# CLINICAL REVIEW

| | |
|---|---|
| Application Type | sBLA |
| Application Number(s) | 103000/ 5310 |
| Priority or Standard | Standard |
| Submit Date(s) | December 20, 2018 |
| Received Date(s) | December 20, 2018 |
| PDUFA Goal Date | October 20, 2019 |
| Division / Office | DNP/OND |
| Reviewer Name(s) | Susanne R. Goldstein, MD |
| Review Completion Date | 10/10/2019 |
| Established Name | OnabotulinumtoxinA |
| (Proposed) Trade Name | Botox |
| Therapeutic Class | Purified Neurotoxin Complex |
| Applicant | Allergan |
| Formulation(s) | Injection IM |
| Dosing Regimen | As needed |
| Indication(s) | Lower 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 lower limb (LL) spasticity in the pediatric population, Study 191622-111, provided evidence of effectiveness and clinically meaningful benefit without changing the known risk profile of BOTOX (OnabotulinumtoxinA).

I recommend APPROVAL of BOTOX for the treatment of:

- lower limb spasticity in the pediatric population with a maximum dose of 8 U/kg (up to 340 U) injected in the distal lower extremity

The PMC for upper limb spasticity and lower limb spasticity in the pediatric population is fulfilled. The PMR for a long-term safety study in the pediatric population treated for spasticity (half upper and half lower limb) is also fulfilled.

## 1.2 Risk Benefit Assessment

The Applicant conducted one pivotal DBPC trial for the treatment of LL spasticity, 191622-111, in the pediatric population.

The efficacy results for BOTOX for the treatment of LL spasticity in pediatric patients in study, 191622-111, is statistically significant for the primary endpoint, the change in MAS from Baseline to the average of weeks 4 and 6 in the gastrocnemius soleus complex (GSC) for the 4 U/kg and 8 U/kg cohorts (-1.0 [p=0.033] and -1.1 [p=0.010] respectively) compared to placebo ( -0.8.) The CGI by the physician, average of Weeks 4 and 6, is statistically significant for the 8 U/kg dose group compared to placebo (1.6 versus 1.4, p=0.023); however, it is not statistically significant for the 4 U/kg dose group compared to placebo (1.5 versus 1.4, p=0.299.) The responder analysis for the MAS, responders with at least 1 grade reduction from Baseline, is nominally significant for the 8 U/kg group at Week 6 (p=0.037.) The proportion of responders for 8 U/kg and 4 U/kg dose was numerically higher than placebo at all study visits. The clinical meaningfulness of the treatment effect as measured by the MAS is supported by the CGI and MAS responder analysis.

Events (TEAEs), Serious Adverse Events (SAEs) and deaths for DBPC study 191622-111, the open label extension study 191622-112, and post-marketing safety update did not reveal any new safety signals.

There were no deaths in the recent studies (DBPC 191622-111, OL 191622-112). There was one death in legacy study OCUL-119-8051; the patient died as a result of herpes simplex virus encephalitis. 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 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 lower limb spasticity in pediatric patients ages 2-17 years of age. The information in the sponsor's submission demonstrates that treatment with BOTOX8 U/kg for LL 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 8 U/kg in the LL (maximum dose of 340 U) of BOTOX, given no sooner than every 12-14 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:

**Postmarketing Requirements**

PMR #3018-1

Randomized, double-blind, adequately controlled, multiple fixed dose, parallel group clinical trial of Botox (OnabotulinumtoxinA) in botulinum toxin-naïve children ages 2 to 17 years with lower extremity spasticity. The minimum duration of the trial should be 12 weeks. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

Final Protocol Submission: 06/10
Study/Trial Completion: 05/17
Final Report Submission: 01/19

PMR #3018-2

Pediatric long-term safety study (minimum 12 months) for the treatment of lower limb spasticity in pediatric patients ages 2 to 17 years. The doses evaluated must be at least as high as those shown effective in the pediatric efficacy study (PMR #3018-1), or those commonly used to treat lower limb spasticity in pediatric patients, if an effective dose is not identified in the pediatric efficacy study (PMR #3018-1). The study must assess distant spread of toxin effects, and the effects of Botox on blood glucose and alkaline phosphatase. The study report must include safety information on at least 300 patients who received 2 injections over a 6- month period, with at least 100 patients who received 4 injections over a 12-month period, with at least 60 patients who received the highest recommended dose (if any).

Final Protocol Submission: 06/10
Study/Trial Completion: 05/18
Final Report Submission: 01/19

**Postmarketing Commitments**

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 Pediatric Research Equity Act (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 Pediatric Research Committee (PeRC) agreed that the product has been fully assessed for use in pediatric patients 2 to less than 17 years of age and labeling will be updated.
- The PeRC also agreed with the fulfillment of PREA PMRs as annotated above.

With the approval of supplemental BLAs, 103000/5309 and 103000/5310, PMRs #3018-1, #3018-2 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,<br><br>Phenol,<br><br>OnabotulinumtoxinA (BOTOX) *Approved April 17, 2015, January 21, 2016*<br><br>OnabotulinumtoxinA (BOTOX) Approved *June 20, 2019*<br><br>abobotulinumtoxinA (Dysport) Approved *July 16, 2015*<br><br>abobotulinumtoxinA (Dysport) Approved *July 30, 2016*<br><br>abobotulinumtoxinA (Dysport) Approved *September 25, 2019* | I.M. for Adult upper limb including thumb, I.M. for Adult LL<br><br>I.M. for Pediatric upper limb<br><br>I.M. for Adult upper limb I.M. for Adult LL<br><br>I.M. for Pediatric lower limb<br><br>I.M. for Pediatric upper 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

The Applicant received Orphan Designation December 1991, for "*the treatment of dynamic muscle contracture in pediatric cerebral palsy patients*."

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 (b) (4) 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., upper limb: 3U/kg, 6U/kg. Lower limb: 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

As noted in Section 2.5, Allergan received Orphan Designation for *the treatment of dynamic muscle contracture in pediatric cerebral palsy patients,* in December 1991. Dysport (abobotulinumtoxinA) received Orphan Designation for the treatment of pediatric lower limb (LL) spasticity secondary to cerebral palsy in October 1999.

Dysport was approved for pediatric LL spasticity July 30, 2016. With this approval, Dysport received orphan exclusivity for the treatment of pediatric LL spasticity secondary to cerebral palsy, which will block the ability of Allergan's approval and ability to market Botox for the treatment of lower limb spasticity in patients 2-17 years old for treatment of spasticity caused by cerebral palsy until the orphan exclusivity has expired.

## 3 Ethics and Good Clinical Practices

The Applicant attested that Study 111 was conducted in conformance with the International Conference on Harmonization (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. Institutional Review Boards or Independent Ethics Committees conducted oversight of study sites. No debarred study personnel participated in Study 111.

### 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 Applicant certified the absence of financial interests or proprietary interest in this product, or a significant equity in the sponsor as defined in 21 CFR 54.2 (b). They did not receive significant payments of other sorts as defined in 21 CFR 54.2 (f): The following is a list of investigators/sub-investigators who submitted a financial disclosure for Study 111:

**Study 191622-111**

- Site 10038 (Dr. Peter McAllister, USA) sub-investigator Caryn McAllister received a grant for research study.

**Study 191622-112**

- Site 10038 (Dr. Peter McAllister, USA) sub-investigator Caryn McAllister 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. The Applicant reported no financial relationship with Dr. McAllister other that as a site principal investigator for Study 111.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

The application relies upon one randomized double-blind placebo-controlled study for to support the efficacy claim; **Study 191622-111 for pediatric lower limb spasticity.**

The pivotal efficacy study for pediatric lower limb spasticity, **Study 191622-111**, was followed by an **open label extension study, Study 191622-112.**

| 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)<br>BOTOX 8 U/kg (not to exceed 300 U) + PT (N = 128)<br>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<br>Cycles 2-5: BOTOX maximum body do se 10 U/kg or 340 U | Lower and upper limb muscles | Up to 5 |

Source: ISS

## 5.2 Review Strategy

Efficacy for the treatment of lower limb (LL) spasticity in the pediatric population is supported by Study 191622-111 and will be reviewed in Section 6.0.

Safety data from the double-blind placebo controlled study191622-111 and open label extension study 191622-1112 was reviewed with pediatric UL spasticity, sBLA 103000/5309 (DARRTS June 20, 2019).

# 6 Review of Efficacy

## 6.1 Indication

## Treatment of LL spasticity in the pediatric population

### 6.2.1

**DESIGN**

Study 111 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 (4 U/kg and 8U/kg) of Botox with standardized physical therapy (PT) in pediatric patients with lower limb spasticity. Three-hundred-eighty-four subjects 2 to 16 years and 11 months of age were enrolled and randomized in a 1:1:1 ratio to the Botox 8 U/kg group, Botox 4 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 PT sessions from Week 2.

The co-primary endpoints are

- Average grade change from baseline in Modified Ashworth Scale – Bohannon (MAS-B) ankle score with knee extended at Weeks 4 and 6

- Average Clinical Global Impression of Overall Change (CGI) by Physician at Weeks 4 and 6

In the statistical analyses, the 6-grade MAS-B raw scores of 0, 1, 1+, 2, 3, and 4 were coded as 0, 1, 2, 3, 4, and 5, respectively.

Subjects were stratified based on the following two factors:

- Age (≤ 6 years and > 6 years)
- Baseline MAS-B ankle score with knee extended (MAS-B = 2 and MAS-B > 2)

**Secondary Endpoints**

- The average CGI by Physician at Weeks 4 and 6 (for non-US FDA analyses)
- Goal Attainment Scale (GAS) by Physician
- Modified Tardieu Scale (MTS) of the ankle with knee extended and knee flexed

**Dosing:**

The dose for each muscle injected is outlined in Table 16.

**Table 16 Dosing Paradigm**

| | Placebo | | 4 U/kg | | 8 U/kg | | All |
|---|---|---|---|---|---|---|---|
| Lower Limb Muscles | Per Muscle | Not to Exceed | Per Muscle | Not to Exceed | Per Muscle | Not to Exceed | No. of Injection Sites |
| Gastrocnemius (medial & lateral heads) | 0 U/kg | 0 U | 2 U/kg | 75.0 U | 4 U/kg | 150 U | 4 |
| Soleus | 0 U/kg | 0 U | 1 U/kg | 37.5 U | 2 U/kg | 75 U | 2 |
| Tibialis posterior | 0 U/kg | 0 U | 1 U/kg | 37.5 U | 2 U/kg | 75 U | 2 |
| Total dose (study limb) | 0 U/kg | 0 U | 4 U/kg | 150 U | 8 U/kg | 300 U | - |

Source: Study report

**Summary of Protocol Amendments**

**Amendment 1, March 30, 2012**

The protocol was amended to provide clarifications, updated information and corrections.

**Amendment 2, January 28, 2014**

The protocol was amended to add assessment of suicidal ideation.

**Amendment 3, July 25, 2016**

Protocol amended primarily to modify the statistical methods (introduction of the Hochberg procedure, change in imputation methods, 152 participants randomized and sensitivity analyses) to reflect the simultaneous changes being made to Protocol 191622-101.

## 6.2.2 Demographics

The demographics and baseline characteristics of each of the cohorts is outlined in Table 17.

**Table 17 Demographics and Baseline Physical Characteristics (mITT Population)**

| | *BOTOX* | | | |
|---|---|---|---|---|
| *Characteristic* | *8 U/kg (N = 127)* | *4 U/kg (N = 125)* | *Placebo (N = 129)* | *Total (N = 381)* |
| **Age, years** | | | | |
| Mean ± SD | 6.7 ± 3.90 | 6.4 ± 3.58 | 6.7 ± 3.89 | 6.6 ± 3.79 |
| Min, Max | 2, 16 | 2, 16 | 2, 15 | 2, 16 |
| ≤ 6, n (%) | 74 (58.3) | 73 (58.4) | 74 (57.4) | 221 (58.0) |
| > 6, n (%) | 53 (41.7) | 52 (41.6) | 55 (42.6) | 160 (42.0) |
| **Sex, n (%)** | | | | |
| Male | 70 (55.1) | 67 (53.6) | 69 (53.5) | 206 (54.1) |
| Female | 57 (44.9) | 58 (46.4) | 60 (46.5) | 175 (45.9) |
| **Race, n (%)** | | | | |
| White | 76 (59.8) | 76 (60.8) | 79 (61.2) | 231 (60.6) |
| Non-white | 51 (40.2) | 49 (39.2) | 50 (38.8) | 150 (39.4) |
| Black | 2 (1.6) | 3 (2.4) | 4 (3.1) | 9 (2.4) |
| Asian | 42 (33.1) | 35 (28.0) | 37 (28.7) | 114 (29.9) |
| Hispanic | 7 (5.5) 10 | (8.0) | 6 (4.7) | 23 (6.0) |
| Other | 0 (0.0) | 1 (0.8) | 3 (2.3) | 4 (1.0) |
| **MAS-B Ankle Score with Knee Extended** | | | | |
| 2 | 66 (52.0) | 66 (52.8) | 68 (52.7) | 200 (52.5) |
| >2 | 61 (48.0) | 59 (47.2) | 61 (47.3) | 181 (47.5) |

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

Source: Tables 14.1-4 and 14.1-5

Source: Study report

***REVIEWER COMMENT:***

***The treatment groups appeared similar in terms of age, sex, race, and baseline MAS-B ankle scores. The average age of the subjects was approximately 6.6 years (SD = 3.8). There were more males than females in the study. The majority of the subjects were white.***

A summary of disease history is presented in Table 18.

**Table 18 Summary of Disease History (mITT Population)**

| | *BOTOX* | | | |
|---|---|---|---|---|
| *Variable* | *8 U/kg (N = 127) n (%)* | *4 U/kg (N = 125) n (%)* | *Placebo (N = 129) n (%)* | *Total (N = 381) n (%)* |
| **Disease Type** | | | | |
| Hemiplegia | 110 (86.6) | 109 (87.2) | 110 (85.3) | 329 (86.4) |
| Monoplegia | 17 (13.4) | 16 (12.8) | 19 (14.7) | 52 (13.6) |
| **Etiology** | | | | |
| Cerebral Palsy | 127 (100.0) | 125 (100.0) | 129 (100.0) | 381 (100.0) |

| Variable | BOTOX 8 U/kg (N = 127) n (%) | BOTOX 4 U/kg (N = 125) n (%) | Placebo (N = 129) n (%) | Total (N = 381) n (%) |
|---|---|---|---|---|
| **Previous Botulinum Toxin** | | | | |
| N | 127 | 125 | 129 | 381 |
| No previous exposure | 57 (44.9) | 61 (48.8) | 65 (50.4) | 183 (48.0) |
| Previous exposure | 70 (55.1) | 64 (51.2) | 64 (49.6) | 198 (52.0) |
| Treated for Spasticity | 68 (98.6) | 64 (100.0) | 63 (98.4) | 195 (99.0) |
| Treated for unreported indication | 1 (1.4) | 0 | 1 (1.6) | 2 (1.0) |
| Mean days since first toxin exposure | 1146.9 | 934.9 | 1045.2 | 1045.0 |
| Mean days since last toxin exposure | 837.6 | 569.0 | 578.3 | 665.7 |

mITT = modified intent-to-treat; N = number of participants who completed the previous botulinum toxin eCRF.

Source: Tables 14.1-6 and 14.1-7
Source: Study report

***REVIEWER COMMENT:***

***The characteristics at baseline were similar across cohorts. Approximately half of the subjects had no previous exposure to botulinum toxin across cohorts. Of the subjects who received prior botulinum toxin therapy, the 8 U/kg cohort had the longest mean duration since last exposure to toxin (838 days) compared to 4 U/kg or placebo (569 days and 578 days respectively.)***

## 6.2.3 Subject Disposition

The disposition of all subjects is presented in Table 19.

**Table 19 Summary of Overall Participant Disposition**

| Participant Status | BOTOX 8 U/kg (N = 128) n (%) | BOTOX 4 U/kg (N = 126) n (%) | Placebo (N = 130) n (%) | Total (N = 384) n (%) |
|---|---|---|---|---|
| Screened (Screen Population) | -- | -- | -- | 466 |
| Not enrolled | -- | -- | -- | 82 |
| Consent withdrawn | | | | 10 |
| Other | | | | 8 |
| Screen failed | -- | -- | -- | 64 |
| Inclusion Criteria | -- | -- | -- | 46 |
| Exclusion Criteria | -- | -- | -- | 20 |
| Randomized | 128 (100.0) | 126 (100.0) | 130 (100.0) | 384 (100.0) |
| Treated (safety population) | 128 (100.0) | 126 (100.0) | 128 (98.5) | 382 (99.5) |
| mITT population[a] | 127 (99.2) | 125 (99.2) | 129 (99.2) | 381 (99.2) |
| Completed Study | 125 (97.7) | 123 (97.6) | 128 (98.5) | 376 (97.9) |
| Prematurely discontinued | 3 (2.3) | 3 (2.4) | 2 (1.5) | 8 (2.1) |
| Personal reasons | 1 (0.8) | 1 (0.8) | 2 (1.5) | 4 (1.0) |
| Protocol violation | 1 (0.8) | 1 (0.8) | 0 (0.0) | 2 (0.5) |
| Lost to follow-up | 0 (0.0) | 1 (0.8) | 0 (0.0) | 1 (0.3) |

| | | | | |
|---|---|---|---|---|
| Other | 1 (0.8) | 0 (0.0) | 0 (0.0) | 1 (0.3) |

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 baseline ankle score with knee extended and ≥ 1 postbaseline measurement at Weeks 2, 4, or 6 for the MAS-B ankle score with knee extended and the CGI by Physician.

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

Source: Study report

***REVIEWER COMMENT:***

***A total of 466 subjects were screened; a total of 384 subjects were randomized in 49 study centers in 9 countries including 22 centers in the United States. Among the randomized subjects, 128 subjects (33.3%) were randomized to the 8 U/kg group, 126 (32.8%) to the 4 U/kg group, and 130 (33.9%) to the placebo group.***

## 6.2.4 Analysis of Primary Endpoint(s)

### Primary Analyses of Primary Efficacy Variable

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized subjects with a valid baseline MAS-B ankle score with knee extended and at least one at least one post-baseline measurement at Weeks 2, 4, or 6 for the MAS-B ankle score with knee extended and the average Clinical Global Impression of Overall Change (CGI) assessed by the physician at Weeks 4 and 6.

The change from baseline in MAS-B ankle score was analyzed using MMRM that included the baseline MAS-B ankle score as the covariate and factors of age 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 ankle score as the covariate and factors of age group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure.

The same Hochberg procedure as proposed in Study 101 was planned to control the family-wise type I error rate for Study 111.

### MAS-B

The primary analysis of the change from baseline in MAS-B ankle score with knee extended is presented in Table 20.

**Table 20 Study 111 primary analysis of MAS-B, mITT population**

| Visit | Statistic | BOTOX 8 U/kg (N = 127) | BOTOX 4 U/kg (N = 125) | Placebo (N = 129) |
|---|---|---|---|---|
| Baseline | n | 127 | 125 | 129 |
| | Mean ± SD | 3.5 ± 0.52 | 3.5 ± 0.53 | 3.5 ± 0.50 |
| Weeks 4 & 6 | n | 123 | 119 | 125 |
| | Mean ± SD | 2.4 ± 0.91 | 2.5 ± 0.86 | 2.7 ± 0.84 |
| | Mean change from baseline ± SD | -1.1 ± 0.94 | -1.0 ± 0.84 | -0.8 ± 0.73 |
| | LS Mean change from baseline (SE) | -1.06 (0.071) | -1.01 (0.072) | -0.80 (0.071) |
| | Difference (SE) | -0.26 (0.099) | -0.21 (0.098) | |
| | 95% CI | -0.453, -0.063 | -0.405, -0.018 | |
| | P-value [a] | 0.010 | 0.033 | |

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 ankle score with knee extended as a covariate and factors of age group, treatment group, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure where age group is represented by stratification categories (≤ 6 years and > 6 years). Estimated differences are based on the least-square means.

Source: Study report

***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 3.1%, 4.8%, and 3.1% for the Botox 8 U/kg group, Botox 4 U/kg group, and placebo group, respectively. Botox 8 U/kg and Botox 4 U/kg groups are statistically significant (p=0.01, p=0.033, respectively) compared to placebo.***

**CGI**

The primary analysis of coprimary endpoint CGI by physician is presented in Table 21.

**Table 21 Study 111 primary analysis of CGI by physician, mITT population**

| Visit | Statistic | BOTOX 8 U/kg (N = 127) | BOTOX 4 U/kg (N = 125) | Placebo (N = 129) |
|---|---|---|---|---|
| Weeks 4 & 6 | n | 123 | 118 | 124 |
| | Mean ± SD | 1.6 ± 1.07 | 1.5 ± 1.03 | 1.4 ± 1.04 |
| | LS Mean (SE) | 1.65 (0.090) | 1.49 (0.091) | 1.36 (0.089) |
| | Difference (SE) | 0.29 (0.125) | 0.13 (0.124) | |
| | 95% CI | 0.040, 0.532 | -0.115, 0.374 | |
| | P-value [a] | 0.023 | 0.299 | |

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 ankle score with knee extended as a covariate and factors of age group, treatment group, visit, treatment-by-visit interaction, study center and previous botulinum toxin exposure where age group is represented by stratification categories (≤ 6 years and > 6 years). Estimated differences are based on the least-square means.

Source: Study report

***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 the Botox and placebo are statistically significant for the 8 U/kg cohort (p=0.023) but did not meet statistical significance for the 4 U/kg cohort (p=0.299.)***

***Based on the pre-specified Hochberg procedure, Botox 8 U/kg was statistically significantly different from placebo; but Botox 4 U/kg was not.***

## Responder Analyses

### Modified Ashworth Scale

The proportion of responders who showed at least a 1-grade reduction from baseline in the MAS-B ankle score is presented in Table 22.

**Table 22 MAS-B Ankle Score: Responders with at Least a 1-Grade Reduction from Baseline (Observed Data, mITT Population)**

| | | BOTOX | | |
|---|---|---|---|---|
| *Visit Week* | *Statistic* | *8 U/kg (N = 127) n/N (%)* | *4 U/kg (N = 125) n/N (%)* | *Placebo (N = 129) n/N (%)* |
| 2 | Responders | 79/126 (62.7) | 75/124 (60.5) | 63/129 (48.8) |
| | P-value vs placebo [a] | 0.013 | 0.018 | |
| 4 | Responders | 85/124 (68.5) | 82/121 (67.8) | 77/127 (60.6) |
| | P-value vs placebo [a] | 0.091 | 0.143 | |
| 6 | Responders | 89/126 (70.6) | 82/121 (67.8) | 76/126 (60.3) |
| | P-value vs placebo [a] | 0.037 | 0.128 | |
| 8 | Responders | 83/122 (68.0) | 81/123 (65.9) | 70/127 (55.1) |
| | P-value vs placebo [a] | 0.027 | 0.043 | |
| 12 | Responders | 51/125 (40.8) | 44/123 (35.8) | 43/128 (33.6) |
| | P-value vs placebo [a] | 0.259 | 0.718 | |

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

[a] P-values are based on Logistic regression model with baseline MAS-B ankle score with knee extended as a covariate 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).

Source: Study report

***REVIEWER COMMENT:***

***The proportion of patients with at least a 1-grade reduction from baseline in the MAS-B score provides additional information regarding the clinical meaningfulness of the change from baseline in MAS. A 1-point change in the MAS is believed to be clinically meaningful to patients. The proportion of patients who experienced at least a 1-grade reduction from baseline in the MAS-B ankle score was greater in both active treatment groups than in the placebo group at every visit. Although, the differences were nominally significant only for the 8 U/kg group at Week 6, the proportion of responders with a 1-point MAS reduction from baseline compared with placebo was nominally significant at Weeks 2 and 8 and the proportion of responders was higher at all weeks (2, 4, 6, 8 and 12) for Botox 8 U/kg and 4 U/kg.***

The proportion of CGI responders (score of at least +1) is shown in Table 23.

**Table 23 CGI by Physician: Responders with a Score ≥ +1 (Observed Data, mITT Population)**

| | | BOTOX | | |
|---|---|---|---|---|
| *Visit Week* | *Statistic* | *8 U/kg (N = 127) n/N (%)* | *4 U/kg (N = 125) n/N (%)* | *Placebo (N = 129) n/N (%)* |
| 2 | Responders | 104/126 (82.5%) | 98/123 (79.7%) | 89/129 (69.0%) |
| | P-value vs placebo [a] | 0.030 | 0.051 | |
| 4 | Responders | 103/124 (83.1%) | 91/120 (75.8%) | 95/127 (74.8%) |
| | P-value vs placebo [a] | 0.206 | 0.752 | |
| 6 | Responders | 104/125 (83.2%) | 95/121 (78.5%) | 94/125 (75.2%) |
| | P-value vs placebo [a] | 0.168 | 0.605 | |
| 8 | Responders | 95/122 (77.9%) | 95/123 (77.2%) | 98/127 (77.2%) |
| | P-value vs placebo [a] | 0.909 | 0.875 | |
| 12 | Responders | 91/125 (72.8%) | 89/123 (72.4%) | 86/128 (67.2%) |
| | P-value vs placebo [a] | 0.217 | 0.197 | |

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

[a] P-values are based on Logistic regression model with 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).

Source: Study report

***REVIEWER COMMENT:***

***While the proportion of CGI 1-grade responders in the 8 U/kg group was generally higher than in placebo, the difference was nominally significant only at Week 2 (p = 0.03). In the 4 U/kg group, no nominally significant difference from placebo was observed in the proportion of responders.***

### 6.2.5 Analysis of Secondary Endpoints(s)

The Hochberg procedure used to control the family-wise type I error was only applied to the coprimary endpoints. Thus, testing should have stopped with the nonsignificant result on the CGI for the Botox 4 U/kg.

- GAS by Physician scores for both the passive and active goals were consistently higher in both BOTOX groups compared with placebo, and the differences were nominally significant for both the active and passive goals at both measured visits in the 8 U/kg group. The percentage of responders who scored 0 or higher (meet or exceed expectation) or -1 or higher (slight improvement but not meet expectation) was consistently higher in both BOTOX groups compared with placebo, and statistically significant differences were seen for some visits in the 8 U/kg cohort.

- Greater improvement was evident in the numerical results of the Modified Tardieu Scale assessment with knee extended after both doses of BOTOX over placebo for R1 ( angle of catch after fast velocity [V3] stretch, R2 (angle defined as the passive joint range of movement following a slow velocity [V1] stretch), and R2-R1 (the level of the dynamic component of spasticity at the joint) at all time points. In the assessment of R2-R1 with knee flexed, nominally significant differences from placebo were seen for BOTOX 8 U/kg dose+ at Weeks 2, 4, and 6; however, no specific weeks was defined the statistical plan.

### 6.2.7 Subpopulations

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

**GENDER**

The analysis of the primary endpoints by gender are presented in Table 24.

**Table 24 Study 111 analyses by gender, mITT population**

| | | MAS-B | | | CGI | | |
|---|---|---|---|---|---|---|---|
| **Female** | | | | | | | |
| Visit | Statistic | Botox 8 U/kg (N = 127) | Botox 4 U/kg (N = 125) | Placebo (N = 129) | Botox 8 U/kg (N = 127) | Botox 4 U/kg (N = 125) | Placebo (N = 129) |
| Baseline | n | 57 | 58 | 60 | -- | -- | -- |
| | Mean±SD | 3.5±0.54 | 3.5±0.54 | 3.4±0.50 | -- | -- | -- |
| Weeks 4&6 | n | 54 | 56 | 58 | 54 | 55 | 58 |
| | Mean±SD | 2.3±0.94 | 2.6±0.90 | 2.6±0.75 | 1.8±1.07 | 1.5±1.03 | 1.4±1.01 |
| | Mean change from Baseline ±SD | -1.2±1.02 | -0.9±0.92 | -0.8±0.67 | -- | -- | -- |
| **Male** | | | | | | | |
| Baseline | n | 70 | 67 | 69 | -- | -- | -- |
| | Mean±SD | 3.5±0.50 | 3.5±0.53 | 3.5±0.50 | -- | -- | -- |
| Weeks 4&6 | n | 69 | 63 | 67 | 69 | 63 | 66 |
| | Mean±SD | 2.5±0.88 | 2.5±0.84 | 2.8±0.90 | 1.5±1.07 | 1.4±1.04 | 1.4±1.07 |
| | Mean change from Baseline ±SD | -1.0±0.87 | -1.0±0.76 | -0.7±0.77 | -- | -- | -- |

Source: selected from Table 1-10.1, Table 1-10.2, Table 1-11.1, and Table 1-11.2 in the integrated summary of efficacy tables, FDA Statistical Review

## RACE

The analysis of the primary endpoints by race are presented in Table 25.

**Table 25 Study 111 analyses by race, mITT population**

| | | MAS-B | | | CGI | | |
|---|---|---|---|---|---|---|---|
| **Non-White** | | | | | | | |
| Visit | Statistic | Botox 8 U/kg (N = 127) | Botox 4 U/kg (N = 125) | Placebo (N = 129) | Botox 8 U/kg (N = 127) | Botox 4 U/kg (N = 125) | Placebo (N = 129) |
| Baseline | n | 51 | 49 | 50 | -- | -- | -- |
| | Mean±SD | 3.5±0.50 | 3.6±0.54 | 3.5±0.50 | -- | -- | -- |
| Weeks 4&6 | n | 49 | 48 | 48 | 49 | 47 | 48 |
| | Mean±SD | 2.4±1.11 | 2.6±0.92 | 2.6±0.87 | 1.5±1.03 | 1.5±1.08 | 1.5±1.20 |
| | Mean change from Baseline ±SD | -1.1±1.14 | -0.9±0.91 | -0.8±0.73 | -- | -- | -- |
| **White** | | | | | | | |
| Baseline | n | 76 | 76 | 79 | -- | -- | -- |
| | Mean±SD | 3.5±0.53 | 3.5±0.53 | 3.5±0.50 | -- | -- | -- |
| Weeks 4&6 | n | 74 | 71 | 77 | 74 | 71 | 76 |
| | Mean±SD | 2.5±0.76 | 2.5±0.83 | 2.7±0.82 | 1.7±1.10 | 1.5±1.00 | 1.3±0.93 |
| | Mean change from Baseline ±SD | -1.0±0.79 | -1.0±0.79 | -0.7±0.73 | -- | -- | -- |

Source: selected from Table 1-5.1, Table 1-5.2, Table 1-7.1, and Table 1-7.2 in the March 7, 2019 response to information request, FDA, Statistical Review

## Age

The analysis of the primary endpoints by age group are presented in Table 26.

**Table 26 Study 111 analyses by age group, mITT population**

| | | MAS-B | | | CGI | | |
|---|---|---|---|---|---|---|---|
| **Age ≤ 6** | | | | | | | |
| Visit | Statistic | Botox 8 U/kg (N = 35) | Botox 4 U/kg (N = 33) | Placebo (N = 34) | Botox 8 U/kg (N = 33) | Botox 4 U/kg (N = 32) | Placebo (N = 32) |
| Baseline | n | 74 | 73 | 74 | -- | -- | -- |
| | Mean±SD | 3.5±0.50 | 3.5±0.53 | 3.5±0.50 | -- | -- | -- |
| Weeks 4&6 | n | 72 | 70 | 71 | 72 | 69 | 70 |
| | Mean±SD | 2.4±0.86 | 2.5±0.84 | 2.8±0.78 | 1.8±1.07 | 1.7±1.05 | 1.2±1.09 |
| | Mean change from Baseline ±SD | -1.1±0.86 | -1.0±0.82 | -1.0±0.73 | -- | -- | -- |
| **Age> 6** | | | | | | | |
| Baseline | n | 53 | 52 | 55 | -- | -- | -- |
| | Mean±SD | 3.5±0.54 | 3.5±0.54 | 3.5±0.50 | -- | -- | -- |
| Weeks 4&6 | n | 51 | 49 | 54 | 51 | 49 | 54 |
| | Mean±SD | 2.4±0.98 | 2.6±0.91 | 2.6±0.91 | 1.5±1.06 | 1.2±0.91 | 1.6±0.93 |
| | Mean change from Baseline ±SD | -1.1±1.05 | -0.9±0.88 | -0.9±0.71 | -- | -- | -- |

Source: Adapted from Applicant, CSR 191622-111, Tables 14.5-1.1 and 14.5-2.1

***REVIEWER COMMENT:***

***There were no significant effects on primary efficacy endpoints, MAS-B and CGI, by age, race or gender.***

**GEOGRAPHIC REGION**

The analysis of the primary endpoints by geographic region are presented in Table 27.

**Table 21 Study 111 analyses by region, mITT population**

| | | MAS-B | | | CGI | | |
|---|---|---|---|---|---|---|---|
| **Non-US** | | | | | | | |
| Visit | Statistic | Botox 8 U/kg (N = 127) | Botox 4 U/kg (N = 125) | Placebo (N = 129) | Botox 8 U/kg (N = 127) | Botox 4 U/kg (N = 125) | Placebo (N = 129) |
| Baseline | n | 97 | 97 | 104 | -- | -- | -- |
| | Mean±SD | 3.4±0.50 | 3.5±0.52 | 3.5±0.50 | -- | -- | -- |
| Weeks 4&6 | n | 96 | 94 | 101 | 96 | 94 | 100 |
| | Mean±SD | 2.5±0.77 | 2.5±0.78 | 2.8±0.78 | 1.7±1.10 | 1.5±1.05 | 1.4±1.06 |
| | Mean change from Baseline ±SD | -1.0±0.79 | -1.0±0.75 | -0.7±0.71 | -- | -- | -- |
| **US** | | | | | | | |
| Baseline | n | 30 | 28 | 25 | -- | -- | -- |
| | Mean±SD | 3.7±0.52 | 3.6±0.57 | 3.6±0.51 | -- | -- | -- |
| Weeks 4&6 | n | 27 | 25 | 24 | 27 | 24 | 24 |
| | Mean±SD | 2.3±1.31 | 2.7±1.12 | 2.5±1.06 | 1.6±1.00 | 1.3±0.96 | 1.4±0.97 |
| | Mean change from Baseline ±SD | -1.4±1.32 | -0.9±1.12 | -1.0±0.76 | -- | -- | -- |

Source: selected from Table 1-3.1, Table 1-3.2, Table 1-4.1, and Table 1-4.2 in the May 1, 2019 response to information request, FDA, Statistical Review

***REVIEWER COMMENT:***

***There was a slightly greater improvement (change from baseline in MAS-B) in the US 8 U/kg cohort than non-US. Otherwise treatment effect was similar across geographic regions.***

## 6.2.10 Additional Efficacy Issues/Analyses

**SUMMARY OF EFFICACY**

The Applicant conducted one pivotal DBPC trial for the treatment of LL spasticity, 191622-111, in the pediatric population.

The efficacy results for the treatment effect of BOTOX for LL spasticity in pediatric patients in the pivotal study, 191622-111, is statistically significant for the primary endpoint, change in MAS from Baseline to the average of weeks 4 and 6 in the plantar flexor muscles for both 4 U/kg and 8 U/kg dose compared to placebo. The CGI by the physician, average of Weeks 4 and 6, is statistically significant for the 8 U/kg dose group compared to placebo; however, it is not statistically significant for the 4 U/kg dose group compared to placebo. The result of the MAS responder analysis is nominally significant for the 8 U/kg group at Week 6, which supports the clinical meaningfulness of the change from baseline in the MAS for Botox 8 U/kg. The proportion of responders is numerically higher for the Botox treated groups compared to placebo at every efficacy visit. The clinical meaningfulness of the results for change from baseline for the MAS is supported by the CGI, and by the MAS comparison of responders for Botox 8 U/kg and 4 U/kg.

Employing the Hochberg procedure, the efficacy results from the pivotal study, are statistically significant for the high dose, 8 U/kg, of BOTOX for the treatment of pediatric lower limb spasticity. The CGI is used to support the clinical meaningfulness of the change from baseline in the MAS. An additional method for determining clinical meaningfulness of change in the MAS, is the responder analysis (proportion of responders.) The difference in the proportion of responders for the Botox 4 U/kg and 8 U/kg shows the change in the MAS is clinically meaningful in more patients treated with either dose of Botox than placebo. Therefore, BOTOX 4 U/kg and 8 U/kg will be described in the label.

### 9.3 Advisory Committee Meeting

NA

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**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.**

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/s/

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SUSANNE R GOLDSTEIN
10/18/2019 04:02:22 PM

GERALD D PODSKALNY
10/18/2019 04:05:10 PM