CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	103000/5309
Priority or Standard	Priority (5309)
Submit Date(s)	December 20, 2018
Received Date(s)	December 20, 2018
PDUFA Goal Date	June 20, 2019
Division / Office	DNP/OND
Reviewer Name(s)	Susanne R. Goldstein, MD
Review Completion Date	June 20, 2019
Established Name	OnabotulinumtoxinA
(Proposed) Trade Name	Botox
Therapeutic Class	Purified Neurotoxin Complex
Applicant	Allergan
Formulation(s)	Injection IM
Dosing Regimen	As needed
Indication(s)	Upper Limb Spasticity
Intended Population(s)	Pediatric

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The results of the pivotal Phase 3 trial for upper limb (UL) spasticity in the pediatric population, Study 191622-101provided evidence of effectiveness and clinically meaningful benefit without change in the known risk profile of BOTOX (OnabotulinumtoxinA).

I recommend APPROVAL of BOTOX for the treatment of:

- upper limb spasticity in the pediatric population with a maximum dose of 6 U/kg injected in the wrist and/or elbow flexors

The Applicant submitted the Phase 3 trial conducted in pediatric patients with lower limb (LL) spasticity, Study 191622-111 and the Open Label extension study, Study 191622-112, (b) (4)

The PMR for a long-term safety study in the pediatric population treated for spasticity (half upper (b) (4) is also fulfilled.

1.2 Risk Benefit Assessment

The Applicant conducted one pivotal, DBPC, trial for the treatment of UL spasticity, 191622-101, in the
pediatric population, to support efficacy

The efficacy results for the treatment effect of BOTOX for UL spasticity in pediatric patients in the pivotal study, 191622-101, is statistically significant for the primary endpoint, change in MAS from Baseline to the average of weeks 4 and 6 in the principal muscle group (PMG), elbow or wrist flexors , for both 3 U/kg and 6 U/kg cohorts (-1.9 [p<0.001] and -1.9 [p,0.001] respectively) compared to placebo (-1.2).The co-primary endpoint, the CGI by the physician, average of Weeks 4 and 6, is not statistically significant for either dose group, 3 U/kg or 6 U/kg (1.9 [p=0.147], 2.0 [p=0.155] respectively) compared to placebo (1.7). The clinical meaningfulness of the treatment effect as measured by the MAS is supported by the 1-point MAS responder analysis. The responder analysis for the MAS, responders with at least 1 grade reduction from

Baseline, is positive (nominal alpha < 0.05) for both the 3 U/kg group and 6 U/kg group at Weeks 4 and 6.

For safety, Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and deaths, the Applicant submitted DBPC studies 191622-101 (UL) and 191622-111(LL), open label extension studies, 191622-105 (UL) and 191622-112 (LL), and post-marketing safety update. There were no new safety signals identified.

There were no deaths in the recent studies (DBPC 191622-101 and 191622-111, OL 191622-105 and 191622-112). There was one death (b) (4) the patient died as a result of herpes simplex virus encephalitis. There were 5 SAEs in the DBPC study for UL spasticity, 191622-101; 3 in the 6 U/kg cohort (seizure, infectious mononucleosis and vomiting, 1 in the 3 U/kg cohort (meningitis) and 1 in the placebo cohort (osteochondrosis.) There were 7 SAEs in the DBPC study for LL spasticity, 191622-111; 3 in the 4 U/kg cohort (tachycardia, tonsillar hypertrophy, seizure) and 4 in the placebo cohort (radicular pain, 2 with seizure, and gastroenteritis.) The most common TEAEs in the Overall Safety Population (DBPC and OL studies for UL and LL spasticity in the pediatric population) were diarrhea, vomiting, injection site pain, nasopharyngitis and upper respiratory tract infection.

The study results provided evidence of effectiveness for the treatment of upper limb spasticity in pediatric patients ages 2-17 years of age. The information in the sponsor's submission demonstrates that treatment with BOTOX 3-6 U/kg for UL spasticity is effective. No new safety signals were identified regarding use of BOTOX for the treatment of spasticity in the pediatric population, ages 2-17 years old. The recommended dose of BOTOX is 6 U/kg in the UL given no sooner than every 12 (b) (4) weeks. A risk mitigation strategy (REMS), additional PMR or PMC are not indicated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This supplement does not require a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

There was substantial evidence of use and adverse events including fatal and nonfatal serious adverse events reported in association with BOTOX as well as other botulinum toxin products used in the treatment of spasticity in adults and children. On April 29, 2009 the FDA imposed Post-marketing Requirements (PMR) and Post-marketing Commitments (PMC) under FADAAA to study BOTOX for the treatment of spasticity in adults and in the pediatric population.

Approval Letter	PMR/PMC set numbers
April 29, 2009	PMR #1-2; PMC (number unassigned)

March 9, 2010 **S5189** UL adult	PREA PMR #1-3
June 1, 2010, request for timelines and PMR/C split of April 29, 2009 PMR/C	PMR #1-2; PMC #3-6 * *(not identical to PMR se numbers in April 29, 2009, letter)*
DARRTS numbers assigned to BLA 103000	2607 series
April 17, 2015, **S5282** thumb approval	2342 series
January 21, 2016, **S5252** LL adult spasticity	3018 series

The approval of BOTOX for the treatment of lower limb spasticity in adults, January 21, 2016, triggered PREA. The pediatric study requirement for children less than 2 years of age will be waived because necessary studies are impossible or highly impracticable, because spasticity is not reliably diagnosed until after two years of age. Pediatric studies for ages 2 to 17 years will be deferred because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The required studies are as follows:

PMRs

In May 2009, the Applicant committed to conduct a juvenile animal toxicology study prior to initiating a clinical trial for pediatric lower limb spasticity.

PMR #2342-1

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

In October 2010, a juvenile toxicity study report was submitted (Study # TX09067, SDN2526). That study was determined to be inadequate by design (review by nonclinical reviewer, Barbara Wilcox, dated March 27, 2014), and the sponsor was required to repeat the study (PMR # (b) (4)). In response to the PMR, the sponsor submitted a new protocol accompanied by a report from a completed dose-ranging study. The dose ranging study (#TX15019) did not include a control group and, thus, was not considered adequate to establish a high dose for the pivotal study.

The applicant submitted in sBLA 103000/5309 (b) (4)

- Study #TX15019, BOTOX: Intramuscular dose-range study in juvenile rats
- Study #1043-T01-065, BOTOX: An intramuscular 12-week toxicity study in juvenile rats, including a 12-week recovery period

These studies were reviewed by the non-clinical reviewer and are discussed in Section 4.0

PMCs

The supplement, sBLA 103000/5282, fulfilled a Post Marketing Commitment (PMC) to evaluate the safety and efficacy of Botox in a controlled clinical trial for the treatment of lower limb spasticity in adults. A PMC fulfilled Letter was sent to the sponsor on May 8, 2014. In addition to that PMC, a post-marketing requirement (PMR) asked for safety information from long-term studies that included treatment of 100 patients (100 adult and 100 pediatric patients), with approximately half treated for upper and the other half treated for lower limb spasticity, for one year. The pediatric upper limb spasticity PMR and PMC were reissued under PREA with the approval of the supplement for treatment of upper limb spasticity (S-5189) in adults, which also fulfilled the PMC to study upper limb spasticity in adult patients.

A meeting with PeRC was held on June 5, 2019:

PeRC Recommendations:

- The PeRC agreed that the product has been fully assessed for use in pediatric patients 2 to less than 17 years of age for the treatment of pediatric upper limb spasticity and labeling will be updated.
- The PeRC also agreed with the Division's recommendation for fulfillment of PREA PMRs as annotated above.

With the approval of supplemental [redacted] (b) (4) 103000/5309 PMRs [redacted] (b) (4) and #2342-1 are fulfilled.

2 Introduction and Regulatory Background

2.1 Product Information

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

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or autonomic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity.

2.2 Tables of Currently Available Treatments for Proposed Indications

Drug	**Preparation**
Systemic	
Baclofen*	Oral and Intrathecal
Dantrolene * (>5 years)	Oral
Diazepam *(>6 months)	Oral
Tizanidine	Oral
Local Injections	
Local anesthetics: Lidocaine, bupivacaine, Etidiocaine	

Ethyl Alcohol, Phenol, OnabotulinumtoxinA (BOTOX) *Approved April 17, 2015, January 21, 2016* abobotulinumtoxinA (Dysport) Approved *July 16, 2015* abobotulinumtoxinA (Dysport) Approved *July 30, 2016*	I.M. for Adult upper limb including thumb, I.M. for Adult LL I.M. for Adult upper limb I.M. for Adult LL I.M. for Pediatric lower limb
Surgical	
Orthopedic procedures: Tendon release/lengthening.	

2.3 Availability of Proposed Active Ingredient in the United States

BOTOX is manufactured by Allergan in the US and it is approved for treatment of adult upper limb spasticity (including thumb), chronic migraine, and urinary incontinence due to detrusor over activity, hyperhidrosis, and cervical dystonia, strabismus, blepharospasm, glabellar lines (Botox Cosmetic), adult upper limb and lower limb spasticity.

2.4 Important Safety Issues with Consideration to Related Drugs

Potential distant spread of toxin (PDSOT) from the area of injection to other sites, producing symptoms consistent with the effects of botulinum toxin, i.e. weakness, is one of the main safety concerns for this class of drug. This effect is included in a boxed warning in the BOTOX label.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

(b) (4)

A pre-sBLA meeting was held March 22, 2018 with Allergan.

The meeting is summarized below:

- To support dosing for treatment of spastic monoplegia, hemiplegia and diplegia, the application needs to include sufficient safety information from patients with each pattern of limb spasticity treated with the highest dose of BOTOX described in labeling.

- Botox labeling describes the treatment of spasticity in adults broadly, which includes the dosing information for upper and lower limb muscles. Labeling includes the highest dose of Botox supported by the clinical trials experience without mention of the number and pattern of limbs treated. Labeling for the treatment of spasticity in children ages 2 to 17 years would likely be similar without limiting treatment to specific patterns of spasticity (e.g., spastic diplegia, monoplegia or hemiplegia).

- Include an MAS responder analysis comparing between treatment groups the proportion of patients treated for upper limb spasticity with BOTOX who experienced a full point improvement for the average of Week 4 and Week 6 in the sBLA.
- Include a clear presentation of the number of patients treated for 4 cycles, every 10 to 14 weeks (or sooner). The table should show the number of patients treated for upper limb spasticity with 6 U/kg (max=200 U) in the upper limbs only, the number of patients who received 300 U (max=300 U) in the lower limbs only, and the number of patients treated with at least 8 U/kg (300 U or higher) total dose, regardless of the limb distribution.

- The Applicant provided clarification for the long-term exposure stating that patients are counted as being treated for treatment of upper limb spasticity if they received treatment in the upper limb only or if they received upper limb and lower limb injections, but exposure is counted based solely on the dose administered in the upper limb. The exposure for treatment of lower limb spasticity is counted the same way. The exposure using the total body dose includes all patients regardless of which limbs were treated in the session.

- The Applicant acknowledged that the number of pediatric patients treated with 6 U/kg for upper limb spasticity every 10-14 weeks for 1-year is currently less than 50 patients.
- Many patients treated in the upper limb only during the controlled portion of the study received upper and lower limb injections during the open label portion of the study.
- Several patients who received the highest dose in the upper limb only injections did not met criteria for retreatment until after 14 weeks. The FDA encouraged the

Applicant to explore different treatment intervals (e.g., ≤12-16 weeks) to support the long-term exposure for the 6 U/kg dose in upper limb spasticity

- Safety data should be grouped by each clinically relevant dose of BOTOX (e.g., UL: 3U/kg, 6U/kg. LL: 4U/kg, 8U/kg.) The safety data should be presented as controlled studies, open-label studies, or post-marketing information.

- Provide safety datasets with one USUBJID for each entry, actual treatment dose expressed as absolute dose (total in U and U/kg for each treatment session, not mean or median dose) and dose category.

- provide exposure tables for individual double-blind, placebo- controlled and open-label separately in the individual study reports, and pooled exposure in the ISS, grouped by the total dose administered and indication.

- present the data for:
    - The actual total dose administered to patients in units (not the mean or median dose) by treatment cycle
    - The actual dose for at least 2 and 4 consecutive injections every 10 to 14 weeks (or sooner).

- The Applicant proposed using dosing categories of ≤4 U/kg, 5-7 U/kg and >8 U/kg for the safety analyses. The FDA stated this is acceptable for analyses of adverse events. For exposure, the Applicant also needs to present exposure using the actual dose and duration between treatments in tables. Cumulative exposure tables can combine patient exposure in DBPC phase with the data from the open-label extensions of these studies.

- In the ISS, present pooled analyses of adverse events grouped by DBPC studies, open- label studies and all studies. The analyses should use the actual dose in categories for upper limb spasticity of ≥3 U/kg-<6U/kg, ≥6U/kg and for lower limb, ≥4U/kg-<8U/kg, ≥8U/kg.

2.6 Other Relevant Background Information

(b) (4)

Dysport (abobotulinumtoxinA) received Orphan Designation for the treatment of pediatric (b) (4) cerebral palsy in October 1999.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The electronic data capture (EDC) was conducted in adherence to the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials [1, 2]. In addition, this study adhered to all local regulatory requirements.

3.2 Compliance with Good Clinical Practices

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the ICH Consolidated Guideline on Good Clinical Practice.

Allergan included a Debarment Certification (module 1.3.3) stating that:

> *Allergan hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal, Drug and Cosmetic Act in connection with this application.*

3.3 Financial Disclosures

The following is a list of investigators/sub-investigators who did not provide financial disclosure information:

Study 191622-105

- Site 10029 (Dr. Ronald Davis, USA), subinvestigator Amy Hill did not provide a financial disclosure
- Site 10039 (Dr. Charles Niesen, USA) subinvestigator Sarah Julian was listed on the 1572 but did not provide a financial disclosure.

Study 191622-112

- Site 10029 (Dr. Ronald Davis, USA), sub-investigator Amy Hill did not provide a financial disclosure

Allergan submitted form 3454 certifying the absence of a disclosable financial relationship with investigators who did not provide financial disclosure information for studies

The following is a list of investigators certifying the presence of financial interests and arrangements.

Study 191622-101

- Site 113001, [redacted] (b) (6) (Principal Investigator), receives a grant to review practice patterns for BTA in Pediatric hypertonia in [redacted] (b) (6) and a grant to evaluate pain in children.
- Site 11301 [redacted] (b) (6) sub-investigator [redacted] (b) (6) receives a grant to review practice patterns for BTA in Pediatric hypertonia in [redacted] (b) (6) and a grant to evaluate pain in children.

Study 191622-111

- Site 10038 [redacted] (b) (6) sub-investigator [redacted] (b) (6) received a grant for research study.

Study 191622-112

- Site 10038 [redacted] (b) (6) sub-investigator [redacted] (b) (6) received a grant for research study.

The applicant described the steps taken to minimize the potential for bias or influence the study results such as, the use of block randomization and blinding of study unknown to site personnel. Study payments were not contingent on the results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

NON-CLINICAL

The nonclinical reviewer's (Dr. Barbara Wilcox) preliminary conclusions are summarized below.

SDN5395 to BLA 103000 contains data to support use of BOTOX for the treatment of spasticity in pediatric patients, including nonclinical studies TX15019 and #TX1043-T01-065 (dose ranging and pivotal juvenile toxicity reports, respectively.)

In #TX15019,

- Sprague-Dawley rats (8/sex/group, 21 days old) received IM injections at doses of 16 or 32 U/kg every 2 weeks for 5 weeks (total of 3 doses).
- Paresis of the injected limb was observed in all rats in both dose groups, as expected.
- Dose-related decreases in food intake and body weight gain were observed in both dose groups.
- At the end of the dosing period, the mean body weight of HD males was 17% lower than LD males.
- Body weight of females in the HD group was 15% lower than in LD females.
- No histopathology was conducted.
- Because no control group was included in the study, the adequacy of the dose levels could not be determined.

In the pivotal study (#1043-T01-065)

- Sprague-Dawley rats (21 days old, 30/sex/group) received IM injections of BOTOX at doses of 0, 8, 16, or 24 U/kg every 2 weeks for 12 weeks (7 total doses).
- A complete battery of developmental endpoints was assessed.
- the BOTOX-related toxicities observed were the expected result of the known pharmacological activity of the drug.
- No unscheduled deaths occurred.
- Dose-related reductions in body weight gain, relative to control, were observed in all dose groups, which correlated with reduced food consumption in males. The magnitude of the effects was greater in males than females: mean body weight gain in HD males was 33% lower than in controls, while mean body weight gain in HD females was reduced 18%, relative to control.
- Clinical observations were described as limited use of the injected hind limb in all dose groups, which persisted through the recovery period for both males and females.

- Sexual maturation was not affected by exposure to BOTOX in any dose group, and no adverse effects were observed on functional developmental parameters (tested at the end of the recovery period).
- No effect of BOTOX was observed on estrous cycling. However, dose-related reductions in mating index and pregnancy rate and a small increase in pre-coital interval were observed in all dose groups, relative to control.
- At the HD, mating index and pregnancy rate were reported as 50%, compared to control values of 100% and 85%, respectively.

- In addition, increased post-implantation loss was observed in the MD and HD females (61.77 and 90.96%, respectively).

- Femurs and tibias of all animals were examined for growth and density. No effects on bone length related to BOTOX were observed.
- However, dose-related effects on bone size, geometry, and density (graded slight to marked) were observed in males and females in all dose groups.
- Testicular toxicity was observed in seminiferous epithelium in 1 of 10 MD males and 3 of 10 HD males; the microscopic findings included tubular degeneration (graded moderate to marked) exfoliated epithelial cells (graded severe) apoptosis and disorganization of elongating spermatids, decreased numbers of elongating spermatids (graded severe), apoptosis of spermatocytes in meiosis, apoptosis of round spermatids, vacuolation of Sertoli cells, and sperm stasis.
- In the epididymis, increased cellular debris, chronic inflammation, germ cell drop-out, and hypospermia were observed. However, at the end of recovery, no BOTOX-related effects were observed; sperm motility and count were similar to controls.
- The applicant considers the testicular effects a result of changes in gait and position. The variation in position (or actual retraction of the testes) in rat could result in increased temperature of the testes. Although this scenario is possible, there are no data (clinical observations or necropsy observations) in the report to indicate that a difference in position (or chryptorchidism) of the testes occurred in the study.
- According to the nonclinical reviewer, the findings are clearly dose-related, and that a relationship to the test article that may be relevant to humans cannot be ruled out.
- BOTOX-related effects on clinical pathology parameters appeared to correlate with the pharmacological effects of BOTOX, specifically reduced food intake, dehydration, and muscle atrophy. The changes included reductions in creatinine in males and females in all dose groups and increased CK in MD and HD males and females. Increased sodium, chloride, and potassium were observed in the MD and HD groups. Changes in hematology parameters were minimal increased in red cell mass, minimal increases in lymphocytes, and minimal increases in platelets.
- At the end of the recovery period only the effects on creatinine persisted. BOTOX -related effects on urinalysis parameters were observed only in HD males and were not observed at the end of the recovery period.

REVIEWER COMMENT:

The nonclinical team will recommend labeling to describe the results of the juvenile toxicology studies to include in labeling. The non-clinical reviewer stated

that no conclusions could be drawn for Study #TX15019 due to lack of a control group. (b) (4) .

The pivotal study, Study #1043-T01-065, was adequate in design and conduct to support the use of BOTOX in children at least 2 years old. PMR #2342-1 has been fulfilled. Please refer to nonclinical review (DARRTS 6/12/2019) for full details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The application relies upon one randomized double-blind placebo-controlled study to support the efficacy claim; **Study 191622-101 for pediatric upper limb spasticity.**

The pivotal efficacy study for pediatric upper limb spasticity, **Study 191622-101**, was followed by an **open label extension study, Study 191622-105.**

Table 1 DBPC and OL Studies Supporting Efficacy Claim for Pediatric UL Spasticity

Study ID (Reference)	Design	Treatment Groups (No. of Patients)	Muscles Injected	No. of Treatments
Phase 3 Primary Efficacy Study				
191622-101 (Module 5.3.5.1, CSR 191622 -101)	Multicenter, double-blind, randomized, parallel group, placebo controlled	BOTOX 3 U/kg (not to exceed 100 U) + OT (N = 78) BOTOX 6 U/kg (not to exceed 200 U) + OT (N = 77) Placebo + OT (N = 89)	Wrist group: flexor carpi ulnaris and flexor carpi radialis, flexor digitorum profundus and flexor digitorum superficialis Elbow group: biceps, brachialis, and brachioradialis	1
Long-term Safety and Efficacy Study				
191622-105 (Module 5.3.5.2, Protocol 191622-105)	Multicenter, open-label	Cycle 1: BOTOX maximum body dose 8 U/kg or 300 U Cycle 2-5: BOTOX maximum body dose 10 U/kg or 340 U	Upper and lower limb muscles	Up to 5

Source: Applicant

(b) (4)

Table 2 DBPC and OL Studies for Pediatric LL Spasticity

Study ID (Reference)	Design	Treatment Groups (No. of Patients)	Muscles Injected	No. of Treatments
		Phase 3 Primary Efficacy Study		
191622-111 (Module 5.3.5.1, CSR 191622-111)	Multicenter, double-blind, randomized, parallel group, placebo controlled	BOTOX 4 U/kg (not to exceed 150 U) + PT (N = 126) BOTOX 8 U/kg (not to exceed 300 U) + PT (N = 128) Placebo + PT (N = 130)	Medial and lateral gastrocnemius, soleus, and tibialis posterior	1
		Long-term Safety and Efficacy Study		
191622-112 (Module 5.3.5.2, Protocol 191622-112)	Multicenter, open-label	Cycle 1: BOTOX maximum body dose 8 U/kg or 300 U Cycles 2-5: BOTOX maximum body dose 10 U/kg or 340 U	Lower and upper limb muscles	Up to 5

Source: Applicant

(b) (4)

(b) (4)

5.2 Review Strategy

Efficacy for the treatment of upper limb (UL) spasticity in the pediatric population is supported by Study 191622-101 and will be reviewed in Section 6.0.

(b) (4)

Safety data from the double-blind placebo controlled study191622-101 and open label extension study 191622-105 will be presented for pediatric UL spasticity in Section 7.0. Safety data from the double-blind placebo controlled study191622-111 and open label extension study 191622-1112 will be presented for pediatric LL spasticity in Section 7.0.

(b) (4)

6 Review of Efficacy

6.1 Indication

Treatment of UL spasticity in the pediatric population

Study 191622-101

6.1.1 Design

Study 101 was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multi-center clinical study to evaluate the safety and efficacy of a single treatment of two doses (3 U/kg and 6 U/kg) of Botox with occupational therapy (OT) in pediatric patients with upper limb spasticity. Approximately 224 subjects 2 to 16 years and 11 months of age were planned to be enrolled and randomized in a 1:1:1 ratio to the Botox 6 U/kg group, Botox 3 U/kg group, or placebo group.

The study consisted of a screening period of up to four weeks. Subjects had post-injection follow-up visits at Weeks 2, 4, 6, 8, and 12 and weekly OT sessions from Week -2 to Week 11.

The co-primary endpoints are

- Average grade change from baseline in Modified Ashworth Scale – Bohannon (MAS-B) score of the principal muscle group (elbow or wrist) at Weeks 4 and 6
- Average Clinical Global Impression of Overall Change (CGI) by Physician at Weeks 4 and 6

The MAS-B has 6 grades:

Table 4 Modified Ashworth Scale Scoring

Score	Coded Score	Definition
0	0	No increase in muscle tone
1	1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is (are) moved in flexion or extension
1+	2	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	3	More marked increase in muscle tone through most of the ROM, but affected parts easily moved. There could be a catch, but movement should have been stiff through most of the range.
3	4	Considerable increase in muscle tone, passive movement difficult
4	5	Affected part(s) rigid in flexion or extension

Source: Applicant

Clinical Global Improvement (CGI)

The CGI by Physician in Study 191622-101 was measured at Weeks 2, 4, 6, 8, and 12. The CGI by Physician is a 9-point scale, evaluated as follows:

-4 Very marked worsening
-3 Marked worsening
-2 Moderate worsening
-1 Slight worsening
-0 Unchanged
+1 Slight improvement
+2 Moderate improvement
+3 Marked improvement
+4 Very marked improvement

The muscle group that had the higher baseline MAS-B score was designated as the principal muscle group (PMG). Subjects were required to have a baseline MAS-B score of 2 or greater in the PMG. When both the wrist and elbow flexors had the same baseline MAS-B score, the elbow flexors were designated as the PMG. In some cases of equal baseline MAS-B scores in wrist and elbow, the PMG designation was changed to ensure that at least 40% of subjects enrolled had elbow flexors spasticity and 40% have wrist/finger flexors spasticity.

Subjects were stratified based on the following three factors:

- Age (≤ 6 years and > 6 years)
- Designated principal muscle group (elbow flexors and wrist flexors)
- Baseline MAS-B score of the principal muscle group (MAS-B = 2 and MAS-B > 2)

The **secondary efficacy** endpoints included the following:

- The average CGI by Physician at Weeks 4 and 6 (for non-US FDA analyses)
- The average change from baseline of MAS-B of the finger flexor muscle group at Weeks 4 and 6
- The Goal Attainment Scale (GAS) by Physician at Weeks 8 and 12
- The MTS of the principal muscle group

DOSING

Dosing for individual muscles for elbow flexors, wrist flexors and finger flexors are outline in Table 5.

Table 5

Table 9-2 Number of BOTOX Units per Kilogram, Maximum Dose, and Number of Injection Sites by Muscle

	BOTOX 3 U/kg		BOTOX 6 U/kg		Placebo		
Upper Limb Muscle	BOTOX Dose per Muscle	Maximum Dose per Muscle	BOTOX Dose per Muscle	Maximum Dose per Muscle	BOTOX Dose per Muscle	Maximum Dose per Muscle	No. Injection Sites
Elbow Flexor Muscle Group							
Biceps	1.5 U/kg	50 U	3.0 U/kg	100 U	0 U/kg	0 U	4
Brachialis	1.0 U/kg	30 U	2.0 U/kg	60 U	0 U/kg	0 U	2
Brachioradialis	0.5 U/kg	20 U	1.0 U/kg	40 U	0 U/kg	0 U	2
Wrist Flexor Muscle Group							
Flexor carpi ulnaris	1.0 U/kg	25 U	2.0 U/kg	50 U	0 U/kg	0 U	2
Flexor carpi radialis	1.0 U/kg	25 U	2.0 U/kg	50 U	0 U/kg	0 U	2
Finger Flexor Muscle Group							
Flexor digitorum profundus	0.5 U/kg	25 U	1.0 U/kg	50 U	0 U/kg	0 U	2
Flexor digitorum superficialis	0.5 U/kg	25 U	1.0 U/kg	50 U	0 U/kg	0 U	2
Total Maximum Dose for the Principal Muscle Group	3 U/kg (not to exceed 100 U)		6 U/kg (not to exceed 200 U		0 U/kg		

No. = number; U = unit

Source: Applicant

Protocol Amendments

Changes in the Conduct of the Study or Planned Analyses

No participants were enrolled under the original protocol (dated 02 December 2011). The protocol was subsequently amended 3 times. The first amendment was on 02 April 2012 and 43 participants were enrolled under this version. The second amendment was on 28 January 2014 and 135 participants were enrolled under this version. The third amendment was on 22 July 2016 and 57 participants were enrolled under this version.

Amendment 1 (02 April 2012)

The first amendment was made to provide clarifications, updated information, and corrections.

Amendment 2 (28 January 2014)

The second amendment was made primarily to add assessment of suicidal ideation and behavior using the C-SSRS as a standard safety measure required by the US FDA's Division of Neurology Products for all ongoing or planned clinical studies, and to incorporate changes in statistical procedures.

Amendment 3 (22 July 2016)

The third amendment was made to decrease the sample size and to incorporate changes in statistical procedures, including:

- Number of participants and sample size calculations were revised such that the estimated number of participants needed to complete study decreased from 351 to 213 based on adjusted treatment differences from upper limb studies
- The intent-to-treat (ITT) population was replaced with the mITT population based on US FDA recommendation
- Added a responder status based on +1 score of CGI by Physician
- The sensitivity analyses of MAS-B and CGI were changed to use the multiple imputation (MI) method for missing values instead of observed cases; sensitivity analyses using last observation carried forward (LOCF) were removed
- The primary MAS-B analysis and FDA coprimary MAS-B and CGI analyses were changed to use MMRM with observed data; ANCOVA with MI and observed data were used as sensitivity analyses
- Changed the multiple testing procedure (gatekeeping procedure) to the Hochberg procedure for the coprimary analysis for FDA

6.1.2 Demographics

The demographic and baseline characteristics are outlined in Table 6.

Table 6 Demographics and Baseline Physical Characteristics (mITT Population)

Characteristic	*BOTOX 6 U/kg (N = 77)*	*BOTOX 3 U/kg (N = 78)*	*Placebo (N = 79)*	*Total (N = 234)*
Age, years				
Mean ± SD	7.6 ± 3.66	8.3 ± 4.48	7.8 ± 4.06	7.9 ± 4.07
Min, Max	2, 16	2, 16	2, 16	2, 16
≤ 6, n (%)	35 (45.5)	33 (42.3)	34 (43.0)	102 (43.6)
> 6, n (%)	42 (54.5)	45 (57.7)	45 (57.0)	132 (56.4)
Sex, n (%)				
Male	50 (64.9)	42 (53.8)	47 (59.5)	139 (59.4)
Female	27 (35.1)	36 (46.2)	32 (40.5)	95 (40.6)
Race, n (%)				
White	51 (66.2)	42 (53.8)	51 (64.6)	144 (61.5)
Non-white	26 (33.8)	36 (46.2)	28 (35.4)	90 (38.5)
Black	3 (3.9)	3 (3.8)	3 (3.8)	9 (3.8)
Asian	19 (24.7)	27 (34.6)	19 (24.1)	65 (27.8)
Hispanic	2 (2.6)	4 (5.1)	5 (6.3)	11 (4.7)
Other	2 (2.6)	2 (2.6)	1 (1.3)	5 (2.1)
Principal Muscle Group				
Elbow Flexors	48 (62.3)	48 (61.5)	48 (60.8)	144 (61.5)
Wrist Flexors	29 (37.7)	30 (38.5)	31 (39.2)	90 (38.5)
MAS-B of Principal Muscle Group				
2	55 (71.4)	57 (73.1)	58 (73.4)	170 (72.6)
>2	22 (28.6)	21 (26.9)	21 (26.6)	64 (27.4)

SD = standard deviation; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat

Source: Tables 14.1-4 and 14.1-5

Source: Applicant

Reviewer Comment:

The demographic and baseline characteristics are similar across treatment cohorts, with approximately 55-57% of subjects greater than 6 years of age, 60-62% with elbow flexors as the PMG of which 70-72% had a baseline MAS of >2. There were more males than females across all treatment cohorts with the greatest difference in the 6 U/kg cohort (65% males) versus 3 U/kg cohort and placebo (54% and 60% respectively.) Of note, there was a higher percentage of Asians in the 3 U/kg cohort versus 6 U/kg or placebo (35% versus 25% and 24% respectively.

A summary of the disease history by cohort is presented in Table 7 below.

Table 7 Summary of Disease History (mITT Population)

Variable	*BOTOX 6 U/kg (N = 77) n (%)*	*BOTOX 3 U/kg (N = 78) n (%)*	*Placebo (N = 79) n (%)*	*Total (N = 234) n (%)*
Disease Type				
Hemiplegia	59 (76.6)	57 (73.1)	68 (86.1)	184 (78.6)
Monoplegia	0	0	0	0
Triplegia	18 (23.4)	21 (26.9)	11 (13.9)	50 (21.4)
Etiology				
Cerebral Palsy	69 (89.6)	69 (88.5)	65 (82.3)	203 (86.8)
Stroke	8 (10.4)	9 (11.5)	14 (17.7)	31 (13.2)
Previous Botulinum Toxin				
No previous exposure	32 (41.6)	33 (42.3)	34 (43.0)	99 (42.3)
Previous exposure for spasticity	45 (58.4)	45 (57.7)	45 (57.0)	135 (57.7)
Mean days since first toxin exposure	1443.7	1139.5	981.7	1188.3
Mean days since last toxin exposure	733.0	763.6	696.9	731.2

mITT = modified intent-to-treat

Source: Tables 14.1-6 and 14.1-7

Source: Applicant

REVIEWER COMMENT:

Slightly more than half the subjects in each cohort (57-58%) had previous exposure to botulinum toxin for spasticity. The majority of subjects in each cohort had spasticity secondary to cerebral palsy (82-90%) versus stroke (10-18%). A greater percentage of subjects in the placebo cohort had hemiplegia versus triplegia (86% v. 13.9%) compared to the 6 U/kg and 3 U/kg treatment cohorts (77% v. 23% and 73% v. 27% respectively).

6.1.3 Subject Disposition

The overall disposition of subjects in presented in Table 8.

Table 8 Summary of Overall Participant Disposition

Participant Status	*BOTOX 6 U/kg (N = 77) n (%)*	*BOTOX 3 U/kg (N = 78) n (%)*	*Placebo (N = 80) n (%)*	*Total (N = 235) n (%)*

Screened (screen population)	--	--	--	292
Not enrolled	--	--	--	57
Consent withdrawn	--	--	--	3
Other	--	--	--	6
Screen failed	--	--	--	48
Inclusion Criteria	--	--	--	33
Exclusion Criteria	--	--	--	16
Randomized	77 (100.0)	78 (100.0)	80 (100.0)	235 (100.0)
Treated (safety population)	77 (100.0)	78 (100.0)	79 (98.8)	234 (99.6)
mITT population[a]	77 (100.0)	78 (100.0)	79 (98.8)	234 (99.6)
Completed Study	75 (97.4)	78(100.0)	79 (98.8)	232 (98.7)
Prematurely discontinued	2 (2.6)	0 (0.0)	1 (1.3)	3 (1.3)
Adverse events	1 (1.3)	0 (0.0)	1 (1.3)[b]	2 (0.9)
Personal reasons	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.4)

CGI = Clinical Global Impression of Overall Change; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat

[a] The mITT population included all randomized participants with a valid MAS-B score of the principal muscle group and ≥ 1 postbaseline measurement at Weeks 2, 4, or 6 for the MAS-B of the principal muscle group and the CGI by Physician.

[b] Participant (b) (6) in the placebo group was withdrawn from the study due to an adverse event before receiving study treatment.

Source: Tables 14.1-1, 14.1-2, and 14.1-3
Source: Applicant

REVIEWER COMMENT:

Overall there were few discontinuations for any reason, in any cohort (1-2%), with only one patient who discontinued from the Botox 6 U/kg group for an adverse event.

6.1.4 Analysis of Primary Endpoint(s)

The efficacy analysis population, the modified intent-to-treat (mITT) population, was defined as all randomized subjects with a valid MAS-B baseline score of the principal muscle group and at least one post-baseline measurement at Weeks 2, 4, or 6 for the MAS-B and CGI by Physician.

The co-primary endpoint of the change from baseline in MAS-B score was analyzed using mixed model repeated measures (MMRM) that included the baseline MAS-B score as the covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure.

The co-primary endpoint of CGI by physician was analyzed using MMRM that included the baseline MAS-B score as the covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure.

The Hochberg procedure was planned to control the family-wise type I error rate. The statistical analysis plan (SAP) defined the following values:
p11: p value for Botox 6 U/kg vs placebo comparing MAS-B
p12: p value for Botox 3 U/kg vs placebo comparing MAS-B
p21: p value for Botox 6 U/kg vs placebo comparing CGI
p22: p value for Botox 3 U/kg vs placebo comparing CGI

$p1 = max(p11, p21)$
$p2 = max(p12, p22)$

and planned to sort p1 and p2 in an increasing order to get p(1) ≤ p(2). The SAP also pre-specified the following decision rule:
Step 1: If p(2) ≤ 0.05, both doses are considered efficacious; otherwise go to step 2.
Step 2: If p(1) ≤ 0.025, its corresponding dose is considered efficacious; otherwise go to step 3.
Step 3: Neither dose is considered efficacious.

(From: FDA Statistical Review)

Modified Ashworth Scale-Bohannon

The primary analysis of the change in baseline score is presented in Table 9.

Table 9 MAS-B Score of the Principal Muscle Group Change from Baseline at Weeks 4 and 6 (MMRM, Observed Data, mITT Population)

Visit	*Statistic*	*BOTOX 6 U/kg (N = 77)*	*BOTOX 3 U/kg (N = 78)*	*Placebo (N = 79)*
Baseline	n	77	78	79
	Mean ± SD	3.3 ± 0.45	3.3 ± 0.45	3.3 ± 0.44
Weeks 4 & 6	n	74	76	75
	Mean ± SD	1.4 ± 1.01	1.4 ± 0.98	2.1 ± 0.90
	Mean Change from Baseline ± SD	-1.9 ± 0.98	-1.9 ± 0.97	-1.2 ± 0.85
	LS Mean Change from Baseline (SE)	-1.87 (0.102)	-1.92 (0.101)	-1.21 (0.102)
	Difference (SE)	-0.66 (0.142)	-0.71 (0.143)	
	95% CI	(-0.938, -0.379)	(-0.992, -0.426)	
	P-value [a]	< 0.001	< 0.001	

CI = confidence interval; LS = least squares; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; MMRM = Mixed Model Repeated Measures; SD = standard deviation; SE = standard error

[a] P-values and 95% confidence intervals for between-group comparisons were obtained from a MMRM model including baseline MAS-B score as a covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age

group, elbow flexors and wrist flexors for designated principal muscle group). Estimated differences are based on the least-square means.

Source: Table 14.2-1
Source: Applicant

REVIEWER COMMENT:

Descriptive statistics in the table were calculated for subjects who had MAS-B scores at both Week 4 and Week 6. The percentages of missing average MAS-B scores at Week 4 and Week 6 were low for all treatment groups: the missing percentages were 3.9%, 2.6%, and 5.1% for the Botox 6 U/kg group, Botox 3 U/kg group, and placebo group, respectively. The treatment difference between the Botox 6 U/kg group and placebo group is statistically significant (p<0.001.) The treatment difference between the Botox 3 U/kg group and placebo group is also statistically significant (p<0.001.)

CGI

The primary analysis for the coprimary CGI by the physician, average of Weeks 4 and 6, is presented in Table 10.

Table 10 CGI by Physician by Visit (MMRM, Observed Data, mITT Population)

		BOTOX		
Visit	*Statistic*	*6 U/kg (N = 77)*	*3 U/kg (N = 78)*	*Placebo (N = 79)*
Weeks 4 & 6	n	74	76	75
	Mean ± SD	2.0 ± 1.01	1.9 ± 1.07	1.7 ± 1.12
	LS Mean (SE)	1.87 (0.108)	1.88 (0.108)	1.66 (0.108)
	Difference (SE)	0.21 (0.150)	0.22 (0.153)	
	95% CI	(-0.082, 0.511)	(-0.079, 0.523)	
	P-value [a]	0.155	0.147	

CGI = Clinical Global Impression of Overall Change; CI = confidence interval; LS = least squares; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; MMRM = Mixed Model Repeated Measures; SD = standard deviation; SE = standard error

[a] P-values and 95% confidence intervals for between-group comparisons were obtained from a MMRM model including baseline MAS-B score as a covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group). Estimated differences are based on the least-square means.

Source: Table 14.2-6
Source: Applicant

REVIEWER COMMENT:

Descriptive statistics in the table were calculated for subjects who had CGI scores at both Week 4 and Week 6. The treatment differences between Botox and placebo favored Botox. However, the p-values of Botox-placebo comparisons for both doses were greater than 0.05.

Based on the pre-specified Hochberg procedure that was planned to handle multiplicity due to multiple endpoints and doses, neither Botox 6 U/kg nor Botox 3 U/kg was statistically significantly different from placebo. However, the purpose of the CGI is to provide information about the clinical meaning of the mean change for the MAS-B. The MAS-B, 1-point responder analysis has been used to support the clinical meaning of the change in MAS-B.

Modified Ashworth Scale 1-Point Responder Analysis

A pre-specified analysis, observed percentages of responders with at least a 1-grade reduction from baseline in MAS-B score, was calculated and reported. (Table 11).

Table 11 MAS-B Score of the Principal Muscle Group: Responders with at Least a 1-Grade Reduction from Baseline (Observed Data, mITT Population)

		BOTOX		
Visit Week	*Statistic*	*6 U/kg (N = 77) n/N (%)*	*3 U/kg (N = 78) n/N (%)*	*Placebo (N = 79) n/N (%)*
2	Responders	62/77 (80.5)	69/78 (88.5)	55/77 (71.4)
	P-value vs placebo [a]	0.140	0.004	
4	Responders	70/77 (90.9)	67/76 (88.2)	58/78 (74.4)
	P-value vs placebo [a]	0.002	0.008	
6	Responders	64/74 (86.5)	70/78 (89.7)	56/76 (73.7)
	P-value vs placebo [a]	0.031	0.007	
8	Responders	70/77 (90.9)	72/77 (93.5)	58/78 (74.4)
	P-value vs placebo [a]	0.002	< 0.001	
12	Responders	49/75 (65.3)	58/78 (74.4)	44/79 (55.7)
	P-value vs placebo [a]	0.293	0.024	

MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; N = number of participants assessed at that visit; n = number of responders

[a] P-values are based on logistic regression model with baseline MAS-B as a covariate and factors of age group, principal muscle group, treatment group, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group).

Source: Table 14.2-4

Source: Applicant

REVIEWER COMMENT:

Responders with at least 1-grade reduction from baseline was statistically significant at Weeks 4 and for both the 6 U/kg and 3 U/kg cohorts and is considered clinically meaningful.

Physician Rated Clinical Global Impression (CGI) Responder Analysis

The proportion of responders with a CGI score of at least +1 is shown in Table 12.

Table 12 CGI by Physician: Responders with a Score ≥ +1 (Observed Data, mITT Population)

Visit Week	*Statistic*	*6 U/kg (N = 77) n/N (%)*	*3 U/kg (N = 78) n/N (%)*	*Placebo (N = 79) n/N (%)*
2	Responders	65/77 (84.4)	66/78 (84.6)	59/77 (76.6)
	P-value vs placebo [a]	0.127	0.081	
4	Responders	67/77 (87.0)	68/76 (89.5)	62/78 (79.5)
	P-value vs placebo [a]	0.118	0.026	
6	Responders	67/74 (90.5)	72/78 (92.3)	62/76 (81.6)
	P-value vs placebo [a]	0.031	0.005	
8	Responders	68/77 (88.3)	69/77 (89.6)	62/78 (79.5)
	P-value vs placebo [a]	0.119	0.043	
12	Responders	62/75 (82.7)	70/78 (89.7)	57/79 (72.2)
	P-value vs placebo [a]	0.111	0.015	

CGI = Clinical Global Impression of Overall Change; mITT = modified intent-to-treat; N = number of participants assessed at that visit; n = number of responders

[a] P-values are based on logistic regression model with factors of age group, principal muscle group, treatment group, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group).

Source: Table 14.2-9

Source: Applicant

REVIEWER COMMENT:

The proportion of CGI responders was higher in both BOTOX groups than in placebo at every study visit. and the differences were nominally significant at Week 6 in the 6 U/kg group (p = 0.031) and Weeks 4and 6 in the 3 U/kg group (p=.031, p=0.005, respectively).

6.1.5 Analysis of Secondary Endpoints(s)

Principal Muscle Group (PMG)

The analysis of the primary endpoints by PMG are presented in Table 13.

Table 13 Study 101 analyses by principal muscle group, mITT population

		MAS-B			CGI		
Principal Muscle Group = Elbow							
Visit	**Statistic**	**Botox 6 U/kg (N = 77)**	**Botox 3 U/kg (N = 78)**	**Placebo (N = 79)**	**Botox 6 U/kg (N = 77)**	**Botox 3 U/kg (N = 78)**	**Placebo (N = 79)**
Baseline	n	48	48	48	--	--	--
	Mean±SD	3.3±0.48	3.3±0.47	3.3±0.47	--	--	--
Weeks 4&6	n	46	46	46	46	46	46
	Mean±SD	1.4±1.00	1.5±0.93	2.1±0.91	2.1±0.82	2.0±0.97	1.7±1.13
	Mean change from Baseline ±SD	-1.9±0.91	-1.9±0.92	-1.3±0.81	--	--	--
Principal Muscle Group = Wrist							
Baseline	n	29	30	31	--	--	--
	Mean±SD	3.2±0.41	3.2±0.41	3.2±0.4	--	--	--
Weeks 4&6	n	28	30	29	28	30	29
	Mean±SD	1.4±1.04	1.2±1.05	2.1±0.90	1.7±1.24	1.8±1.21	1.7±1.13
	Mean change from Baseline ±SD	-1.8±1.08	-2.0±1.05	-1.1±0.91	--	--	--

Source: selected from Table 14.5-1.2 and Table 14.5-2.2 in the clinical study report body of Study 191622-101, FDA Statistical Review

REVIEWER COMMENT:

The change in MAS-B was similar for elbow and wrist flexors in the 3 U/kg and 6 U/kg cohorts (-1.8 to -2.0) compared to placebo (-1.1 to -1.3). The CGI was greater for elbow flexors for the 3 U/kg and 6 U/kg cohorts (2.1, 2.0 respectively) than for wrist flexors (1.7, 1.8 respectively), which was similar to placebo (1.7, 1.7).

Finger Flexors

The change in MAS-B from Baseline to average of Weeks 4 and 6 for finger flexors is shown in the table below.

Table 14 MAS-B Score of Finger Flexor Muscle Change from Baseline by Visit (ANCOVA using Observed Data, mITT Population)

Visit	*Statistic*	*BOTOX 6 U/kg (N = 29)*	*BOTOX 3 U/kg (N = 30)*	*Placebo (N = 31)*
Baseline	n	29	30	31
	Mean ± SD	2.7 ± 0.77	2.5 ± 0.73	2.7 ± 0.82
Week 4 & 6	n	28	30	29
	Mean ± SD	1.3 ± 1.07	1.1 ± 0.81	1.8 ± 0.98
	Mean Change from Baseline ± SD	-1.3 ± 0.98	-1.4 ± 1.13	-1.0 ± 0.89
	LS Mean Change from Baseline (SE)	-1.41 (0.184)	-1.46 (0.169)	-1.02 (0.170)
	Difference (SE)	-0.39 (0.239)	-0.44 (0.247)	
	95% CI	(-0.861, 0.091)	(-0.933, 0.051)	
	P-value [a]	0.111	0.078	

Source: Final Study Report

The MAS responder analysis for the finger flexor muscles is shown in the table below.

Table 15 MAS-B Score of Finger Flexor Muscle: Responders with at Least a 1-Grade Reduction from Baseline (Observed Data, mITT Population)

Visit Week	*Statistic*	*BOTOX 6 U/kg (N = 29) n/N (%)*	*BOTOX 3 U/kg (N = 30) n/N (%)*	*Placebo (N = 31) n/N (%)*
2	Responders	21/29 (72.4)	21/30 (70.0)	21/31 (67.7)
	P-value vs placebo [a]	0.687	0.888	
4	Responders	22/29 (75.9)	22/30 (73.3)	19/30 (63.3)
	P-value vs placebo [a]	0.217	0.126	
6	Responders	21/28 (75.0)	25/30 (83.3)	21/30 (70.0)
	P-value vs placebo [a]	0.401	0.050	
8	Responders	24/29 (82.8)	24/29 (82.8)	20/30 (66.7)
	P-value vs placebo [a]	0.118	0.071	
12	Responders	18/29 (62.1)	20/30 (66.7)	18/31 (58.1)
	P-value vs placebo [a]	0.491	0.113	

MAS-B = Modified Ashworth Scale -- Bohannon; mITT = modified intent-to-treat; N = number of participants assessed at that visit; n = number of responders

[a] P-values are based on a logistic regression model with a covariate of baseline MAS-B score of the finger flexor muscle group and factors of age group, treatment group, study center and previous botulinum toxin exposure where age group is represented by stratification categories (≤ 6 years and > 6 years for Age group).

Source: Final Study Report

REVIEWER COMMENT:

The change in MAS-B for finger flexors from Baseline to the average of Weeks 4 and 6 was not statistically significant for 6 U/kg or 3 U/kg dose (p=0.111, p=.078 respectively.) The responder analysis for MAS-B was nominally significant only for 3 U/kg cohort at Week 6 (p=0.05.)

6.1.7 Subpopulations

Analyses of the effect of gender, race, age and geographic region on th primary endpoints, change in MAS-B and CGI, were conducted by the applicant and replicated by the statistical reviewer.

GENDER

The analysis of the primary endpoints by gender are presented in Table 16.

Table 16 Study 101 analyses by gender, mITT population

		MAS-B			CGI		
Female							
Visit	**Statistic**	**Botox 6 U/kg (N = 77)**	**Botox 3 U/kg (N = 78)**	**Placebo (N = 79)**	**Botox 6 U/kg (N = 77)**	**Botox 3 U/kg (N = 78)**	**Placebo (N = 79)**
Baseline	n	27	36	32	--	--	--
	Mean±SD	3.3±0.45	3.2±0.42	3.2±0.42	--	--	--
Weeks 4&6	n	26	35	32	26	35	32
	Mean±SD	1.4±0.84	1.2±0.80	2.1±0.73	1.9±1.05	2.1±1.17	1.6±1.04
	Mean change from Baseline ±SD	-1.8±0.94	-2.0±0.85	-1.1±0.72	--	--	--
Male							
Baseline	n	50	42	47	--	--	--
	Mean±SD	3.3±0.46	3.3±0.47	3.3±0.46	--	--	--
Weeks 4&6	n	48	41	43	48	41	43
	Mean±SD	1.4±1.10	1.5±1.11	2.1±1.01	2.0±1.00	1.7±0.95	1.8±1.19
	Mean change from Baseline ±SD	-1.9±1.01	-1.8±1.07	-1.2±0.93	--	--	--

Source: selected from Table 1-1.1, Table 1-1.2, Table 1-2.1, and Table 1-2.2 in the integrated summary of efficacy tables, Statistical Reviewer

RACE

The analysis of the primary endpoints by race are presented in Table 17.

Table 17 Study 101 analyses by race, mITT population

		MAS-B			CGI		
Non-White							
Visit	**Statistic**	**Botox 6 U/kg (N = 77)**	**Botox 3 U/kg (N = 78)**	**Placebo (N = 79)**	**Botox 6 U/kg (N = 77)**	**Botox 3 U/kg (N = 78)**	**Placebo (N = 79)**
Baseline	n	26	36	28	--	--	--
	Mean±SD	3.2±0.40	3.1±0.35	3.1±0.26	--	--	--
Weeks 4&6	n	25	34	28	25	34	28
	Mean±SD	1.3±0.99	1.4±0.97	2.1±0.86	2.1±1.07	1.7±1.30	1.7±1.16
	Mean change from Baseline ±SD	-1.9±1.04	-1.8±1.05	-0.9±0.80	--	--	--
White							
Baseline	n	51	42	51	--	--	--
	Mean±SD	3.3±0.48	3.4±0.49	3.4±0.49	--	--	--
Weeks 4&6	n	49	42	47	49	42	47
	Mean±SD	1.5±1.02	1.4±1.00	2.0±0.93	1.9±0.98	2.0±0.83	1.7±1.11
	Mean change from Baseline ±SD	-1.9±0.96	-2.0±0.91	-1.4±0.84	--	--	--

Source: selected from Table 1-1.1, Table 1-1.2, Table 1-3.1, and Table 1-3.2 in the March 7, 2019 response to information request, Statistical Reviewer

AGE

The analysis of the primary endpoints by age are presented in Table 18.

Table 18 Study 101 analyses by age group, mITT population

		MAS-B			CGI		
Age ≤ 6							
Visit	Statistic	Botox 6 U/kg (N = 35)	Botox 3 U/kg (N = 33)	Placebo (N = 34)	Botox 6 U/kg (N = 33)	Botox 3 U/kg (N = 32)	Placebo (N = 32)
Baseline	n	35	33	34	--	--	--
	Mean±SD	3.3±0.47	3.3±0.48	3.3±0.46	--	--	--
Weeks 4&6	n	33	32	32	33	32	32
	Mean±SD	1.3±1.15	1.4±1.14	2.0±0.88	2.0±1.10	1.7±1.08	1.8±1.31
	Mean change from Baseline ±SD	-2.0±1.13	-2.0±1.05	-1.3±0.88	--	--	--
Age> 6							
Baseline	n	42	45	45	--	--	--
	Mean±SD	3.3±0.45	3.2±0.42	3.2±0.43	--	--	--
Weeks 4&6	n	41	44	43	41	44	43
	Mean±SD	1.5±0.88	1.4±0.86	2.1±0.92	1.9±0.95	2.0±1.05	1.6±0.97
	Mean change from Baseline ±SD	-1.7±0.83	-1.9±0.92	-1.2±0.83	--	--	--

Source: Applicant, CSR 191622-101, Tables 14.5-1.1 and 14.5-2.1

REVIEWER COMMENT:

Treatment effect for the primary endpoints, change in MAS-B and CGI, are similar for gender. There was a slightly greater placebo effect for MAS-B in White versus Non-whites (-1.4 versus -0.9.). The treatment effect as measured by change in MAS-B was slightly larger for patients > 6 years old than for patients ≤ 6 years old for the 6 U/kg cohort (-2.0 versus -1.7) .

Geographic Region

The analysis of the primary endpoints by geographic region are presented in Table 19.

Table 19 Study 101 analyses by region, mITT population

		MAS-B			CGI		
Non-US							
Visit	Statistic	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)
Baseline	n	60	58	53	--	--	--
	Mean±SD	3.3±0.47	3.3±0.46	3.3±0.48	--	--	--
Weeks 4&6	n	60	57	53	60	57	53
	Mean±SD	1.4±1.05	1.5±1.01	2.1±0.93	2.0±1.07	1.9±1.15	1.7±1.15
	Mean change from Baseline ±SD	-1.9±1.04	-1.8±0.98	-1.2±0.89	--	--	--
US							
Baseline	n	17	20	26	--	--	--
	Mean±SD	3.2±0.39	3.2±0.41	3.1±0.33	--	--	--
Weeks 4&6	n	14	19	22	14	19	22
	Mean±SD	1.3±0.85	0.9±0.78	1.9±0.83	1.8±0.70	1.7±0.77	1.7±1.08
	Mean change from Baseline ±SD	-1.8±0.67	-2.3±0.87	-1.2±0.75	--	--	--

Source: selected from Table 1-1.1, Table 1-1.2, Table 1-2.1, and Table 1-2.2 in the May 1, 2019 response to information request, Statistical Reviewer

REVIEWER COMMENT:

There was a greater change in MAS-B for 3 U/kg cohort in the US population compared to the non-US population (-2.3 versus -1.8). The CGI was similar across geographic regions.

SUMMARY OF EFFICACY

The Applicant conducted one pivotal, DBPC, trial for the treatment of UL spasticity, 191622-101.

The efficacy results for the treatment effect of BOTOX for UL spasticity in pediatric patients in the pivotal study, 191622-101, is not statistically significant for the coprimary endpoints. However, the change in MAS from Baseline to the average of weeks 4 and 6 in the PMG (elbow or wrist flexors) is positive with a nominal p-value < 0.05 for the 6 U/kg dose (high dose). The CGI by the physician, average of Weeks 4 and 6, is not statistically significant for either dose group, 3 U/kg or 6 U/kg, compared to placebo under the Hochberg method selected by the applicant to control Type I error. The responder analysis for the MAS, responders with at least 1 grade reduction from Baseline, is nominally significant for the 3 U/kg group at weeks 4 and 6 and is nominally

significant for the 6 U/kg group at Weeks 4and 6. The clinical meaningfulness of the treatment effect as measured by the MAS is supported by the MAS responder analysis.

7 Review of Safety

Safety Summary

7.1 Methods

(b) (4) clinical studies were submitted in support of the safety of BOTOX for treatment of (b) (4) upper limb spasticity in pediatric patients. (b) (4) studies were initiated in 2012 and completed recently and are referred to as the **recent studies**.

Table 20. Overview of Studies of BOTOX in Pediatric Spasticity

Study Identifier	Diagnosis/ Inclusion	Study Design	Test Product(s); Dosage Regime; Route	No. of Tx/ Duration of Follow-up	Total Per-protocol Dose
		RECENT STUDIES			
191622-101	Cerebral palsy or stroke, 2-16 years of age, single arm-sparing monoplegic, hemiplegic or triplegic with spasticity of the upper limb involving the elbow and/or wrist flexors	Multicenter Double-blind Randomized Parallel-group Placebo- control	BOTOX 3 U/kg (not to exceed 100 U) BOTOX 6 U/kg (not to exceed 200 U) Placebo IM injections Wrist group: flexor carpi ulnaris and flexor carpi radialis, flexor digitorum profundus and flexor digitorum superficialis Elbow group: biceps, brachialis, and brachioradialis	1 treatment with 12- week follow-up	3 U/kg (not to exceed 100 U) or 6 U/kg (not to exceed 200 U)
191622-111	Cerebral palsy, 2-16 years of age, ≥10 kg, monoplegic or hemiplegic with contracture, MAS score ≥ 2 for ankle plantar flexors	Multicenter Double-blind Randomized Parallel-group Placebo-control	BOTOX 4 U/kg (not to exceed 150 U) BOTOX 8 U/kg (not to exceed 300 U) Placebo IM injections into gastrocnemius, soleus and tibialis posterior	1 treatment with 12-week follow-up	4 U/kg (not to exceed 150 U) or 8 U/kg (not to exceed 300 U)

Study Identifier	Diagnosis/ Inclusion	Study Design	Test Product(s); Dosage Regime; Route	No. of Tx/ Duration of Follow-up	Total Per-protocol Dose
		RECENT STUDIES			
191622-105	Rollover: Successful completion of Study 191622-111 *De novo*: See inclusion for 191622-111	Multicenter, open-label	5 treatment cycles: Cycle 1: Max body dose 8 U/kg or 300 U Cycle 2-5: Max body dose 10 U/kg or 340 U IM injections Upper and lower limb muscles	Up to 5 treatments within 48 weeks (exit visit up to Week 60)	Cycle 1: Max body dose 8 U/kg or 300 U Cycle 2-5: Max body dose 10 U/kg or 340 U
191622-112	Rollover: Successful completion of Study 191622-111 *De novo*: See inclusion for 191622-111	Multicenter, open-label	5 treatment cycles: Cycle 1: Max body dose 8 U/kg or 300 U Cycle 2-5: Max body dose 10 U/kg or 340 U IM injections Lower and upper limb muscles	Up to 5 treatments within 48 weeks (exit visit up to Week 60)	Cycle 1: Max body dose 8 U/kg or 300 U Cycle 2-5: Max body dose 10 U/kg or 340 U

(b) (4)

[redacted]

Source: Applicant

7.2 Adequacy of Safety Assessments

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

Upper Limb (UL) Spasticity

The UL exposure for 4 consecutive treatments in one year is displayed in Table 21.

Table 21 Number of Patients With the Maximum Number of BOTOX Treatment Cycles Given at Consecutive 10- to 14-week Re-treatment Intervals: Any BOTOX Exposure in Upper Limb (Overall Safety Population)

BOTOX Treatment Cycles	Upper Limb BOTOX Dose		
	≥ 3 U/kg (or 100 U) N = 306	**≥ 6 U/kg (or 200 U) N = 175**	**All BOTOX**
Within 28 Weeks			
1	131 (42.8%)	109 (62.3%)	127 (35.8%)
≥ 2 (within 10-14 weeks)	175 (57.2%)	66 (37.7%)	228 (64.2%)
≥ 2	209 (68.3%)	77 (44.0%)	271 (76.3%)
Within 56 Weeks			
1	131 (42.8%)	109 (62.3%)	127 (35.8%)
2 (within 10-14 weeks)	60 (19.6%)	25 (14.3%)	63 (17.7%)
3 (within 10-14 weeks)	36 (11.8%)	17 (9.7%)	53 (14.9%)
≥ 4 (within 10-14 weeks)	79 (25.8%)	24 (13.7%)	112 (31.5%)
2	62 (20.3%)	24 (13.7%)	61 (17.2%)
3	53 (17.3%)	24 (13.7%)	64 (18.0%)
≥ 4	111 (36.3%)	34 (19.4%)	166 (46.8%)

Source: Applicant

Lower Limb (LL) Spasticity

The LL exposure for 4 consecutive treatments in one year is displayed in Table 222.

Table 22 Number of Patients With the Maximum Number of BOTOX Treatment Cycles Given at Consecutive 10- to 14-week Re-treatment Intervals: Any BOTOX Exposure in Lower Limb (Overall Safety Population)

BOTOX Treatment Cycles	Lower Limb BOTOX Dose		
	≥ 4 U/kg (or 150 U) N = 848	≥ 8 U/kg (or 300 U) N = 359	All BOTOX N = 868
Within 28 Weeks			
1	260 (30.7%)	207 (57.7%)	249 (28.7%)
≥ 2 (within 10-14 weeks)	588 (69.3%)	152 (42.3%)	619 (71.3%)
Within 56 Weeks			
1	260 (30.7%)	207 (57.7%)	249 (28.7%)
2 (within 10-14 weeks)	183 (21.6%)	66 (18.4%)	184 (21.2%)
3 (within 10-14 weeks)	139 (16.4%)	23 (6.4%)	140 (16.1%)
≥ 4 (within 10-14 weeks)	266 (31.4%)	63 (17.5%)	295 (34.0%)

Source: Applicant

REVIEWER COMMENT:

A total of 112 patients were treated for UL spasticity and 295 patients with LL spasticity were treated for 4 consecutive injections (10-14 weeks) for one year.

7.3 Major Safety Results

7.3.1 Deaths

There was 1 patient death in the Overall Safety Population. [redacted](b) (4). The patient died as a result of HSV encephalitis. There were no deaths in the recent studies for UL and/or LL spasticity.

7.3.2 Nonfatal Serious Adverse Events

UL spasticity

In the DBPC study, 191622-101, there were 5 SAEs; 3 in the 6 U/kg cohort, 1 in the 3 U/kg cohort and 1 in the placebo cohort.

Table 23 Study 191622-101 Serious Adverse Events (Safety Population)

USUBJID	AGE	RACE	SEX	Study Day	Actual Arm	Preferred Term	Serious	Outcome
191622101 [redacted](b) (6)	2	WHITE	F	29	BOTOX 6U/kg + OT	Seizure	Y	Recovered/Resolved
191622101 [redacted](b) (6)	2	WHITE	M	80	BOTOX 6U/kg + OT	Infectious mononucleosis	Y	Recovered/Resolved
				108	BOTOX 6U/kg + OT	Stomatitis	Y	Recovered/Resolved
191622101 [redacted](b) (6)	6	WHITE	F	83	BOTOX 6U/kg + OT	Pyrexia	Y	Recovered/Resolved
				83	BOTOX 6U/kg + OT	Vomiting	Y	Recovered/Resolved
191622101 [redacted](b) (6)	3	ASIAN	M	56	BOTOX 3U/kg + OT	Meningitis	Y	Recovered/Resolved
191622101 [redacted](b) (6)	6	WHITE	M	67	Placebo + OT	Osteochondrosis	Y	Recovered/Resolved

Source: FDA

#1 Participant (b) (6) was a 2-year-old white girl who entered the double-blind Study 191622-101 with hemiplegic spasticity from stroke since (b) (6) and had right hemiparesis. The participant was randomized to receive a single dose of BOTOX 6 U/kg (90 U) into the right upper limb, plus standardized occupational therapy. On (b) (6) the participant received injections of 6 U/kg of double-blind BOTOX into the 3 elbow flexors (biceps, brachialis, and brachioradialis) of the right arm.

The participant's other medical history included dyskinesia, insomnia, developmental delay, neck mass, and seizure (since (b) (6)), all of mild severity, and neonatal hyperbilirubinemia and acute respiratory distress syndrome. Concomitant medications included melatonin for sleep disorder. During the study, paracetamol for viral upper respiratory tract infection and lidocaine patch for injection site pain were administered.

The participant had a history of sleep disturbance for over a year and had been under medical care and follow up for frequent nocturnal arousals of uncear etiology. A magnetic resonance imaging scan on (b) (6) showed cystic encephalomalacia at the left middle cerebral artery, which was thought to have occurred at the time of birth. The participant's mother reported that the child would wake up and stay awake for approximately 30 minutes holding her right hand.

On (b) (6), 29 days after administration of BOTOX 6 U/kg, the participant had a night- time waking episode suspected to be a seizure of mild intensity, reported as a serious adverse event. The participant was hospitalized overnight for video electroencephalogram to rule out seizures and had a waking episode that night in the hospital. No seizure activity was observed. The mother stated at the time of the video electroencephalogram that it had been 3 weeks since the last waking episode. The result of the video electroencephalogram was negative for seizure and showed left central slowing consistent with a history of left middle cerebral artery infarction. No epileptiform waves were identified. The event resolved without sequelae on (b) (6) ; the participant was discharged home on that day.

The seizure was considered serious as it resulted in hospitalization. The participant completed the study on (b) (6)

#2 Participant (b) (6) was a 2-year-old white boy who entered the double-blind Study 191622-101 with right hemiplegic spasticity from cerebral palsy since (b) (6). The participant was randomized to receive a single dose of BOTOX 6 U/kg (90 U) into the right upper limb, plus standardized occupational therapy. On (b) (6), the participant received injections of 6 U/kg of double-blind BOTOX into the 3 elbow flexors (biceps, brachialis, and brachioradialis) of the right arm.

No other medical history was reported; the participant had pharyngitis during screening that was treated with Augmentin (starting on (b) (6)) and ibuprofen. No other concomitant medications were reported at baseline.

On (b) (6), 80 days after administration of BOTOX 6 U/kg, the participant experienced infectious mononucleosis of moderate severity. On that day, the participant had lymphadenitis. Neck pain and swelling were noted by his parents, with fever and rhinitis. The child was taken to the hospital for the lymphadenopathy and was admitted on (b) (6) for lymphadenitis and infectious mononucleosis confirmed by serology testing. Treatment included intravenous sodium chloride fluid replacement, probiotics during antibiotic treatment, clemastine fumarate, oral clindamycin and cloxacillin sodium, inosine pramobex, and ibuprofen. The serious adverse event of infectious mononucleosis resolved without sequelae on (b) (6) the date of discharge was not reported.

On (b) (6), 108 days after administration of BOTOX 6 U/kg, the participant had a fever of 38ºC and moderate stomatitis. The participant was admitted to the hospital on (b) (6) for oral stomatitis (mucositis) and a sore throat. At admission, C-reactive protein was elevated (no values were reported). Treatment included Nystatin (oral swab), oral fluconazole and benzydamine hydrochloride buccal aerosol. The participant was discharged home in good condition on (b) (6) . The serious adverse event of stomatitis resolved without sequelae on an unspecified day in (b) (6).

The infectious mononucleosis and stomatitis were considered serious due to hospitalization. The participant was discontinued from the study on (b) (6) as a result of the serious adverse event of stomatitis**.**

#3 Participant (b) (6) was a 6-year-old white girl who entered the double-blind Study 191622-101 with left hemiplegic spasticity from cerebral palsy since (b) (6). The participant was randomized to receive a single dose of BOTOX 6 U/kg into the left upper limb, plus standardized occupational therapy. On (b) (6), the participant received injections of double-blind BOTOX 6 U/kg (111 U) into the 3 elbow flexors (biceps, brachialis, and brachioradialis) of the left arm.

Other medical history included amblyopia, strabismus, hydrocephalus and ventriculo-peritoneal shunts. No concomitant medications were reported at baseline.

On (b) (6) 83 days after the administration of BOTOX 6U/kg, the participant experienced severe vomiting and pyrexia. The child was admitted to the hospital for vomiting and pyrexia on (b) (6) and diagnosed with a damaged ventricular-peritoneal shunt valve, which resulted in vomiting and fever. On (b) (6), the damaged valve in the ventriculo-peritoneal shunt was replaced. No other treatment was reported. No date of discharge was reported. The serious adverse events of vomiting and pyrexia resolved without sequelae on (b) (6).

The vomiting and pyrexia were considered serious due to hospitalization.

No other adverse events were reported. The consent for study participation was withdrawn and the date of study exit was (b) (6).

#4 Participant (b) (6) was a 3-year-old Asian boy who entered the double-blind Study 191622-101 with triplegic spasticity of both lower limbs and left arm from cerebral palsy since (b) (6) The participant was randomized to receive a single dose of BOTOX 3 U/kg into the left upper limb, plus standardized occupational therapy. On (b) (6) the participant received injections of double-blind BOTOX 3 U/kg (42 U) into the 3 elbow flexors (biceps, brachialis, and brachioradialis) of the left arm.

Other medical history included neonatal jaundice and neonatal asphyxia. No concomitant medications were reported at baseline.

On (b) (6), 56 days after the administration of BOTOX 3 U/kg, the participant experienced severe meningitis, which became a serious adverse event on (b) (6) when he was hospitalized in the pediatric department with nausea, vomiting, headache, and mild fever. He was admitted to rule out meningitis. A spinal tap under ketamine and midazolam sedation was performed on (b) (6), no results were reported. Treatment included intravenous acetylcysteine, propacetamol hydrochloride, dexamethasone, mannitol, ampicillin sodium, cefotaxime sodium, and oral astemizole, ibuprofen, levocloperastine fendizoate, lactobacillus rhamnosus, domeperidone, and cefpodoxime proxetil. The meningitis resolved without sequelae on (b) (6), and he was discharged on that day.

The meningitis was considered serious due to hospitalization. The cause of the meningitis was not reported.

The participant completed the study on (b) (6)

REVIEWER COMMENT:

The SAEs described in narratives 1 and 3 appear to be related to the underlying disease, cerebral palsy, seizures and hydrocephalus. The SAE described in narrative 2, stomatitis and infectious mononucleosis are of unclear etiology; infections are common in this age group particularly with underlying developmental disability. The etiology of the SAE described in narratives 2 and 4 are not clear, but unlikely related to the study drug since they occurred 108 and 56 days, respectively, after injection with study drug.

LL Spasticity

In the DBPC study, 191622-111, there were 7 SAEs; 4 in the 4 U/kg cohort and 4 in the placebo cohort.

Table 24 Study 191622-111 Serious Adverse Events (Safety Population)

USUBJID	AGE	RACE	SEX	Study Day	Actual Arm	Preferred Term	Serious	Outcome
191622111 (b) (6)	5	WHITE	M	1	BOTOX 4U/kg	Extrasystoles, tachycardia	Y	Recovered/Resolved
191622111 (b) (6)	3	WHITE	F	61	BOTOX 4U/kg	Tonsillar hypertrophy	Y	Recovered/Resolved
191622111 (b) (6)	3	ASIAN	F	82	BOTOX 4U/kg	Seizure	Y	Recovered/Resolved
191622111 (b) (6)	15	WHITE	M	55	Placebo	Radicular pain	Y	Recovered/Resolved
191622111 (b) (6)	2	WHITE	F	83	Placebo	Seizure	Y	Recovered/Resolved
191622111 (b) (6)	2	ASIAN	M	65	Placebo	Seizure	Y	Recovered/Resolved
191622111 (b) (6)	3	ASIAN	M	29	Placebo	Gastroenteritis	Y	Recovered/Resolved

Source: FDA

#1 Participant (b) (6) was a 5-year-old white boy who entered the double-blind Study 191622-111 with hemiplegia from cerebral palsy. The participant had hemiplegic spasticity of the right leg since (b) (6). The participant was randomized to receive a single dose of BOTOX 4 U/kg (56.4 U) into the right lower limb, plus standardized physical therapy. On (b) (6), the participant received injections of 4 U/kg of BOTOX into the 3 ankle plantar flexors (gastrocnemius, soleus, and tibialis posterior) of the right leg.

The participant's other medical history included premature birth (29 weeks). There were no concomitant medications reported.

On (b) (6), the participant was given Nubain and diazepam as preparation for study drug injection followed by the BOTOX 4 U/kg injection. The participant experienced serious adverse events of tachycardia (tachycardia (180/min) and extrasystoles of moderate intensity. During the study drug injection, the participant became agitated with consecutive hyperventilation, tetanic cramps, tachycardia and bigeminy.

Following the injections of BOTOX, the participant became agitated, heart rate increased from 120 beats/min to 180 beats/ min, bigeminy occurred for about 10 seconds, and respiration rate increased to approximately 40 breaths/minute. The participant was administered oxygen by laryngeal mask, as well as nitrous oxide and Ringer solutions. To perform precise and safe injection, sevoflurane was given for deep sedation. Study drug administration was continued; the symptoms resolved within 10 seconds of administration of sevoflurane and the participant recovered within 5 minutes. No further adverse events were observed, and the participant was discharged home**.** The tachycardia and extrasystoles were considered serious as they were medically significant. The tachycardia and extrasystoles were considered as due to the stressful situation of the participant and the pain caused by the injections and were related to study drug administration procedure.

The participant completed the study on (b) (6).

 # 2 Participant (b) (6) was a 3-year-old white girl who entered the double-blind Study 191622-111 with hemiplegia from cerebral palsy. The participant had hemiplegic spasticity of the right arm and leg since (b) (6) The participant was randomized to receive a single dose of BOTOX 4 U/kg (65.2 U) into the right lower limb, plus standardized physical therapy. On (b) (6), the participant received injections of 4 U/kg of BOTOX into the 3 ankle plantar flexors (gastrocnemius, soleus, and tibialis posterior) of the right leg.

The participant's other medical history included gastroesophageal reflux disease, recurrent upper respiratory tract infections, pharyngitis, and acute bronchitis. Concomitant medications included probiotics and gastrotuss for gastroesophageal reflux disease, and cod liver oil for upper respiratory tract infection.

On (b) (6) 61 days after administration of BOTOX 4 U/kg, the participant was hospitalized for planned adenotomy for tonsillar hypertrophy reported as a serious adverse event of moderate intensity. This was not planned at the time the participant entered the study. The date of discharge was not reported. The tonsillar hypertrophy was considered resolved on (b) (6).

The tonsillar hypertrophy was considered serious due to hospitalization for adenotomy to treat the tonsillar hypertrophy. The participant completed the study on (b) (6)

#3 Participant (b) (6) was a 3-year-old Asian girl who entered the double-blind Study 191622-111 with hemiplegia from cerebral palsy. The participant had hemiplegic spasticity of the right arm and leg since (b) (6). The participant was randomized to receive a single dose of BOTOX 4 U/kg (67.2 U) into the right lower limb, plus standardized physical therapy. On (b) (6) 16, the participant received injections of 4 U/kg of BOTOX into the 3 ankle plantar flexors (gastrocnemius, soleus, and tibialis posterior) of the right leg.

The participant's medical history included encephalitis and seizures. Concomitant medications included oral valproic acid 700 mg BID and topiramate 12.5 mg BID for seizures. According to the mother, the participant had regular follow ups with her pediatrician and given the anticonvulsant medication on a daily basis. The participant had a scar in her brain from encephalitis and brain infection when she was 9 months old.

On (b) (6), 82 days after administration of BOTOX 4 U/kg, the participant was hospitalized for a serious adverse event of seizure of mild intensity. That morning, while waking the child, the mother noted drooling around the angle of the child's lips, which was a symptom associated with prior seizures. While the child remained sleeping, the mother took her to the local hospital which was 10 minutes away. At their arrival, the child was still asleep and the seizure had stopped. The mother reported that in the past the child's seizures were related to a rapid change of weather condition similar to this time, and that the child never had a fever with a seizure.

There was no fever and her serum electrolytes were normal. She was treated with intravenous diazepam followed by diazepam rectal suppository. The participant awoke after an hour, asking for food, and ate well. She was admitted to the hospital overnight for observation. She had no further seizures. The seizure resolved on (b) (6) and the participant was discharged in good condition. She was to continue with diazepam and her other anticonvulsant medications.

The seizure was considered serious as it resulted in hospitalization. The investigator considered the serious adverse event of seizure to be not related to the study treatment. Allergan agreed with this assessment.

The participant completed the study on (b) (6).

REVIEWER COMMENT:

The SAEs do not appear to be drug (BOTOX) related. SAE #1 may be secondary to either the sedation (Nubain and Diazepam) and/or agitation related to the injection procedure. SAE #2 and SAE #3 are most likely related to underlying medical condition, cerebral palsy, seizures and developmental delay.

7.3.3 Dropouts and/or Discontinuations

UL Spasticity

- Patient (b) (6), a 2-year-old white male, was discontinued from Study 191622-101 on day 124 of BOTOX treatment due to a serious AE of infectious mononucleosis and stomatitis.

LL Spasticity

- Patient [redacted] (b) (6), a 3-year-old Asian male, was discontinued from Study [redacted] (b) (6) on day 96 of BOTOX treatment after being diagnosed with malignant neoplasm of the kidney.

7.3.5 Submission Specific Primary Safety Concerns

Possible Distant Spread of Toxin (PDSOT)

The Applicant used the Preferred Terms from MedDRA version 21.0 to evaluate for Possible Distant Spread of Toxin.

Table 25 MedDRA Version 21.0 Preferred Terms, by SOC, Evaluated for Possible Distant Spread of Toxin

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

Source:Applicant

UL Spasticity

A total of 8 patients experienced adverse events related to PDSOT in the DBPC study, 191622-101; 3 in the 6 U/kg cohort, 3 in the 3 U/kg cohort and 2 in the placebo cohort.

Table 26 Study 191622-101-Patients Reporting Possible Distant Spread of Toxin Events

SOC/ Preferred Term	BOTOX 6 U/kg (N = 77) n (%)	BOTOX 3 U/kg (N = 78) n (%)	BOTOX Total (N = 155) n (%)	Placebo (N = 79) n (%)
Overall	3 (3.9)	3 (3.8)	6 (3.9)	2 (2.5)
Gastrointestinal disorders				
Constipation	2 (2.6)	0	2 (1.3)	1 (1.3)
Musculoskeletal and connective tissue disorders				
Muscular Weakness	1 (1.3)	3 (3.8)	4 (2.6)	1 (1.3)

SOC = System organ class

Source: Table 14.3-7

Source: Applicant

Below are brief narratives for the PDSOT events on active treatment.

1. **Participant** (b) (6) was a 9-year-old black girl with hemiplegia spasticity from cerebral palsy of the left arm and leg since (b) (6). On (b) (6), the participant received injections of 3 U/kg of double-blind BOTOX into the 3 elbow flexors (biceps, brachialis, and brachioradialis) of the left arm. On (b) (6), 5 days after administration of BOTOX 3 U/kg, the participant experienced a nonserious adverse event of muscular weakness of mild intensity that was described as weaker in the right arm and leg. No treatment was reported. The investigator assessed the event of muscular weakness as related to the study treatment. The muscular weakness resolved without sequelae on (b) (6)

2. **Participant** (b) (6) was a 9-year-old white girl with hemiplegic spasticity from stroke of the right arm and leg since (b) (6). On (b) (6), the participant received injections of 3 U/kg of double-blind BOTOX into the 2 wrist flexors (carpi ulnaris and radialis) and 2 finger flexors (digitorum profundus and superficialis) of the right arm. On (b) (6), the day of the administration of BOTOX 3 U/kg, the participant experienced a nonserious adverse event of muscular weakness of mild intensity. The child reported a loss of grip strength in the right hand. No treatment was given. The investigator assessed the event of muscular weakness as related to the study treatment. The muscular weakness resolved without sequelae on (b) (6)

3. **Participant** (b) (6) was a 6-year-old white girl with hemiplegic spasticity of the left arm and leg from cerebral palsy since (b) (6). On (b) (6), the participant received injections of double-blind BOTOX 6 U/kg (119.4 U) into the 2 wrist flexors (carpi ulnaris and radialis) and 2 finger flexors (digitorum profundus and superficialis) of the left wrist. On (b) (6) 16 days after the administration of BOTOX 6 U/kg, the participant experienced a nonserious adverse event of muscular weakness of mild severity described as

weakening of I-Iv fingers of left hand. No treatment was given. The investigator assessed the event of muscular weakness as related to the study treatment. The muscular weakness resolved without sequelae on [redacted].

4. **Participant** [redacted] was a 16-year-old Asian boy with triplegic spasticity from cerebral palsy of both lower limbs and left arm since [redacted] On [redacted], the participant received injections of double-blind BOTOX 3 U/kg (100 U) into the 3 elbow flexors (biceps, brachialis, and brachioradialis) of the left arm. On [redacted],10 days after the administration of BOTOX 3 U/kg, the participant experienced a nonserious adverse event of left arm muscular weakness of mild severity. As a result of the weakness, the participant fell on [redacted] while walking using a walker. He was not injured by the fall. No treatment was reported. The investigator assessed the event of muscular weakness as related to the study treatment. The muscular weakness resolved without sequelae on [redacted].

5. **Participant** [redacted] was a 4-year-old Asian boy with hemiplegic spasticity of the left arm and leg from cerebral palsy since [redacted]. On [redacted], the participant received injections of double-blind BOTOX 6 U/kg (96 U) into the 3 elbow flexors (biceps, brachialis, and brachioradialis) of the left arm. On [redacted], 49 days after the administration of BOTOX 6 U/kg, the participant experienced a nonserious adverse event of constipation of mild severity. Treatment included glycerin enema, Medilac-S, mosapride citrate, and macrogol. The constipation resolved on [redacted]. The investigator assessed the events of constipation and fecaloma as not related to the study.

6. **Participant** [redacted] was a 4-year-old white girl with hemiplegic spasticity from stroke of the left arm and leg since [redacted] Also, the participant had constipation. On [redacted], 59 days after administration of BOTOX 6 U/kg, the participant experienced a nonserious adverse event of worsening of constipation of moderate intensity. The child was taken to the emergency room with abdominal pain, and was diagnosed with constipation. No new treatment was given and she was sent home. The investigator assessed the event of constipation as not related to the study treatment. The constipation resolved without sequelae on [redacted]

REVIEWER COMMENT:

Narratives 2-4 are likely unrelated to spread of toxin, a known adverse effect of botulinum toxins. In narrative 1, the subject was injected on the left side for spastic hemiplegia and developed mild weakness on the right side. Narratives 5 and 6 describe adverse events of isolated constipation, which do not appear to be drug related.

LL Spasticity

A total of 2 patients experienced adverse events related to PDSOT DBPC study, 191622-111; 1 in the 8 U/kg cohort and 1 in the placebo cohort.

Table 27 Number (%) of Participants Reporting Possible Distant Spread of Toxin Events by Treatment Group (Safety Population)

	BOTOX			
SOC/ Preferred Term	*8 U/kg (N = 128) n (%)*	*4 U/kg (N = 126) n (%)*	*Total (N = 254) n (%)*	*Placebo (N = 128) n (%)*
Overall	1 (0.8)	0	1 (0.4)	1 (0.8)
Gastrointestinal disorders				
Constipation	1 (0.8)	0	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	0	0	0	1 (0.8)

SOC = system organ class

Source: Table 14.3-7

Source: Applicant

- **Participant** (b) (6) was a 2-year-old Asian girl who entered the study with hemiplegia from cerebral palsy. The participant was randomized to receive a single dose of BOTOX 8 U/kg (104 U) into the right lower limb, plus standardized PT. On (b) (6) the participant received injections of 8 U/kg of BOTOX into the 3 ankle plantar flexors (gastrocnemius, soleus, and tibialis posterior) of the right leg. On (b) (6), 90 days after administration of BOTOX 8 U/kg, the participant experienced a nonserious adverse event of constipation of mild intensity that was ongoing. The participant was treated with lactulose, magnesium hydroxide, and glycerol suppository for the constipation and the participant completed the study on (b) (6). The investigator assessed the event as not related to the study treatment.

REVIEWER COMMENT:

The subject experienced constipation 90 days after receiving injections with study drug; this appears to be unrelated to study drug.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Double Blind Placebo Controlled Studies

The common adverse events (≥2%) for pediatric UL spasticity are presented in Table 28.

UL Spasticity Study 191622-101

Table 28 Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Pediatric Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trial

Adverse Reactions	BOTOX 3 Units/kg (N=78) %	BOTOX 6 Units/kg (N=77) %	Placebo (N=79) %
Infections and infestations			
Upper respiratory tract infection[1]	10	17	9
Rhinitis	4	0	1
General disorders and administration site conditions			
Injection site pain	3	4	1
Gastrointestinal disorders			
Constipation	0	3	1
Diarrhea	4	0	1
Nausea	0	4	0
Musculoskeletal and connective tissue disorders			
Muscular weakness	4	1	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	0	4	1
Nervous system disorders			
Seizure[2]	1	5	0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion	0	3	1
Injury, poisoning and procedural complications			
Ligament sprain	3	0	1

Source: FDA

REVIEWER COMMENT:

The most common adverse event across all treatment groups was upper respiratory tract infection, which was slightly higher in 8 U/kg cohort compared to 4 U/kg and placebo cohorts.

The common adverse events (≥2%) for pediatric LL spasticity are presented in Table 29.

LL spasticity Study 191622-111

Table 29 Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Pediatric Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial

Adverse Reactions	BOTOX 4 Units/kg N=126 %	BOTOX 8 Units/kg N=128 %	Placebo N=128 %
Infections and infestations			
Upper respiratory tract infection	8	6	7
Tonsillitis	2	2	1
Varicella	0	2	0
Pharyngitis	4	1	0
General disorders and administration site conditions	6	4	5
Pyrexia	0	2	0
Injection site erythema	2	2	0
Injection site pain			
Respiratory, thoracic and mediastinal disorders			
Cough	5	3	2
Oropharyngeal pain	0	2	1
Gastrointestinal disorders			
Dental caries	0	2	1
Diarrhea	3	1	2
Injury, poisoning and procedural complications			
Ligament sprain	1	2	0
Skin abrasion	0	2	0
Metabolism and nutrition disorders			
Decreased appetite	0	2	0

Source: FDA

REVIEWER COMMENT:

Upper respiratory tract infection was the most common TEAE in across all treatment groups.

In comparison, the most common TEAEs in **ADULT** UL and LL spasticity from the BOTOX label are presented in the tables below:

Table 30 Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by System Organ Class	BOTOX 251 Units-360 Units (N=115)	BOTOX 150 Units-250 Units (N=188)	BOTOX <150 Units (N=54)	Placebo (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)

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

Source: BOTOX label, 5/2018

Table 31 Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 6)

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

Source: BOTOX label, 5/2018

REVIEWER COMMENT:

The most common TEAEs in UL and LL spasticity in adults, musculoskeletal, infections, gastrointestinal and general disorders, are similar to those seen in the pediatric patients with UL and LL spasticity treated with BOTOX.

7.4.2 Laboratory Findings

There were no cases of Hy's Law during the DBPC studies, 191622-101 and 191622-111.

The Applicant evaluated indicators of bone metabolism, blood glucose, calcium, 25-hydroxylvitamin D, HbA1c, alkaline phosphatase, alkaline phosphatase-bone fraction, during the study.

UL Spasticity

A table of mean change in laboratory indicators for bone metabolism (glucose, calcium, 25-hydroxylvitamin D, hemoglobin A1c, alkaline phosphatase, bone-specific alkaline phosphatase**)** in pediatric patients with UL spasticity is summarized in the table below.

Table 32 Summary of Change from Baseline in Laboratory Indicators of Bone Metabolism (Safety Population)

		BOTOX		
Visit	***Statistic***	***6 U/kg (N = 77)***	***3 U/kg (N = 78)***	***Placebo (N = 79)***
Blood Glucose (mmol/L)				
Baseline	n	77	77	77
	Mean	5.02	5.02	5.03
Week 12	n	70	67	75
	Mean	5.01	5.07	5.01
Change from Baseline	n	70	66	73
	Mean	0.01	0.09	-0.04
Calcium (mmol/L)				
Baseline	n	77	77	77
	Mean	2.465	2.475	2.459
Week 12	n	70	68	75
	Mean	2.466	2.444	2.447
Change from Baseline	n	70	67	73
	Mean	0.001	-0.019	-0.004
25- Hydroxylvitamin D (nmol/L)				
Baseline	n	76	78	77
	Mean	53.4	51.8	61.0
Week 12	n	68	68	72
	Mean	54.3	53.7	58.5
Change from Baseline	n	67	68	70
	Mean	1.2	1.4	-1.5
Hemoglobin A1c (%)				
Baseline	n	76	77	77
	Mean	5.13	5.17	5.12
Week 12	n	70	70	74
	Mean	5.13	5.17	5.15
Change from Baseline	n	69	69	72
	Mean	-0.01	-0.00	0.04
Alkaline Phosphatase (U/L)				
Baseline	n	77	76	77
	Mean	226.2	202.4	211.4
Week 12	n	67	67	73
	Mean	220.9	199.1	212.4
Change from Baseline	n	67	66	71
	Mean	-4.0	4.2	-3.2
Bone-specific Alkaline Phosphatase (U/L)				
Baseline	n	77	76	77
	Mean	150.3	135.0	138.5
Week 12	n	67	67	73
	Mean	148.0	132.2	139.7

Change from Baseline	n	67	66	71
	Mean	-1.5	3.0	-1.6

Source: Applicant

REVIEWER COMMENT:

There were minimal changes in laboratory values (1-2%) from baseline to Week 12.

LL Spasticity

A table of mean change in laboratory indicators for bone metabolism (glucose, calcium, 25-hydroxylvitamin D, hemoglobin A1c, alkaline phosphatase, bone-specific alkaline phosphatase) in pediatric patients with LL spasticity is summarized in the table below.

Table 33 Summary of Change from Baseline in Laboratory Indicators of Bone Metabolism (Safety Population)

		BOTOX		
Visit	*Statistic*	*8 U/kg (N = 128)*	*4 U/kg (N = 126)*	*Placebo (N = 128)*
Blood Glucose (mmol/L)				
Baseline	n	126	122	128
	Mean	4.98	5.01	5.00
Week 12	n	117	115	121
	Mean	5.02	5.00	5.07
Change from Baseline	n	117	113	121
	Mean	0.04	0.01	0.07
Calcium (mmol/L)				
Baseline	n	127	123	129
	Mean	2.485	2.484	2.468
Week 12	n	119	118	122
	Mean	2.476	2.473	2.477
Change from Baseline	n	119	117	122
	Mean	-0.010	-0.014	0.012
25- Hydroxyl Vitamin D (nmol/L)				
Baseline	n	125	123	127
	Mean	54.6	58.2	57.2
Week 12	n	117	115	123
	Mean	52.5	57.4	55.7
Change from Baseline	n	115	114	122
	Mean	-0.8	-1.3	-1.3
Hemoglobin A1c (%)				
Baseline	n	126	122	126
	Mean	5.14	5.10	5.16
Week 12	n	114	117	119
	Mean	5.14	5.15	5.18
Change from Baseline	n	114	115	117
	Mean	-0.00	0.05	0.02
Alkaline Phosphatase (U/L)				
Baseline	n	121	121	124

	Mean	222.9	226.8	224.4
Week 12	n	116	111	120
	Mean	225.5	216.6	250.1
Change from Baseline	n	112	108	116
	Mean	0.2	-10.5	26.0
Bone-specific Alkaline Phosphatase (U/L)				
Baseline	n	120	121	124
	Mean	150.1	149.0	149.3
Week 12	n	116	111	119
	Mean	148.5	144.1	168.5
Change from Baseline	n	111	108	115
	Mean	-2.6	-4.0	19.2

Source: Applicant

REVIEWER COMMENT:

Mean values for these endpoints were similar in all treatment groups at baseline, and mean changes to Week 12 were minimal and showed no drug-related changes, with the exception of AP-bone fraction, which showed a slight decrease from baseline in the BOTOX groups and an increase in the placebo group.

7.4.3 Vital Signs

There were no significant changes in vital signs in any of the cohorts for patients with UL or LL spasticity.

7.4.4 Electrocardiograms (ECGs)

ECGs were obtained only at Baseline in the DBPC studies.

7.4.6 Immunogenicity

In the current submission for pediatric patients with spasticity, Study 191622-111 is the only study that provides relevant immunogenicity data for the current BOTOX drug product.

In Study 191622-111, blood serum samples were collected at baseline and Week 12/exit visit. Results for serum binding anti-BOTOX antibodies were reported as negative, positive, or inconclusive for each participant. Samples that were confirmed positive for binding were subsequently tested for neutralizing anti-BOTOX antibodies using a mouse protection assay. A total of 7 patients across the 2 BOTOX groups (4 U/kg and 8 U/kg) were positive for binding anti-BOTOX antibodies during the study. Of these, 1 patient in the BOTOX 8 U/kg group was negative for neutralizing anti-BOTOX antibodies at baseline and positive Week 12 (Table 34.)

Table 34 Summary of Toxin-Binding Antibody Safety Population

Visit	Assay Result	BTX 8U/kg		BTX 4U/kg		Placebo		Total	
Screeni	N	9		9		9		28	
	Negative	8	(94.6%)	9	(100.0%)	9	(94.7%)	27	(96.5%)
	Positive	4	(4.3%)	0	(0.0%)	4	(4.2%)	8	(2.8%)
	Inconclu	1	(1.1%)	0	(0.0%)	1	(1.1%)	2	(0.7%)
Week 12	N	9		9		9		28	
	Negative	9	(95.8%)	9	(98.9%)	8	(92.6%)	27	(95.8%)
	Positive	4	(4.2%)	1	(1.1%)	7	(7.4%)	1	(4.2%)

Source: Applicant

REVIEWER COMMENT:

A total of 7 participants across the 2 BOTOX groups were positive for binding antibodies (BABs) during the study: 6.3% (6/95) and 1.1% (1/95) of participants in the BOTOX 8 and 4 U/kg groups, respectively. Of the 6 BAB-positive participants in the BOTOX 8 U/kg group, 4 participants were positive for BABs at screening; 3 of these were confirmed to have had previous exposure to botulinum toxin and 1 did not. Of these 4 participants that were positive for BABs at screening, 2 were also positive for BABs at Week 12, one participant was negative for BABs at Week 12, and the

Week 12 sample from 1 participant was not collected. An additional 2 participants in the BOTOX 8 U/kg group were positive for BABs at Week 12 only. One participant in the BOTOX 4 U/kg group was negative for BABs at screening but positive at Week 12 with a titer of 5.

The Applicant reviewed the ISS safety database for AEs coding to the MedDRA PTs of antibody test positive, antinuclear antibody positive, drug resistance, and neutralizing antibodies positiveNone of these AEs was identified in the ISS safety database.

Hypersensitivity Reactions

BOTOX is a biological product comprised of an exogenous protein derived from the Clostridium botulinum bacteria, along with [redacted] (b) (4) human albumin, and thus has the potential to elicit hypersensitivity type reactions in humans.

The ISS safety database was reviewed by the Applicant, for the 11AEs coding to the MedDRA PTs for hypersensitivity. During DBPC exposure in the Overall Safety Population (UL and LL spasticity), the following PTs potentially indicating hypersensitivity were identified: drug eruption (n = 1, in the All BOTOX group) and hypersensitivity (n = 2; 1 in the All BOTOX group, 1 in the placebo group). Both events in the All BOTOX group occurred in the low dose cohort.

The approved Botox label includes a statement in Warnings and Precautions describing hypersensitivity reactions with the use of Botox.

7.5.3 Drug-Demographic Interactions

Age

UL Spasticity

TEAEs by age group, ≤ 6 years old, >6 years old with UL spasticity are presented in Table 35.

Table 35 Study 101 Treatment Emergent Adverse Reactions by Age, ≤ 6-years-old group (≥2%) and > 6 (Safety Population)

AEBODSYS	AEDECOD	Total Botox <=6 N=102 %	Total Botox >6 N=132 %
Infections and infestations	Upper respiratory tract infection	6	4
	Viral upper respiratory tract infection	5	4
Gastrointestinal disorders	Vomiting	4	1
General disorders and administration site conditions	Pyrexia	3	2
Gastrointestinal disorders	Diarrhea	3	0
	Constipation	2	0
Nervous system disorders	Seizure	2	1
Respiratory, thoracic and mediastinal disorders	Cough	2	1
	Rhinorrhea	2	1
Injury, poisoning and procedural complications	Head injury	2	0
Infections and infestations	Rhinitis	2	1

Source:FDA

REVIEWER COMMENT:
Gastrointestinal disorders (diarrhea, vomiting and constipation) were more common in ≤6 year old group compared to >6 year old group. Rates of infection (upper respiratory infection) were similar for both age groups.

LL Spasticity

TEAEs by age group, ≤ 6 years old, >6 years old with LL spasticity are presented in Table 36.

Table 36 Study 111 Treatment Emergent Adverse Reactions by Age, ≤ 6-years-old group (≥2%)and > 6

AEBODSYS	AEDECOD	Botox 8U/kg =< 6	Botox 8U/kg >6	Botox 4U/kg =<6	Botox 4 U/kg >6	Placebo =<6	Placebo >6
		N=74 %	N=54 %	N=73 %	N=53 %	N 74 %	N= 54 %
Infections and infestations	Viral upper respiratory tract infection	14	4	16	4	18	17
General disorders and administration site conditions	Pyrexia	7	0	10	2	5	6
Infections and infestations	Upper respiratory tract infection	7	6	11	4	9	4
	Rhinitis	4	0	1	0	0	6
	Tonsillitis	4	0	3	0	0	2
General disorders and administration site conditions	Injection site erythema	3	0	0	0	0	0
Infections and infestations	Bronchitis	3	2	4	0	4	2
	Sinusitis	3	2	0	0	1	2
	Varicella	3	0	0	0	0	0
Nervous system disorders	Seizure	3	2	1	0	3	0
Respiratory, thoracic and mediastinal disorders	Cough	3	4	5	4	3	2
Gastrointestinal disorders	Diarrhoea	1	0	3	4	3	0
General disorders and administration site conditions	Injection site pain	1	4	1	2	0	0
Infections and infestations	Ear infection	1	0	1	0	1	2
	Gastroenteritis	1	0	0	2	1	2
	Pharyngitis	1	0	3	6	0	0
Blood and lymphatic system disorders	Lymphadenopathy	0	0	0	2	0	0

Ear and labyrinth disorders	Middle ear inflammation	0	0	0	2	0	0
Gastrointestinal disorders	Abdominal discomfort	0	2	0	0	0	2
	Abdominal pain	0	0	1	0	5	0
	Abdominal pain upper	0	0	0	2	0	0
	Dental caries	0	4	0	0	0	2
	Enteritis	0	0	0	0	0	2
	Flatulence	0	2	1	0	0	0
	Gastritis	0	2	0	0	0	0
	Nausea	0	0	1	0	0	2
	Vomiting	0	2	1	2	4	2
General disorders and administration site conditions	Fatigue	0	0	0	2	0	0
	Gait disturbance	0	2	0	0	0	0
	Injection site discomfort	0	2	0	0	0	0
Immune system disorders	Hypersensitivity	0	0	0	0	0	2
Infections and infestations	Conjunctivitis	0	2	0	0	1	2
	Cystitis	0	0	0	0	0	2
	Gastroenteritis viral	0	2	0	0	0	0
	Influenza	0	0	0	0	0	2
	Nasopharyngitis	0	0	0	2	0	2
	Pharyngitis bacterial	0	2	0	0	0	0
	Scarlet fever	0	0	0	0	0	2
	Viral infection	0	0	0	2	0	0
Injury, poisoning and procedural complications	Contusion	0	2	0	0	1	0
	Fall	0	2	0	0	0	0
	Laceration	0	2	0	0	0	0
	Ligament sprain	0	4	0	2	0	0
	Radius fracture	0	0	0	2	0	0
	Road traffic accident	0	2	0	0	0	0
	Skin abrasion	0	4	0	0	0	0
Metabolism and nutrition disorders	Decreased appetite	0	4	0	0	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	0	2	0	0	0	0
	Groin pain	0	0	0	2	0	0
	Myalgia	0	2	0	0	1	0

	Pain in extremity	0	6	1	4	3	2
Nervous system disorders	Clonus	0	0	0	2	0	0
	Headache	0	4	0	2	0	6
	Migraine	0	0	0	2	0	0
	Radicular pain	0	0	0	0	0	2
	Tremor	0	0	0	0	0	2
Psychiatric disorders	Anxiety	0	0	0	2	0	0
	Irritability	0	2	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Dysphonia	0	0	0	0	0	2
	Oropharyngeal pain	0	6	0	0	0	2
	Rhinitis allergic	0	2	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	0	2	3	0	4	4
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract inflammation	0	2	0	0	0	0
Skin and subcutaneous tissue disorders	Dermatitis	0	0	0	0	0	2
Skin and subcutaneous tissue disorders	In growing nail	0	2	0	0	0	0
Skin and subcutaneous tissue disorders	Onychoclasis	0	2	0	0	0	0
Skin and subcutaneous tissue disorders	Rash	0	2	1	0	1	0
Skin and subcutaneous tissue disorders	Urticaria	0	0	0	0	0	2

Source: FDA

REVIEWER COMMENT:

Adverse events of infections, specifically upper respiratory infections, were greater in the < 6 years old population compared to the >6 years old population in 4 U/kg and 8 U/kg cohorts. The rates were similar for both age groups in the placebo cohort.

Gender

TEAEs by gender are presented in the tables below for UL and LL spasticity in the pediatric population.

UL spasticity

Table 37 Study 101 Treatment Emergent Adverse Reactions ≥ 2% Botox Greater in Females and Greater than Placebo

AEBODSYS	AEDECOD	All Female Botox %	All Male Botox %	All Female Placebo %	All Male Placebo %
Infections and infestations	Viral upper respiratory tract infection	10	7	9	4
Respiratory, thoracic and mediastinal disorders	Rhinorrhea	10	0	3	0
Gastrointestinal disorders	Vomiting	6	2	3	4
Infections and infestations	Upper respiratory tract infection	3	7	3	2
Musculoskeletal and connective tissue disorders	Muscular weakness	3	1	0	2
Infections and infestations	Bronchitis	3	1	0	2
Gastrointestinal disorders	Nausea	3	2	0	0
Musculoskeletal and connective tissue disorders	Joint range of motion decreased	3	0	0	0
Nervous system disorders	Seizure	3	2	0	0
Nervous system disorders	Partial seizures	3	1	0	0
Immune system disorders	Seasonal allergy	3	0	0	2

Source: FDA

Lower Limb Spasticity

Table 38 Study 111 Treatment Emergent Adverse Reactions ≥ 2% Botox Greater in Females and Greater than Placebo

		All Female Botox N=115 (%)	All Male Botox N=138 (%)	Placebo Female N=60 (%)	Placebo Male N=68 (%)
AESOC	AEDECOD				
Infections and infestations	Viral upper respiratory tract infection	25	16	20	15
General disorders and administration site conditions	Pyrexia	8	12	5	6
Infections and infestations	Upper respiratory tract infection	8	19	10	4
Musculoskeletal and connective tissue disorders	Pain in extremity	7	3	0	4
Respiratory, thoracic and	Cough	7	9	2	3

mediastinal disorders					
General disorders and administration site conditions	Injection site pain	5	3	0	0
Infections and infestations	Pharyngitis	5	4	0	0
Gastrointestinal disorders	Diarrhoea	3	4	3	0
General disorders and administration site conditions	Injection site erythema	3	0	0	0
	Bronchitis	3	6	3	3
	Tonsillitis	3	4	2	0
Injury, poisoning and procedural complications	Skin abrasion	3	0	0	0
Nervous system disorders	Seizure	3	3	2	1
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	3	1	0	1
Blood and lymphatic system disorders	Lymphadenopathy	2	0	0	0
	Lymphopenia	2	0	0	0
	Thrombocytosis	2	0	0	0
Ear and labyrinth disorders	Middle ear inflammation	2	0	0	0
Eye disorders	Eye pruritus	2	0	0	0
Gastrointestinal disorders	Abdominal pain	2	0	2	4
	Constipation	2	0	0	0
	Flatulence	2	1	0	0
	Vomiting	2	3	5	1
General disorders and administration site conditions	Gait disturbance	2	0	0	0
	Injection site discomfort	2	0	0	0
	Peripheral swelling	2	0	0	0
Infections and infestations	Conjunctivitis	2	0	2	1
	Croup infectious	2	0	0	0
	Ear infection	2	1	0	3
	Gastroenteritis	2	1	2	1
	Gastroenteritis viral	2	0	0	0
	Hordeolum	2	0	0	0
	Nasopharyngitis	2	0	0	1
	Otitis media acute	2	0	0	0

	Rhinitis	2	4	0	4
	Sinusitis	2	3	0	3
	Varicella	2	1	0	0
	Viral infection	2	0	0	0
Injury, poisoning and procedural complications	Contusion	2	0	0	1
	Laceration	2	0	0	0
	Ligament sprain	2	3	0	0
	Procedural pain	2	0	0	0
	Radius fracture	2	0	0	0
	Road traffic accident	2	0	0	0
Metabolism and nutrition disorders	Decreased appetite	2	1	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	2	0	0	0
	Groin pain	2	0	0	0
	Muscle spasms	2	1	0	0
Nervous system disorders	Clonus	2	0	0	0
	Drooling	2	0	0	0
	Migraine	2	0	0	0
Psychiatric disorders	Irritability	2	0	0	0
Respiratory, thoracic and mediastinal disorders	Tonsillar hypertrophy	2	0	0	0
	Wheezing	2	0	0	0
Skin and subcutaneous tissue disorders	Acne	2	0	0	0
	Rash	2	1	2	0

Source: FDA

REVIEWER COMMENT:

Viral respiratory infections were slightly higher for females compared to males for BOTOX and placebo groups, while upper respiratory infections and pyrexia were higher for males in the BOTOX group.

RACE

Treatment emergent adverse events by race for UL and LL spasticity in the pediatric population, are presented in the tables below.

UL Spasticity

Table 39 Study 101 Treatment Emergent Adverse Reactions ≥ 4% by Racial Group and Dose

AESOC	AEDECOD	BOTOX 3U/kg + OT, Caucasian N=42 %	BOTOX 3U/kg + OT, Non-Caucasian N=36 %	BOTOX 6U/kg + OT, Caucasian N=51 %	BOTOX 6U/kg + OT, Non-Caucasian N=26 %	Placebo + OT, Caucasian N=51 %	Placebo + OT, Non-Caucasian N=28 %
Infections and infestations	Viral upper respiratory tract infection	7	3	4	15	2	14
Infections and infestations	Upper respiratory tract infection	7	3	4	19	0	7
Infections and infestations	Rhinitis	7	0	0	0	2	0
Infections and infestations	Hand-foot-and-mouth disease	0	0	0	4	0	0
Infections and infestations	Herpangina	0	0	0	4	0	0
Infections and infestations	Nasopharyngitis	0	0	0	4	0	0
Infections and infestations	Otitis media	0	0	0	4	0	0
Infections and infestations	Sinusitis	0	0	0	4	0	0
Infections and infestations	Urinary tract infection	0	0	0	4	0	0
Gastrointestinal disorders	Vomiting	2	3	6	0	4	4
Gastrointestinal disorders	Diarrhoea	7	0	0	0	0	4
Gastrointestinal disorders	Constipation	0	0	2	4	0	4
Gastrointestinal disorders	Nausea	0	0	4	4	0	0
Gastrointestinal disorders	Anal incontinence	0	0	0	4	0	0
Gastrointestinal disorders	Dental caries	0	0	0	4	0	0
Gastrointestinal disorders	Fecaloma	0	0	0	4	0	0
General disorders and administration site conditions	Pyrexia	7	0	2	8	2	14
General disorders and	Injection site pain	2	3	6	0	0	4

administration site conditions							
General disorders and administration site conditions	Asthenia	0	3	0	4	0	0
General disorders and administration site conditions	Fatigue	0	3	0	4	0	0
General disorders and administration site conditions	Feeling hot	0	0	0	4	0	0
General disorders and administration site conditions	Medical device pain	0	0	0	4	0	0
Musculoskeletal and connective tissue disorders	Pain in extremity	2	0	0	8	6	4
Musculoskeletal and connective tissue disorders	Muscular weakness	2	6	2	0	2	0
Injury, poisoning and procedural complications	Ligament sprain	5	0	0	0	2	0
Injury, poisoning and procedural complications	Skin abrasion	2	0	0	4	0	4
Injury, poisoning and procedural complications	Fall	0	0	0	4	2	0
Injury, poisoning and procedural complications	Concussion	0	0	0	4	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	0	4	0	2	7
Respiratory, thoracic and mediastinal disorders	Rhinorrhea	0	0	6	0	0	4
Respiratory, thoracic and	Nasal congestion	0	0	0	8	0	4

mediastinal disorders							
Respiratory, thoracic and mediastinal disorders	Productive cough	0	0	0	4	0	0
Nervous system disorders	Headache	5	0	2	0	4	7
Nervous system disorders	Seizure	0	3	2	4	0	0
Nervous system disorders	Partial seizures	0	0	4	0	0	0
Nervous system disorders	Balance disorder	0	0	0	4	0	0
Renal and urinary disorders	Pollakiuria	0	0	0	4	0	0
Vascular disorders	Haematoma	0	0	0	4	0	0

LL Spasticity

Table 40 Study 111 Adverse reactions by race and dose ≥ 4% in Botox

AESOC	AEDECOD	BOTOX 4U/kg + PT, Caucasian N=77 %	BOTOX 4U/kg + PT, Non-Caucasian N=49 %	BOTOX 8U/kg + PT, Caucasian N=77 %	BOTOX 8U/kg + PT, Non-Caucasian N=51 %	Placebo + PT, Caucasian N=78 %	Placebo + PT, Non-Caucasian N=50 %
Infections and infestations	Viral upper respiratory tract infection	9	14	8	12	13	24
Infections and infestations	Upper respiratory tract infection	10	4	6	6	8	6
Nervous system disorders	Seizure	0	2	0	6	1	2
General disorders and administration site conditions	Pyrexia	5	8	4	4	5	6

Gastrointestinal disorders	Diarrhoea	4	2	0	2	3	0
General disorders and administration site conditions	Injection site pain	3	0	4	0	0	0
Infections and infestations	Bronchitis	3	2	4	0	5	0
Infections and infestations	Pharyngitis	6	0	1	0	0	0
Infections and infestations	Rhinitis	1	0	4	0	3	2
Musculoskeletal and connective tissue disorders	Pain in extremity	4	0	4	0	0	6
Respiratory, thoracic and mediastinal disorders	Cough	8	0	5	0	3	2
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	0	0	4	0	1	0

REVIEWER COMMENT:

Viral upper respiratory tract infections are more common in non-Caucasian patients for 6 U/kg and placebo cohorts for UL spasticity. Similarly, viral upper respiratory tract infections are higher for non-Caucasians for the 8 U/kg and placebo groups for LL spasticity.

7.5.4 Drug-Disease Interactions

Epilepsy

A summary of patients who experienced a seizure in double blind placebo-controlled trials is summarized below.

Table 41 Summary of DBPC Seizure Events by Patient

Patient ID	Tx Group	Age/Sex/Race/Wt/Ht	TEAE Seizure Severity	Onset Day	Prior/Con Seizure Meds
Subjects with a reported medical history of seizure					

(b) (6)	Placebo	4/F/C/13.0/95/0	Moderate	107	Con
	4 U/kg	3/F/B/14.0/95.0	Serious	**2**, 77	P/Con
	4 U/kg	3/F/B/16.0/100.0	Mild	63, 110	P/Con
	3 U/kg	2/F/W/15.0/92.8	Mild	29	--
	6 U/kg	13/M/W/51.0/152.0	Mild	88	P/Con
	6 U/kg	4/M/A/16.0/100.1	Mild	80	P/Con
	6 U/kg	4/F/W/16.0/99.5	Mild	75	Con
	8 U/kg	5/F/W/20.0/117.9	Severe	271, 280	P/Con
	Placebo	2/F/W/14.0/102.0	Mild	83	Con
	8 U/kg	4/M/A/18.3/103.5	Moderate	21, 92	P/Con
	8 U/kg	9/M/A/32.0/126.6	Moderate	63	Con
	8 U/kg	2/F/A/10.8/82.3	Moderate	44, 106, 165	P/Con
	4 U/kg	3/F/A/16.8/101.0	Mild	82	P/Con
	Placebo	8/M/C/45.0/--	Moderate	**5**, 47, 55	UNK
Subjects without reported medical history of seizure					
(b) (6)	4 U/kg	7/F/C/25.0/--	Mild	**5**	UNK
	3 U/kg	11/M/A/48.0/152.9	Mild	25	--
	3 U/kg	8/M/A/29.1/125.0	Moderate	109	--
	Placebo	2/M/A/13.6/88.1	Severe	65	Con

DBPC Exposure - Overall Safety Population included all treated patients from studies 191622-101, 191622-111, (b) (4) and 191622-021. F = female; M = male; C = Caucasian; W = white; B = black; A = Asian; Wt = weight; Ht = height; p = prior use of seizure mediation reported; Con = concomitant use of seizure medication reported; -- = no reported use of prior or concomitant seizure medications; UNK = unknown.

[a] Onset technically outside the duration of the DBPC study: seizure included as DBPC analysis because while the patient rolled over into the extension study, they had not received retreatment in the OL phase yet.

Source: Listings 3-1 and Listing 4-1. Prior and concomitant medications obtained from individual CSRs, 191622-101 CSR, Listing 16.2.4.2, 191622-111 CSR, Listing 16.2.4.2, 191622-021, Listing 16.2.9-4.

Source: Applicant

REVIEWER COMMENT:

There were two subjects enrolled in double blind placebo-controlled trial for UL spasticity, (b) (6), who experienced a seizure after receiving 3 U/kg BOTOX, who had no history of seizures. One subject enrolled in double blind placebo-controlled trial for LL spasticity, (b) (6), who experienced a seizure after receiving placebo.

7.6.3 Pediatrics and Assessment of Effects on Growth

Nonclinical juvenile rat toxicology studies found microstructure bone changes after bi-weekly BOTOX injections at ≥ 56 U/kg over 12 weeks. The doses were well above those used in the pediatric patient population and were accompanied by muscle atrophy and limb disuse as well as overall weight loss in animals treated with BOTOX

compared to control animals. There were no AEs in any of the clinical studies submitted that are suggestive of bone-related pathology and clinical bone-related laboratory tests, and physical examination results were normal over ~ 60 weeks of continuous BOTOX treatment for spasticity in cerebral palsy children.

7.7 Additional Submissions / Safety Issues

120-Day SAFETY UPDATE

Safety data from open label extension studies, 191622-105 (UL) and 191622-112 (LL) were included in the original submission with data cut off of May 21, 2018. All patients had been enrolled but 69 patients were still ongoing. Since the initial submission, these 69 patients have completed the open label studies and form the basis of the 120-day Safety Update.

EXPOSURE

Updated exposure for patients with pediatric UL spasticity treated with BOTOX is presented in Table 42.

Table 42 Number of Patients with the Maximum Number of BOTOX Treatment Cycles Given at Consecutive 10- to 14-week Re-treatment Intervals: Any BOTOX Exposure in Upper Limb (Overall Safety Population)

BOTOX Treatment Cycles	Upper Limb BOTOX Dose		
	≥ 3 U/kg (or 100 U) N = 306	≥ 6 U/kg (or 200 U) N = 175	All BOTOX N = 355
Within 28 Weeks			
1	131 (42.8%)	109 (62.3%)	~~127 (35.8%)~~ **126 (35.5%)**
≥ 2 (within 10-14 weeks)	175 (57.2%)	66 (37.7%)	~~228 (64.2%)~~ **229 (64.5%)**
≥ 2	209 (68.3%)	77 (44.0%)	271 (76.3%)
Within 56 Weeks			
1	131 (42.8%)	109 (62.3%)	~~127 (35.8%)~~ **126 (35.5%)**
2 (within 10-14 weeks)	~~60 (19.6%)~~ **59 (19.3%)**	25 (14.3%)	~~63 (17.7%)~~ **62 (17.5%)**
3 (within 10-14 weeks)	~~36 (11.8%)~~ **37 (12.1%)**	17 (9.7%)	~~53 (14.9%)~~ **55 (15.5%)**
≥ 4 (within 10-14 weeks)	79 (25.8%)	24 (13.7%)	112 (31.5%)
2	~~62 (20.3%)~~ **61 (19.9%)**	24 (13.7%)	~~61 (17.2%)~~ **60 (16.9%)**
3	~~53 (17.3%)~~ **52 (17.0%)**	24 (13.7%)	~~64 (18.0%)~~ **62 (17.5%)**
≥ 4	~~111 (36.3%)~~ **113 (36.9%)**	34 (19.4%)	~~166 (46.8%)~~ **169 (47.6%)**

Source: Applicant

Updated exposure for patients with pediatric LL spasticity treated with BOTOX is presented in Table 43.

Table 43 Number of Patients with the Maximum Number of BOTOX Treatment Cycles Given at Consecutive 10- to 14-week Re-treatment Intervals: Any BOTOX Exposure in Lower Limb (Overall Safety Population)

BOTOX Treatment Cycles	Lower Limb BOTOX Dose		
	≥ 4 U/kg (or 150 U) N = ~~848~~ **849**	≥ 8 U/kg (or 300 U) N = 359	All BOTOX N = 868
Within 28 Weeks			
1	~~260~~ **261** (30.7%)	~~207 (57.7%)~~ **206 (57.4%)**	~~249 (28.7%)~~ **248 (28.6%)**
≥ 2 (within 10-14 weeks)	588 (69.3%)	~~152 (42.3%)~~ **153 (42.6%)**	~~619 (71.3%)~~ **620 (71.4%)**
Within 56 Weeks			
1	~~260~~ **261** (30.7%)	~~207 (57.7%)~~ **206 (57.4%)**	~~249 (28.7%)~~ **248 (28.6%)**
2 (within 10-14 weeks)	183 (21.6%)	~~66 (18.4%)~~ **67 (18.7%)**	~~184 (21.2%)~~ **185 (21.3%)**
3 (within 10-14 weeks)	~~139 (16.4%)~~ **138 (16.3%)**	~~23 (6.4%)~~ **21 (5.8%)**	~~140 (16.1%)~~ **139 (16.0%)**
≥ 4 (within 10-14 weeks)	~~266~~ **267** (31.4%)	~~63 (17.5%)~~ **65 (18.1%)**	~~295 (34.0%)~~ **296 (34.1%)**

Source: Applicant

REVIEWER COMMENT:

The number of subjects exposed for 4 consecutive injection cycles (within 10-14 weeks) remains the same for UL spasticity, and increased by 1 patient in the 4 U/kg cohort and 2 patients in the 8 U/kg cohort for patients with LL spasticity.

During open label extension studies, subjects were allowed to increase the total dose of BOTOX received (UL and LL) to 10 U/kg or 340 U. A summary of subjects exposed to ≥ 8 U/kg and 10 U/kg to the cutoff date for the 120-day update is presented in Table 44.

Table 44 Patient Exposure by Number of Treatments Received: Any BOTOX Exposure (Overall Safety Population) to 120-day cutoff date

No. of Treatments Received	Number of Patients (%)		
	≥ 8 U/kg (or 300 U) N = 504	10 U/kg (or 340 U) N = ~~166~~ **167**	All BOTOX N = 933
At least 1	504 (100.0%)	~~166~~ **167** (100.0%)	933 (100.0%)
At least 2	~~354 (70.2%)~~ **355 (70.4%)**	123 (~~74.1~~ **73.7**%)	797 (85.4%)
At least 3	270 (53.6%)	~~82 (49.4%)~~ **84 (50.3%)**	~~715 (76.6%)~~ **716 (76.7%)**
At least 4	~~209 (41.5%)~~ **213 (42.3%)**	35 (~~21.1~~ **21.0**%)	~~622 (66.7%)~~ **623 (66.8%)**
At least 5	~~116 (23.0%)~~ **120 (23.8%)**	0[a]	~~439 (47.1%)~~ **446 (47.8%)**

Studies included 191622-101, 191622-105, 191622-111, 191622-112, (b) (4) BTOX 121-8051, and 191622-021.

[a] 5 treatments were not possible within the constraints of the recent open label study design. Source: Module 5.3.5.3, 120-day Update Table 2-2.1.1 and Table 2-2.1.2

Source: Applicant

REVIEWER COMMENT:

167 subjects received at least one treatment of BOTOX 10 U/kg and 35 subjects received at least 4 treatments of BOTOX 10 U/kg.

There were no new deaths in the 120-day Safety Update.

SAEs

SAEs for open label studies for UL spasticity, 191622-105, and LL spasticity, 191622-112, are presented in Table 45. Note: The incidence of events were ≤ 1%.

Table 45 Serious Adverse Events Open Label Studies 191622-105 (UL) and 191622-112 (LL) 120 Day update

		BOTOX		
AESOC	**AEDECOD**	**>=4.5-<7.5 U/kg**	**>=7.5-<=10 U/kg**	**<4.5 U/kg**
Nervous system disorders	Febrile convulsion	2	2	0
	Epilepsy	1	2	0
	Hemiplegia	2	0	1
	Status epilepticus	2	1	0
Infections and infestations	Pneumonia	4	1	0
	Pharyngitis	4	0	0
	Bronchitis	2	0	0

There was one new case of **PDSOT** in a patient being treated with BOTOX for UL spasticity. The patient reported weakness in hand grip 3 days after receiving BOTOX 300 U in the right UL, which last for 85 days.

Table 46 Patients with PDSOT from 120-day Safety Update

Study Number [a] Patient ID	**Treatment Immediately**	**Treatment Cycle / Dose/**	**Verbatim Term AE Onset**	**Severity AE Outcome**	**Applican tComment**
Age/Sex/Race	**Preceding AE/**	**Dose per Muscle**	**Post Dose[a]**		
Weight	**Total Dose**		**AE Duration**		
	Limb/muscle(s)		**AE Treatment**		
(b) (6)	**Injected**				
	BOTOX/ 300 U	#1 Placebo	Muscular	Moderate	Local to area of
	(UL)	**#2 BOTOX/**	weakness/decreased	recovered/	injection
10/M/W		**300 U (UL)**	hand grip right hand	resolved	
44.9 kg	divided among	#3 BOTOX/	Day 3 of Tx #2		
	right UL muscles:	270 U (UL)	85 days		
	BIC, BCL, BCD,	#4 BOTOX/	Yes		
	FCR, FCU, FDP,	300 U (UL)			
	FDS, PT				

M = Male; W = white; BIC = biceps; BCL = brachialis; BCD = brachioradialis; FCU = flexor carpi ulnaris; FCR = flexor carpi radialis; FDP = flexor digitorum profundus; FDS = flexor digitorum superficialis; PT = pronator teres; Tx = treatment; UL = upper limb

[a] Source: Module 5.3.5.3, 120-day Update Listings 1-1, 2-2, 2-3, 3-3

Source: Applicant

Clinical Laboratories:

Chemistry

The ISS 120 day update for chemistry and electrolytes above the upper limit of normal (ULN) by dose group is presented in Table 47.

Table 47 ISS 120 Day Update All BOTOX

		BOTOX													
		<4.5 U/kg				>=4.5-<7.5 U/kg		>=7.5-<=10 U/kg			Placebo				
		CRIT2				CRIT2		CRIT2			CRIT2				
PARAM	AVISIT	> 1.1 x ULN	> 1.5 x ULN	> 3x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male	> 1.1 x ULN	> 1.5 x ULN	> 1.1 x ULN	> 1.5 x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male	> 1.1 x ULN	> 1.5 x ULN	> 3 x ULN	> 5x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male
Albumin	Baseline	2	0	0	0	2	0	4	0	0	2	0	0	0	0
	Final Value Post-Baseline	0	0	0	0	2	0	1	0	0	1	0	0	0	0
Alkaline Phosphatase	Baseline	0	0	0	1	0	0	0	0	0	0	0	0	0	1
	Final Value Post-Baseline	0	0	0	1	0	0	0	0	1	0	0	0	0	2
Alkaline Phosphatase Iso-Liver	Baseline	0	0	1	0	0	0	0	0	0	0	0	0	1	0
	Final Value Post-Baseline	0	0	1	0	0	0	0	2	0	0	0	0	2	0
Aspartate Aminotransferase	Final Value Post-Baseline	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Bicarbonate	Baseline	0	0	0	0	0	0	0	0	0	0	0	0	0	0

		BOTOX													
		<4.5 U/kg				>=4.5-<7.5 U/kg		>=7.5-<=10 U/kg			Placebo				
		CRIT2				CRIT2		CRIT2			CRIT2				
PARAM	AVISIT	> 1.1 x ULN	> 1.5 x ULN	> 3x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male	> 1.1 x ULN	> 1.5 x ULN	> 1.1 x ULN	> 1.5 x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male	> 1.1 x ULN	> 1.5 x ULN	> 3 x ULN	> 5x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male
	Final Value Post-Baseline	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bilirubin	Baseline	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Bone Specific Alkaline Phosphatase	Baseline	0	0	16	0	0	4	0	8	0	0	0	0	16	0
	Final Value Post-Baseline	0	0	9	0	0	3	0	7	0	0	0	0	11	0
Calcium	Baseline	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Creatinine	Final Value Post-Baseline	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Glucose	Baseline	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	Final Value Post-Baseline	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Phosphate	Baselin	0	0	0	0	0	0	1	0	0	0	0	0	0	0

		BOTOX													
		<4.5 U/kg				>=4.5-<7.5 U/kg		>=7.5-<=10 U/kg			Placebo				
		CRIT2				CRIT2		CRIT2			CRIT2				
PARAM	AVISIT	> 1.1 x ULN	> 1.5 x ULN	> 3x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male	> 1.1 x ULN	> 1.5 x ULN	> 1.1 x ULN	> 1.5 x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male	> 1.1 x ULN	> 1.5 x ULN	> 3 x ULN	> 5x ULN	>=1.2xULN for 2-12 yrs male & female and 13-15 yrs male
	e														
	Final Value Post-Baseline	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Potassium	Baseline	0	0	0	0	1	0	1	0	0	0	0	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0	0	0	0	1	0	0	0	0

REVIEWER COMMENT:

The only notable laboratory value >5x ULN, is the bone specific alkaline phosphatase. This was elevated across all treatment groups including placebo at baseline, with slight decrease in incidence at final post-baseline visit. This is most likely related to age and development of the patients, not drug related.

Hematology

The ISS 120 day update for hematology above the upper limit of normal (ULN) by dose group is presented in Table 48.

Table 48 Hematology ULN by dose group

		BOTOX					
		<4.5 U/kg	>=4.5-<7.5 U/kg			>=7.5-<=10 U/kg	
		CRIT2	CRIT2			CRIT2	
PARAM	AVISIT	> 2 x ULN	> 1.1 x ULN	> 1.5 x ULN	> 2 x ULN	> 1.1 x ULN	> 2 x ULN
Eosinophils	Baseline	2	0	0	21	0	9
	Final Value Post-Baseline	5	0	0	19	0	12
Erythrocytes	Baseline	0	1	0	0	1	0
	Final Value Post-Baseline	0	2	0	0	0	0

		BOTOX					
		<4.5 U/kg	>=4.5-<7.5 U/kg			>=7.5-<=10 U/kg	
		CRIT2	CRIT2			CRIT2	
PARAM	AVISIT	> 2 x ULN	> 1.1 x ULN	> 1.5 x ULN	> 2 x ULN	> 1.1 x ULN	> 2 x ULN
Hematocrit	Baseline	0	0	0	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0
Hemoglobin	Baseline	0	0	0	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0
Leukocytes	Baseline	0	0	1	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0
Lymphocytes	Baseline	0	0	0	0	0	0
Monocytes	Baseline	0	0	0	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0
Neutrophils	Baseline	0	0	1	0	0	0
	Final Value Post-Baseline	0	0	1	0	0	0
Platelets	Baseline	0	0	0	0	0	0
	Final Value Post-Baseline	0	0	0	0	0	0

REVIEWER COMMENT:

There were no clinically significant abnormalities in hematologic parameters noted.

SUMMARY OF SAFETY

There were no deaths during the double-blind placebo controlled studies.

The TEAEs included in the BOTOX label from studies completed for the approval of UL and LL spasticity in adults, which includes a maximum dose 400 U, are similar to the TEAEs experienced by pediatric patients treated with BOTOX for UL and LL spasticity. The most common TEAEs in both populations are gastrointestinal disorders, general disorders and administration site conditions and infections and infestations.

There were no clinically significant laboratory or vital sign findings, during the studies.

8 Postmarket Experience

A postmarketing safety report analysis of BOTOX, BOTOX COSMETIC, VISTABEL, VISTABEX, or VISTA 50 (referred to in this section as BOTOX) in the treatment of spasticity was conducted. The most frequently reported AEs in relation to the indications of upper limb or lower limb spasticity are consistent with those seen in the clinical trials and are therefore listed in the current or draft

labeling for upper limb.

Method: The postmarketing database was queried for reports in pediatric patients (selected age groups: adolescent, child, infant, and neonate) received between 01 January 1990 and 30 June 2018 in which BOTOX was used for the indication PT equal to cerebrovascular accident, diplegia, hemiparesis, hemiplegia, hereditary spastic paraplegia, muscle spasticity, muscle contracture, joint contracture, paraparesis, paresis, quadriplegia, paraplegia, muscle spasms.

Results: There were 557 reports retrieved representing patients treated for spasticity. These comprised the following: lower limb spasticity (308), both upper and lower limb spasticity (50), upper limb spasticity (88), and unknown spasticity indication with no specific limb identified (96).

The majority of the 557 reports were received from the US (218), Australia (72), Japan (45), France (32), Sweden (27), Poland (26), Canada (20), and Germany and Netherlands (18). The sources of reports were from spontaneous (334),literature (112), sponsored study (64), regulatory authorities (41), and unsponsored study (6).

There were 264 reports meeting seriousness criteria, of which 254 reports were medically confirmed. Of the 557 reports, 191 reports were female patients, and 279 reports were male patients. Gender was not reported in 87 reports.

There were 557 reports received during the period 01 January 1990 to 30 June 2018 for the treatment of spasticity (regardless of limb). The most frequently reported AE PTs, excluding 70 events where off-label use was entered as an event PT[3], were muscular weakness (80), pyrexia (57), seizure (45), asthenia (41), vomiting (32), rash (32), dysphagia (31), overdose (21), pneumonia (20), urticaria (20), eyelid ptosis (19), and fatigue (19). Of note, reports coding to the PT of asthenia generally reflected verbatim reports of “weakness” or “generalized weakness.”

The majority of AEs reported were in the general disorders and administration site conditions SOC (258), nervous system disorders SOC (236), and musculoskeletal and connective tissue disorders SOC (155).

9 Appendices

9.1 Literature Review/References

NA

9.2 Labeling Recommendations

Recommendations for the labeling:

Section 1.4 **Pediatric Spasticity**

Pediatric Upper Limb Spasticity
BOTOX is indicated for the treatment of upper limb spasticity in pediatric patients 2 years of age and older.

Section 2.6

Pediatric Spasticity

General
Localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended. The maximum dose should not exceed 8 Units/kg body weight or 300 Units, whichever is lower *[see Boxed Warning and Warnings and Precautions (5.2, 5.6)]*. Additional *general* adult spasticity dosing information is also applicable to pediatric spasticity patients *[see Dosage and Administration (2.5)]*.

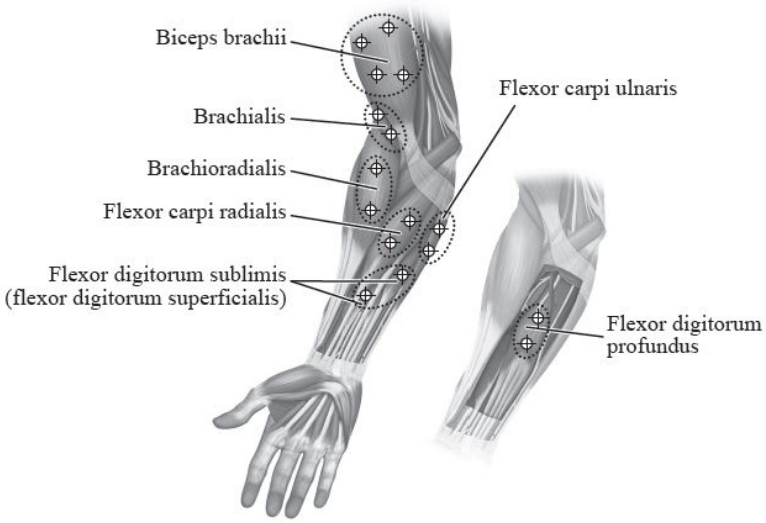
Pediatric Upper Limb Spasticity
The recommended dose for treating pediatric upper limb spasticity is 3 Units/kg to 6 Units/kg divided among the affected muscles (see Table 5 and Figure 4). The total dose of BOTOX administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower.

Table 5: BOTOX Dosing by Muscle for Pediatric Upper Limb Spasticity

Muscle	Recommended Dose and Number of Sites
Biceps Brachii	1.5 Units/kg to 3 Units/kg divided in 4 sites
Brachialis	1 Units/kg to 2 Units/kg divided in 2 sites
Brachioradialis	0.5 Units/kg to 1 Units/kg divided in 2 sites
Flexor Carpi Radialis	1 Units/kg to 2 Units/kg divided in 2 sites

Flexor Carpi Ulnaris	1 Units/kg to 2 Units/kg divided in 2 sites
Flexor Digitorum Profundus	0.5 Units/kg to 1 Units/kg divided in 2 sites
Flexor Digitorum Sublimis	0.5 Units/kg to 1 Units/kg divided in 2 sites

Figure 4: Injection Sites for Pediatric Upper Limb Spasticity



Section 5.10

Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
Bronchitis was reported more frequently as an adverse reaction in adult patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In adult patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (10% at 3 Units/kg and 17% at 6 Units/kg) compared to placebo (9%).

Section 6.1

Pediatric Upper Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX in pediatric patients ages 2 years and older with upper limb spasticity appear in Table 20. In a double-blind, placebo-controlled trial (Study 1), 78 patients were treated with 3 Units/kg of BOTOX, and 77 patients received 6 Units/kg to a maximum dose of 200 Units of

BOTOX, and were compared to 79 patients who received placebo *[see Clinical Studies (14.5)]*. Adverse reactions were reported more frequently in the group treated with 6 Unit/kg of BOTOX compared to the group treated with 3 Units/kg. Patients were followed for an average of 91 days after injection.

Table 20: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Pediatric Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 1)

Adverse Reactions	BOTOX 3 Units/kg (N=78) %	BOTOX 6 Units/kg (N=77) %	Placebo (N=79) %
Infections and infestations			
Upper respiratory tract infection[1]	10	17	9
Rhinitis	4	0	1
General disorders and administration site conditions			
Injection site pain	3	4	1
Gastrointestinal disorders			
Constipation	0	3	1
Diarrhea	4	0	1
Nausea	0	4	0
Musculoskeletal and connective tissue disorders			
Muscular weakness	4	1	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	0	4	1
Nervous system disorders			
Seizure[2]	1	5	0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion	0	3	1
Injury, poisoning and procedural complications			
Ligament sprain	3	0	1

1=Includes upper respiratory tract infection and viral upper respiratory tract infection
2=Includes seizure and partial seizure

Section 14.5

Pediatric Spasticity

Pediatric Upper Limb Spasticity

The efficacy and safety of BOTOX for the treatment of upper limb spasticity in pediatric patients ages 2 years and older was evaluated in Study 1, a randomized, multi-center, double-blind, placebo-controlled study. Study 1 included 234 pediatric patients (77 BOTOX 6 Units/kg, 78 BOTOX 3 Units/kg, and 79 placebo) with upper limb spasticity (modified Ashworth Scale elbow or wrist score of at least 2) because of cerebral palsy or stroke. A total dose of 3 Units/kg BOTOX (maximum 100 Units), 6 Units/kg BOTOX (maximum 200 Units), or placebo was injected intramuscularly and divided between the elbow or wrist and finger muscles (see Table 39). Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection.

Muscles Injected	BOTOX 3 Units/kg* (maximum Units per muscle)	BOTOX 6 Units/kg** (maximum Units per muscle)	Number of Injection Sites
Elbow Flexor Muscles			
Biceps	1.5 Units/kg (50 Units)	3 Units/kg (100 Units)	4
Brachialis	1 Units/kg (30 Units)	2 Units/kg (60 Units)	2
Brachioradialis	0.5 Units/kg (20 Units)	1 Units/kg (40 Units)	2
Wrist and Finger Muscles			
Flexor carpi radialis	1 Units/kg (25 Units)	2 Units/kg (50 Units)	2
Flexor carpi ulnaris	1 Units/kg (25 Units)	2 Units/kg (50 Units)	2
Flexor digitorum profundus	0.5 Units/kg (25 Units)	1 Units/kg (50 Units)	2
Flexor digitorum sublimis	0.5 Units/kg (25 Units)	1 Units/kg (50 Units)	2

* did not exceed a total dose of 100 Units
** did not exceed a total dose of 200 Units

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) principal muscle group score (elbow or wrist) at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement).

Table 40: Co-Primary Efficacy Endpoints Results in Study 1 (Pediatric Upper Limb Spasticity)

	BOTOX 3 Units/kg (N=78)	BOTOX 6 Units/kg (N=77)	Placebo (N=79)
Mean Change from Baseline in Principal Muscle Group (Elbow or Wrist) on the modified Ashworth Scale			
Week 4 and 6 Average	-1.92†	-1.87*	-1.21
Mean Clinical Global Impression Score			
Week 4 and 6 Average	1.88†	1.87†	1.66

* $p<0.05$ † Not statistically significant vs. placebo

Compared to placebo, significant improvements in MAS change from baseline were observed at all timepoints for BOTOX-treated patients (see Figure 15 and Figure 16). Athough CGI scores numerically favored BOTOX over placebo, the difference was not statistically significant. A subgroup of patients where the primary targeted muscle group was the finger flexors did not show a significant improvement on the change from baseline to the average of modified Ashworth Scale score for weeks 4 and 6.

Figure 15: Modified Ashworth Scale Score for Study 1 (Pediatric Upper Limb Spasticity) – Mean Change from Baseline by Visit

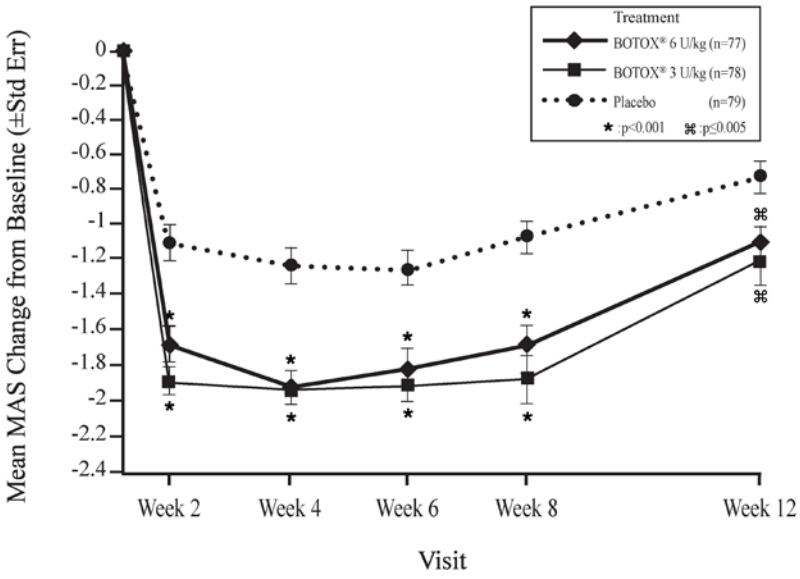
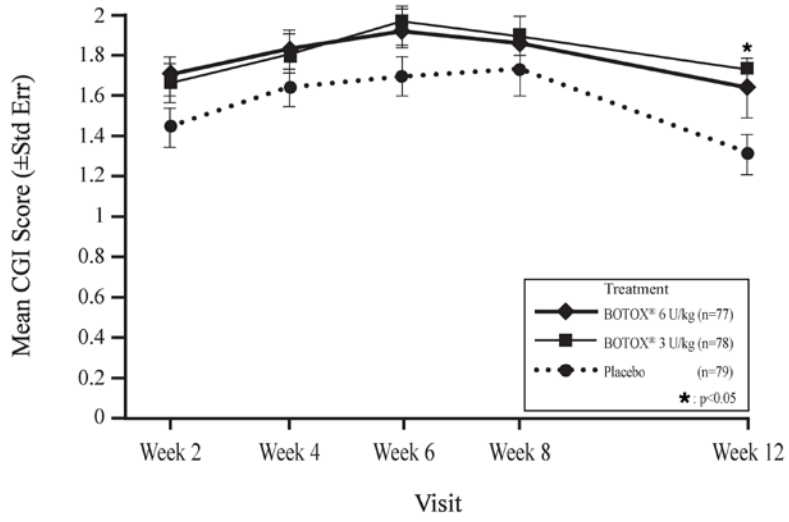


Figure 16: Clinical Global Impression of Overall Change for Study 1 (Pediatric Upper Limb Spasticity) – Mean Scores by Visit



9.3 Advisory Committee Meeting

NA

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSANNE R GOLDSTEIN
06/20/2019 11:06:11 AM

GERALD D PODSKALNY
06/20/2019 11:07:56 AM