X the no observable adverse effect level (NOAEL) (see Table 2 below). An LD_{50} was not determined.

Table 2. Multiples of exposure

Toxicity	Species	NOAEL (U/kg)	Safety Multiple based on dose per unit body weight (U/kg)
Systemic toxicity by the bladder injection route	rat (single dose)	50	15
	monkey (single dose)	24	7.2
	monkey (multiple dose)	12	3.6

Multiples calculated based on a human dose of **200 U** or **3.33 U/kg**

In the monkey, the observed lethal dose of 36 U/kg by the bladder route is very close to that reported by Scott and Suzuki (1988) for injection by the intramuscular route. They reported an LD_{50} of 39 U/kg for a single injection to the calf muscles of *Macaca fascicularis* (N=7), with a similarly steep dose response curve: the NOAEL was <33 U/kg. Thus, we can conclude that systemic toxicity via the intradetrusor route will occur at doses comparable to those observed by the intramuscular route and that administration of BTxA to the intradetrusor does not appear to carry any additional risk of systemic toxicity in humans compared to other approved routes of administration.

Local toxicity:

The second most important safety concern for BTxA administration to the detrusor muscle is local toxicity to the bladder muscle. Local toxicity was assessed in two ways: by measuring bladder function (urinalysis), and by histology. Doses were administered at concentrations of up to 500 U/ml in the rat and 180 U/mL in the monkey, which were 71x and 26X the clinical concentration. It should be noted that, in the nonclinical studies, it was impractical to divide the dose into more than a few injections, which means that there may have been a smaller amount of the bladder surface area exposed to BTxA but at higher concentrations compared to humans.

Overall, the nonclinical studies conducted in support of this application demonstrated little local toxicity to the bladder. The sponsor reported no problems with micturition in either rat or monkey, and no alterations of urine volume or quality. There were expected findings of inflammation at the presumed sites of injection that may have been more severe with repeated injection.

Surprisingly, there were no histological findings of atrophy in the bladder in the nonclinical reports. BTxA is well known to produce atrophy of skeletal muscle, which occurs as a secondary consequence of BTxA-induced denervation. It is not known whether the very different pattern of innervation or some other intrinsic difference between smooth and skeletal muscle can account for this observation (see also Watanbe et al., 2010). The nonclinical studies are consistent with published clinical findings of no significant histological changes in subjects treated with BTxA for neurogenic bladder (Haferkamp et al., 2004, and Pascali et al., 2011). (b) (4)

Other significant findings:

The most significant adverse event in the nonclinical studies, development of bladder stones, appeared in the 'off-target' injection studies. One of two male monkeys injected with the comparatively low dose of 6.8 U/kg (total) into the prostatic urethra and proximal rectum developed caliculi. The sponsor has also reported bladder stone formation in monkeys in a repeat dose prostate injection study (TX05055) at higher doses of 12 and 20 U/kg. It is assumed that the stone formation was a result of incomplete voiding resulting from bladder flaccidity due to diffusion of BTxA from the injection site. Although the sponsor claims this is a species specific finding, it has also been reported in one rat study (Watanabe et al., 2010), and can presumably result in humans whenever there is chronic urine retention. However, the clinical safety database for this BLA showed no difference in the incidence of bladder stones between control and treated subjects (about 1% each).

Summary:

Nonclinical studies in the rat and monkey indicate that there are no significant new toxicities associated with injection of BTxA to the bladder. Systemic toxicity occurred at doses comparable to those observed for BTxA by the intramuscular route. Degenerative changes to the bladder were not observed. Bladder stone formation is a possible risk of peribladder or bladder injection with BTxA, likely due to bladder flaccidity and incomplete voiding.

12 Appendix

Table 3. Clinical studies conducted

Study	Study Design
191622-511	Phase 2, multicenter, parallel design in patients with urinary incontinence caused by detrusor overactivity. Single treatment.
191622-518	Phase 2 (Dose-response), multicenter, parallel design in patients with urinary incontinence due to neurogenic detrusor overactivity. Up to 2 treatments.
191622-515	Phase 3 (Pivotal), multicenter, parallel design in patients with urinary incontinence due to neurogenic detrusor overactivity. Up to 2 treatments.
191622-516	Phase 3 (Pivotal), multicenter, parallel design in patients with urinary incontinence due to neurogenic detrusor overactivity. Up to 2 treatments.
191622-094	Phase 3 (Long-term), multicenter, follow-up study of patients from 191622-515 and 191622-516 studies Multiple treatments.
191622-082	Phase 3 (Special Population), multicenter, parallel design in patients with urinary incontinence due to neurogenic detrusor overactivity and also have respiratory impairment. Up to 2 treatments.

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14 Signatures

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