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Study ID: 191622-101

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Double-blind Study

Protocol Amendment 3 Date: July 22, 2016

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STUDY TITLE

BOTOX® Treatment in Pediatric Upper Limb Spasticity: Double-blind Study

Protocol Number:	191622-101 Amendment 3
EudraCT Number:	2012-000062-38
Phase:	3
Name of Investigational Product:	BOTOX® (botulinum toxin type A) purified neurotoxin complex (US Adopted Name is onabotulinumtoxinA)
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500 Allergan Ltd. 1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire SL7 1YL United Kingdom Tel: +44 (0) 1628 494444 Fax: +44 (0) 1628 494449
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[redacted]

Allergan Signatory: [redacted]

Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

STUDY LOCATION:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: BOTOX® (botulinum toxin type A) purified neurotoxin complex (US Adopted Name is onabotulinumtoxinA)

Phase: 3

Study Objectives: To evaluate the safety and efficacy of a single treatment of 2 doses (3 U/kg and 6 U/kg) of BOTOX with standardized occupational therapy (OT) in pediatric patients with upper limb spasticity

Clinical Hypotheses:

1) A single treatment of BOTOX at doses of 3 U/kg and 6 U/kg in the upper limb has an acceptable safety profile.
2) BOTOX with standardized OT is more effective than placebo with standardized OT as measured by a reduction in muscle tone on the Modified Ashworth Scale - Bohannon (MAS-B). For United States (US) Food and Drug Administration (FDA) only, the hypothesis is that BOTOX with standardized OT is more effective than placebo with standardized OT as measured by a reduction in muscle tone on the MAS-B and improvement on the Clinical Global Impression of Overall Change (CGI) by Physician.

Study Design

Structure: Multicenter, randomized, double-blind, placebo-controlled, parallel-group

Duration: 16 weeks (up to 4 weeks of screening and 12 weeks of posttreatment follow-up)

Study Treatment Groups: *(BOTOX doses are expressed as units per total body weight)*

3 U/kg BOTOX + OT

6 U/kg BOTOX + OT

Placebo + OT

Control: Placebo

Dosage/Dose Regimen:

There will be 1 treatment cycle in the study. Only 1 affected upper limb (referred to as the study limb) will be treated.

Patients will be randomized among the following treatment groups in a 1:1:1 ratio: 3 U/kg (not to exceed 100 U) + OT, 6 U/kg (not to exceed 200 U) + OT, or placebo + OT. The randomized doses are to be administered to the principal muscle group.

Each patient will have either the elbow flexors or the wrist flexors designated as the principal muscle group for analysis purposes. If wrist flexors are designated as the principal muscle group, finger flexors in the study limb must also be injected. See Figure 1 for a flowchart for determining the muscle group(s) for injection and Table 3 for the dose requirements.

Randomization/Stratification:

Patients will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio within each combination of strata. The stratification categories are as follows:

- Age (≤ 6 years and > 6 years)
- Designated principal muscle group (elbow flexors and wrist flexors)
- Baseline (day 1) MAS-B score of principal muscle group (MAS-B = 2 and MAS-B > 2)

Visit Schedule:

There will be 8 visits and approximately 13 weekly OT sessions during the study:

Visit 1: Week -4 to week -2 (screening)
Visit 2: Week -2 (initiation of standardized weekly OT)
Visit 3: Day 1 (randomization and treatment)
Visit 4: Week 2 (follow-up visit)
Visit 5: Week 4 (follow-up visit)
Visit 6: Week 6 (follow-up visit)
Visit 7: Week 8 (follow-up visit)
Visit 8: Week 12 (exit visit)

Study Population Characteristics

Number of Patients:

Approximately 224 patients will be enrolled to ensure that at least 213 patients (71 per treatment group) will complete the study.

Condition/Disease:

Medically stable monoplegic, hemiplegic, or triplegic children with spasticity of the upper limb involving the elbow and/or wrist flexor muscles with single-arm sparing due to cerebral palsy or stroke.

Key Inclusion Criteria:

- Male or female, 2 to 16 years and 11 months of age (prior to 17th birthday) at the day 1 visit
- Minimum weight of 10 kg at the screening and day 1 visits
- Upper limb monoplegic, hemiplegic, or triplegic spasticity (spasticity confirmed by Hypertonia Assessment Tool [HAT]) with single-arm sparing (only 1 arm requiring botulinum toxin treatment for spasticity during the study) resulting from cerebral palsy, or post-stroke with the stroke onset prior to age 2 and at least 12 months prior to the day 1 visit
- [redacted]

- [redacted]

Key Exclusion Criteria:

- [redacted]
- Any medical condition that may put the patient at increased risk with exposure to Botulinum Toxin Type A Purified Neurotoxin Complex, including diagnosed muscular dystrophy (eg, Duchenne's muscular dystrophy), myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, mitochondrial disease, or any other significant disease that might interfere with neuromuscular function
- [redacted]
- Uncontrolled epilepsy defined as more than 1 generalized seizure in any month within the 3 months prior to the day 1 visit or history of any of the following within 9 months prior to the day 1 visit: prolonged seizures or repetitive seizure activity requiring administration of a rescue benzodiazepine (oral, rectal, etc) more than once a month, seizures lasting more than 10 minutes, status epilepticus, or epilepsy with autonomic involvement
- [redacted]
- Botulinum toxin therapy of any serotype for any condition within 6 months prior to the day 1 visit
- [redacted]
- History of surgical intervention of the study limb (except for tendon lengthening more than 12 months prior to the day 1 visit) or planned surgical intervention of any limb(s) during the study.
- Previous casting within 6 months prior to the day 1 visit or splinting with a dynamic splint (eg, Dynasplint® or UltraFlex®) within 3 months prior to the day 1 visit for spasticity of the study limb or the affected lower limb(s), or planned casting or splinting with a dynamic splint (eg, Dynasplint or UltraFlex) for spasticity of the study limb or affected lower limb(s) during the study
- [redacted]

Response Measures

Efficacy:

Primary efficacy measures:

- MAS-B of the principal muscle group (elbow or wrist)
- CGI by Physician (co-primary efficacy measure for US FDA only)

Secondary efficacy measures:

- CGI by Physician (for non-US FDA analyses)
- MAS-B of the finger flexor muscle group
- Goal Attainment Scale (GAS) by Physician
- Modified Tardieu Scale (MTS) of the principal muscle group

[redacted]

Safety:

- Adverse events
- Physical examination
- Urine pregnancy tests (for all females of childbearing potential)
- Hematology and serum chemistry
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature)
- Body weight
- Columbia-Suicide Severity Rating Scale (C-SSRS, for patients ≥ 6 years of age at day 1)

General Statistical Methods and Types of Analyses:

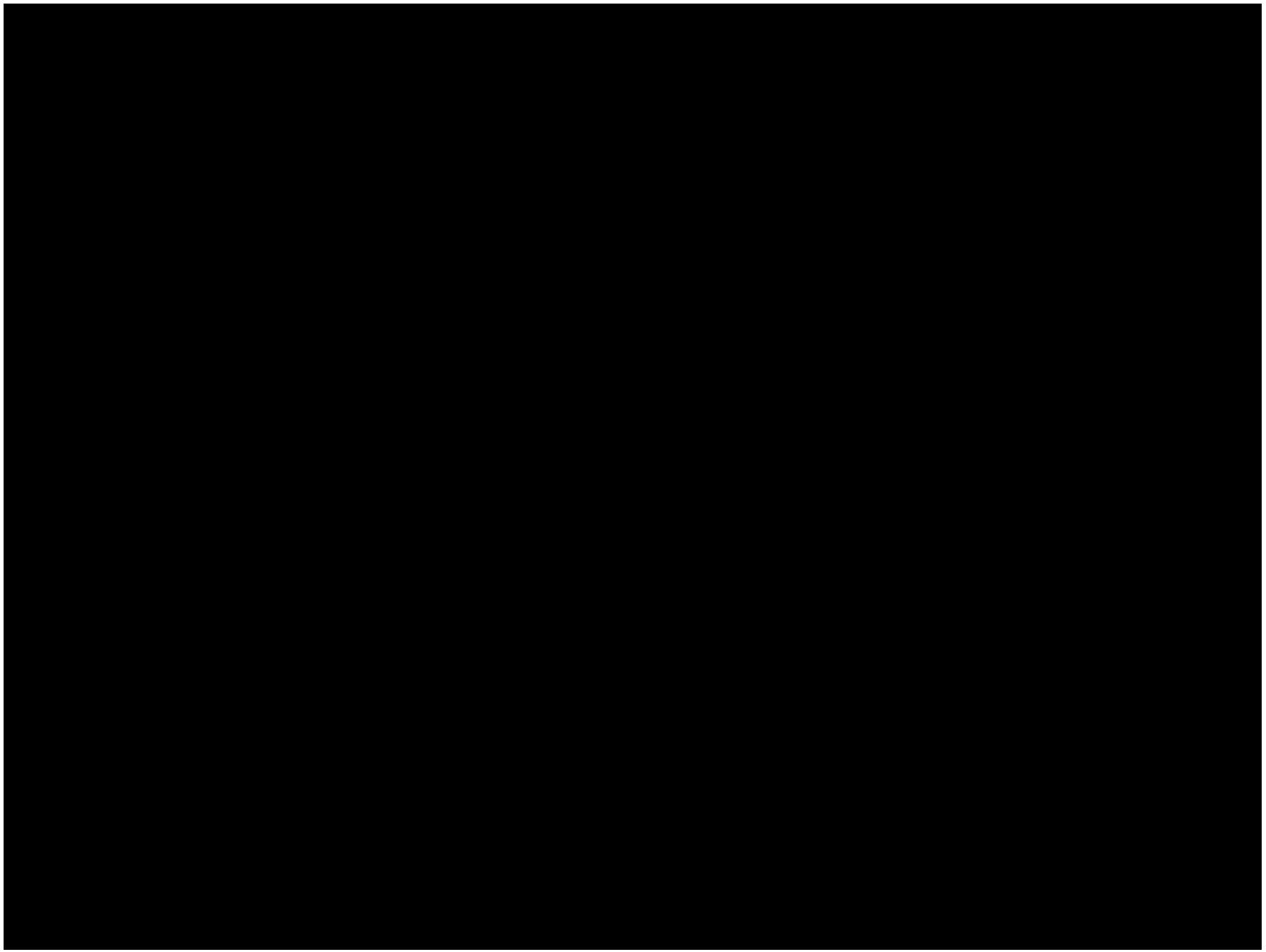
Safety data will be analyzed on the basis of all treated patients based on treatment received, defined as the safety population. Efficacy data will be analyzed on the basis of the modified intent-to-treat (mITT) population, defined as all randomized patients with a valid MAS-B baseline score of the principle muscle group and at least one post-baseline measurement at weeks 2, 4, or 6 for the MAS-B of the principle muscle group and the CGI by Physician. The primary efficacy endpoint will be the average grade change from baseline in the MAS-B of the principal muscle group at weeks 4 and 6. For US FDA only, the average grade change from baseline in MAS-B of the principal muscle group at weeks 4 and 6 and the average CGI by Physician at weeks 4 and 6 will be analyzed as co-primary endpoints. Analysis of covariance (ANCOVA) will be performed with factors of age group, principal muscle group, treatment group, study center, and previous botulinum toxin exposure, and a covariate of baseline MAS-B. Continuous secondary and other efficacy variables will be summarized by treatment group and analyzed by ANCOVA. Categorical efficacy variables, such as the responder status for MAS-B, will be analyzed by logistic regression. All statistical tests will be 2-sided with a significance level of 0.05. Safety variables, such as the adverse event incidence rate, vital signs and changes from baseline in vital signs, the incidence of suicide-related events, and laboratory test values and their changes from baseline, will be summarized by treatment group.

Sample Size Calculation:

Approximately 224 patients will be enrolled to ensure that at least 213 patients (71 per treatment group) will complete the study. Using a 2-sample t-test, a significance level of 0.05, and the assumptions in the table below, the power for MAS-B change from baseline is 86% (PASS, Hintze, 2008). The calculation is based on assumptions for the 6 U/kg group and the placebo group. Since there are 2 co-primary endpoints for the US FDA analysis, for the 6 U/kg group the power for CGI by Physician is calculated to be 94%, and the overall power for the US FDA co-primary endpoints will be at least 81%. The assumptions for MAS-B and CGI treatment differences were based on completed Studies 191622-008, BTOX-133/134/8051, BTOX-418/422-8051, BTX108509 and 112958, with standard deviation assumptions based on observed masked data from this ongoing study.

Endpoint	Average difference between 6 U/kg BOTOX group and placebo group at Weeks 4 and 6	Standard Deviation	Power
MAS-B Change from Baseline	-0.5	0.98	86%
CGI by Physician (Co-primary for US FDA Analysis)	0.6	1.02	94%
Overall Power			81%

CGI = Clinical Global Impression of Overall Change; MAS-B = Modified Ashworth Scale - Bohannon



1. Background and Clinical Rationale

1.1 Pediatric Spasticity

Spasticity is classically defined as a disorder of the sensorimotor system characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex (Lance, 1980). The most common cause of focal spasticity in children is cerebral palsy. Cerebral palsy is a disorder caused by a non-progressive insult of the central nervous system (CNS) that occurs prenatally, perinatally, or during the first 2 years of life and can result in functional motor impairment, irregular movement, and abnormal posture. The increase in the muscle-stretch reflex causes muscle contraction of abnormal strength and duration. Spastic muscles show "velocity-dependent" resistance to passive movement and exaggerated tendon jerks (Lance, 1980).

The patterns of spasticity depend on the areas of the developing brain that are damaged. In patients with hemiplegic spasticity, one half of the body (1 arm and 1 leg) is affected with spasticity. Approximately 25% of children with cerebral palsy present with hemiplegic spasticity in which the upper limb is usually more affected than the lower limb (Stanley et al, 2000). Spastic diplegia is characterized by spasticity of both legs with relative sparing of the arms. Although the arms are less affected, they may still show abnormal reflexes and reduced dexterity. Spastic triplegia is characterized by spasticity affecting both lower extremities and 1 arm is usually affected more severely than the other. Spastic quadriplegia affects all 4 limbs and is the most severe but least common form of spastic cerebral palsy, affecting approximately 20% of patients. Since both cerebral hemispheres are affected, intellectual impairment is common. Patients with quadriplegia may also have severe dysarthria, dysphagia, and other comorbidities such as epilepsy and blindness. Spasticity and abnormal muscle tone contribute both to impairment of function and reduced longitudinal muscle growth in children with cerebral palsy (Dunne et al, 1995).

Cerebral palsy is the most common etiology associated with pediatric spasticity with a prevalence rate of approximately 2.5 in 1000 live births, a number that has increased from 1.5 in 1000 live births 40 years ago (Odding et al, 2006) and is considered to be the most severe childhood physical disability (Beckung and Hagberg, 2002). Essentially all patients with cerebral palsy have impaired motor function with spasticity affecting as many as 90%. Other less prevalent types of disorders associated with pediatric spasticity include posttraumatic brain or spinal cord injury, multiple sclerosis, and other neurodegenerative conditions (Hawamdeh et al, 2007). All of these conditions are associated with significant morbidity and mortality and present an unmet medical need with limited treatment options.

A less prevalent type of disorder associated with pediatric spasticity is stroke. Information on the prevalence of childhood post-stroke spasticity in published literature is limited. The United States (US) mortality rate attributable to stroke in children (1 to 5 years of age) is 0.6 per 100,000. The case fatality rate for childhood stroke is reported to range from 7% to 28% (Lynch et al, 2002). Based on studies evaluating the effects of stroke by degree of motor impairment, the rate of motor deficit in pediatric post-stroke patients ranges from 40% to about 70% (Brower et al, 1996; De Schryver et al, 2000; Keidan et al, 1994). Given the low incidence of stroke in children and assuming the lowest case-fatality rate (7%) along with the worst case scenario of 70% prevalence of motor deficits, the maximum number of children with post-stroke spasticity in the US is estimated to be less than 1500.

1.2 Management of Spasticity in Children

Management of spasticity associated with cerebral palsy is focused on helping the child achieve maximal potential in growth and development. Most patients are managed with a combination of treatment modalities, including non-pharmacologic, systemic pharmacologic, local pharmacologic, and surgical treatments.

Non-pharmacologic and non-surgical treatments for spasticity aim to strengthen weakened muscles, weaken spastic muscles, and improve joint range of motion as well as motor development (Koman et al, 2004). These interventions include occupational therapy (OT), physical therapy (PT), orthotics, splints, casting and other devices, or any combination of these methods. PT and OT are regarded as essential for successful medical and surgical interventions (Butler and Darrah, 2001; Dumas et al, 2001), but the overall evidence supporting this is weak (Lannin et al, 2006). A recent study has demonstrated the enhanced effectiveness of OT used in combination with BOTOX® (botulinum toxin type A purified neurotoxin complex [US Adopted Name, onabotulinumtoxinA], hereafter referred to as BOTOX) (Wallen et al, 2007*)*.

Systemic pharmacologic treatments include anti-spastic drugs such as baclofen, dantrolene, diazepam, scopolamine, and tizanidine (Gracies et al, 1997; O'Flaherty and Waugh, 2003; Scheinberg et al, 2006; Steinbok, 2006). The aim of systemic pharmacologic management is to reduce the muscle overactivity associated with spasticity. Mechanisms of action vary but the result is either a suppression of muscle excitation or an enhancement of neural inhibition. Response to these medications is variable and unpredictable (O'Flaherty and Waugh, 2003). Major drawbacks of systemic anti-spastic therapy include the lack of specificity of targeting muscle groups and CNS side effects such as drowsiness, constipation, and cognitive impairment. Local pharmacologic treatments include phenol or alcohol injections for

specific chemolysis of targeted nerves. The main risks of phenol are its potential to cause irreversible damage to the nerve and nearby structures, as well as reduce sensation and cause dysesthesias and neuropathic pain (Gracies et al, 1997). Intrathecal baclofen is reserved for patients with disabling general spasticity that is unresponsive to conservative pharmacotherapy (Koman et al, 2004).

Orthopedic procedures such as contracture release, tendon lengthening, and tendon transfer can reduce spasticity symptoms that may result in improved access for hygiene and brace (orthotic) tolerability. These surgical procedures may also result in pain reduction, as well as reduction in bone deformity (osteotomy). However, many forms of surgery are best delayed until tendons and joints have grown to a reasonable proportion of their adult size, since it is more difficult to predict the outcome of surgery in younger children. Surgical procedures have been reported as delayed due to the ability of botulinum toxin (type A) therapy to minimize fixed muscle shortening and soft tissue and skeletal deformation associated with spasticity (Molenaers et al, 2006).

Neurosurgical procedures include selective dorsal rhizotomy and selective peripheral neurotomy (Chambers, 1997; Steinbok, 2006). Selective dorsal rhizotomy is used to treat severe spasticity of the lower extremities that interferes with mobility or positioning. It is usually most effective in a small number of select diplegic or quadriplegic children with cerebral palsy who are expected to be independent ambulators. In children with underlying muscle weakness, rhizotomy can worsen rather than improve function.

1.3 BOTOX for Management of Pediatric Spasticity

Botulinum neurotoxin type A (BoNT-A) blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BoNT-A produces localized chemical denervation of the muscle, resulting in focal muscle weakness. This muscle weakness is reversible through nerve ending recovery over a period of 3 or more months. Relaxation of rigid muscles by BoNT-A allows a child to participate in PT or OT, which encourages the use of both targeted and antagonistic muscles with goals of muscle stretching, strengthening, improved motor control, and acquisition of new skills. There has been considerable experience worldwide since the early 1990s with the use of BOTOX in the treatment of spasticity associated with cerebral palsy.

1.3.1 Use of BOTOX in Pediatric Lower Limb Spasticity

Allergan has completed 5 trials with BOTOX for the treatment of lower limb spasticity in children with cerebral palsy. These studies have demonstrated an acceptable safety profile of BOTOX at the dose ranges evaluated for this patient population. Study OCUL-118-8051, a placebo-controlled study, included 145 patients (72 BOTOX; 73 placebo) with equinus foot deformity who were 2 to 14 years old. Patients received injections of BOTOX (4 to 8 U/kg; note that BOTOX doses throughout this protocol are expressed per body weight) or placebo. The proportion of responders based on gait pattern score was significantly greater ($p \leq 0.05$) in the BOTOX group compared to the placebo group at weeks 2, 8, and 12.

Study OCUL-119-8051, an open-label multiple-treatment extension of study OCUL-118-8051, included 207 patients who received injections of BOTOX at 4 U/kg. For the first 2 years of the study the proportion of responders ranged from 39% to 64%.

Study OCUL-120-8051, a placebo-controlled study, included 35 ambulatory patients with equinus foot deformity (17 BOTOX; 18 placebo) who were 2 to 14 years old. Patients randomized to BOTOX received 4 U/kg in the affected limb. The proportion of responders based on gait pattern score was significantly greater ($p \leq 0.05$) in the BOTOX group compared to the placebo group at weeks 8 and 12. Twenty-five of the 35 patients entered a 2-year, multiple-treatment open-label follow-up study (BTOX-121-8051).

The fifth study (191622-021), a placebo-controlled study, included 149 patients with equinus foot deformity (73 BOTOX; 76 placebo) who were 2 to 8 years old. Patients randomized to BOTOX received 4 U/kg in each affected limb (up to a maximum of 8 U/kg). No significant differences in the proportion of responders based on the gait pattern score were observed between the 2 treatment groups.

1.3.2 Use of BOTOX in Upper Limb Pediatric Spasticity

Allergan has supported several investigator-initiated trials evaluating the effect of BOTOX in children with upper limb spasticity associated with cerebral palsy. Boyd et al conducted a single-center study in Australia, enrolled 30 children (15 pairs with matched age, gender, and side of hemiplegia) aged 5 to 15 years (mean 9 years) with hemiplegic cerebral palsy (Boyd et al, 2003). This study was a single treatment study with 3 months follow-up and compared training alone to training combined with BOTOX injections. Doses of 0.5 to 2.0 U/kg per muscle were injected into selected upper limb muscles with a mean BOTOX dose of 4.9 ± 1.6 U/kg (range 3.1 to 8.4 U/kg). BOTOX was significantly more effective

than the control (training alone) at week 3 (p = 0.002) and at week 12 (p = 0.0001) based on the Melbourne Assessment score.

Koman et al enrolled 50 patients with cerebral palsy ages 3 to 18 years (mean age 9 years) in a 26-week double-blind, placebo-controlled study (Koman et al, 2004a). Enrollment included patients with hemiplegia (n = 30), diplegia (n = 7), or quadriplegia (n = 13). The patients were randomized to BOTOX (n = 28) or placebo (n = 22). Three injections of BOTOX were administered at weeks 0, 8, and 20 at a dose based on the patient's weight, the size of the target muscle(s), and the total number of muscles to be injected. The mean dose of BOTOX was 4.9 U/kg for the first treatment session, 4.4 U/kg for the second treatment session, and 4.6 U/kg for the third treatment session. The results on the Melbourne Assessment showed a significantly improved total score with BOTOX compared to placebo at 20 weeks (p = 0.04) and 26 weeks (p < 0.0001).

Lowe et al conducted a randomized, controlled study in 42 children with hemiplegic cerebral palsy aged 2 to 8 years (mean 4 years; Lowe et al, 2006). The study compared the effect of a single injection of BOTOX (1 to 2 U/kg per muscle group, maximum total body dose 8 U/kg) plus OT to OT alone (control). The follow-up period was 6 months. At the primary efficacy timepoint of month 6, both groups improved from baseline on the Quality of Upper Extremity Skills Test (QUEST) but the between-group difference was not significant. At week 4, however, 67% of children treated with BOTOX had a clinically significant 20% improvement in total QUEST and 71% had a clinically significant improvement at week 12, compared with 19% of control children at week 4 and 33% at week 12 (between-group comparisons p = 0.004 and p = 0.03, respectively). Spasticity, as measured by the Modified Ashworth Scale-Bohannon (MAS-B) (Bohannon and Smith, 1987), was significantly reduced in the BOTOX group compared to the control group at weeks 4 and 12.

The above studies, and additional published studies, provide evidence of the clinical utility and safety of BOTOX in the management of upper and lower limb pediatric spasticity.

1.4 Dose Justification

The purpose of this study is to further investigate the safety and efficacy of BOTOX treatment in pediatric patients with upper limb spasticity caused by cerebral palsy or stroke.

Three treatment groups were selected for the study:

- 3 U/kg not to exceed 100 U + OT
- 6 U/kg not to exceed 200 U + OT
- Placebo + OT

The assigned dose is required to be injected solely into the principal muscle group.

The BOTOX doses were selected based on Allergan clinical trial experience in pediatric spasticity, clinical expert advice, published literature including consensus guidelines for botulinum toxin type A treatment of pediatric spasticity, and nonclinical toxicology data.

The 5 completed Allergan-sponsored clinical trials in pediatric lower limb spasticity used doses ranging from 4 to 8 U/kg (Studies OCUL-118-8051, OCUL-119-8051, OCUL-120-8051, BTOX-121-8051, and 191622-021). Pediatric upper limb studies supported by Allergan (investigator-initiated) used doses from 5 to 8 U/kg. All of these studies demonstrated an acceptable safety profile and all but 1 study (191622-021) documented statistically significant improvement in a variety of efficacy outcomes.

The higher dose of 6 U/kg to the principal muscle group in the present study is further supported by the dose ranges described in the literature. All of the randomized, controlled studies in upper limb pediatric spasticity that were reviewed have used total body doses of 8 U/kg or less with the exception of 3 studies. Wallen et al (2007) and Russo et al (2007) evaluated doses up to 13 U/kg (mean 8.1 ± 2.9 U/kg) and 11.6 U/kg (mean 8.0 ± 2.2 U/kg), respectively; however, those studies included injections to additional upper limb muscles such as the shoulder muscles that are not eligible for injection in this study.
Pieber et al (2011) evaluated doses up to 12 U/kg but the dosing details are not provided in the publication.

The doses in the present study are further supported by the consensus guidelines issued by several expert bodies, which are based on many of the published studies as well as clinical experience. The Cochrane review focused on the effect of botulinum toxin type A in the management of upper limb spasticity in children and concluded that doses of BOTOX from 0.5 to 16 U/kg or up to a total of 220 to 410 U in a broad range of upper limb muscles, including shoulder muscles for the studies reporting higher doses, are safe (Hoare et al, 2010). The European consensus paper recently recommended a dose range of 1 to 20 U/kg with a maximum total dose of 400 U, regardless of location of injection (Heinen et al, 2010). The higher dose ranges were based on studies that allowed injections to multiple muscles of

varying size in the upper and/or lower limbs (Heinen et al, 2006; Molenaers et al, 2009). Nevertheless the per-site maximum recommended dose was 50 U, which is consistent with the per-site maximum dose in the present study. In an evidence-based review, the American Academy of Neurology concluded that botulinum toxin doses ranging from 2 to 30 U/kg for treatment of the upper and lower limbs are effective and generally safe (Delgado et al, 2010). The upper limb doses from the studies supporting the recommendation for upper limb treatment do not exceed the per-muscle doses (U/kg) in the 6 U/kg dose group in the current study. The international consensus statement published in 2010 recommends per-muscle doses ranging from 0.5 to 4 U/kg with a total dose per treatment session not to exceed 16 U/kg or 400 U. The per-muscle dose for the muscles in the principal muscle groups (elbow and wrist) in the 6 U/kg dose group in the present study is within these recommended dose ranges (Fehlings et al, 2010). The 3 and 6 U/kg doses are therefore considered to be appropriate doses in this study.

In addition, the safety of the proposed doses in this study is supported by the no-observable-adverse-effect levels (NOAELs) established in BOTOX toxicology studies. In single and repeated-dose studies in rats, 10 and 16 U/kg were defined as NOAELs, respectively. In monkeys, the single-dose intramuscular NOAEL was determined to be 16 U/kg when administered into the gastrocnemius muscle. In repeated-dose toxicity studies in monkeys involving multiple injection sites that more closely mimic clinical use, the NOAEL was 8, 12, or 16 U/kg for 2, 4, or 6 injection sites, respectively.

Based on the above considerations, the doses in this study for the treatment of the upper limb are considered to be safe and appropriate to evaluate efficacy in this population.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the safety and efficacy of a single treatment of 2 doses (3 U/kg and 6 U/kg) of BOTOX with standardized OT in pediatric patients with upper limb spasticity.

2.2 Clinical Hypotheses

1. A single treatment of BOTOX at doses of 3 U/kg and 6 U/kg in the upper limb has an acceptable safety profile.

2. BOTOX with standardized OT is more effective than placebo with standardized OT as measured by a reduction in muscle tone on the MAS-B. For US Food and Drug Administration (FDA) only, the hypothesis is that BOTOX with standardized OT is more effective than placebo with standardized OT as measured by a reduction in muscle tone on the MAS-B and improvement on the Clinical Global Impression of Overall Change (CGI) by Physician.

3. Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week study evaluating 2 doses of BOTOX, 3 U/kg and 6 U/kg, and placebo with standardized OT for the treatment of monoplegic, hemiplegic, or triplegic children with upper limb spasticity. Patients who successfully complete this study without major protocol deviations (eg, noncompliance to protocol-required procedures) will be given the option of enrolling in the open-label extension Study 191622-105 if they meet eligibility criteria.

The maximum study duration per patient will be approximately 16 weeks (including up to 4 weeks in the screening period). Patients will complete 8 study visits as follows: screening (week -4 to week -2), initiation of standardized OT (week -2), randomization and treatment visit (day 1), and post-injection follow-up visits at weeks 2, 4, 6, 8, and 12. All patients will receive weekly OT sessions from week -2 through week 11.

There will be 1 treatment cycle in the study. Only 1 affected upper limb (referred to as the study limb) will be treated. Patients will be randomized in a 1:1:1 ratio to one of the following treatment groups: 3 U/kg BOTOX (not to exceed 100 U) + OT, 6 U/kg BOTOX (not to exceed 200 U) + OT, or placebo + OT.

3.1 Safety Data Review Committee

The safety of the study participants will be monitored by a Safety Data Review Committee (SDRC) composed of at least 2 non-Allergan physicians and a study-independent statistician. Additional ad hoc participants (eg, physician specialists) may be invited to participate in review meetings depending on the safety findings and required scope of expertise.

The SDRC will conduct periodic review and assessments of the blinded adverse events data throughout the study to ensure the safety of study participants. The SDRC may elect to review additional safety parameters (eg, laboratory data), unblind the data, or change the frequency of their review meetings depending upon emerging safety findings or changes in patient enrollment rates.

For additional details regarding SDRC membership, standard operational procedures, frequency of review meetings, and other details, please refer to the SDRC charter.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 224 patients will be enrolled to ensure that at least 213 patients (71 per treatment group) will complete the study.

4.2 Study Population Characteristics

Medically stable monoplegic, hemiplegic, or triplegic children with spasticity of the upper limb involving the elbow and/or wrist flexor muscles with single-arm sparing due to cerebral palsy or stroke are eligible for enrollment in this study.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, 2 to 16 years and 11 months of age (prior to 17th birthday) at the day 1 visit
2. Minimum weight of 10 kg at the screening and day 1 visits
3. Upper limb monoplegic, hemiplegic, or triplegic spasticity (spasticity confirmed by Hypertonia Assessment Tool [HAT]) with single-arm sparing (only 1 arm requiring botulinum toxin treatment for spasticity during the study) resulting from cerebral palsy, or post-stroke with the stroke onset prior to age 2 and at least 12 months prior to the day 1 visit
4. [redacted]

6. [redacted]

13. [redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. [redacted]

2. Any medical condition that may put the patient at increased risk with exposure to Botulinum Toxin Type A Purified Neurotoxin Complex, including diagnosed muscular dystrophy (eg, Duchenne's muscular dystrophy), myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, mitochondrial disease, or any other significant disease that might interfere with neuromuscular function

3. [redacted]

4. [redacted]

11. Uncontrolled epilepsy defined as:

    a. more than 1 generalized seizure in any month within the 3 months prior to the day 1 visit, or

    b. history of any of the following within 9 months prior to the day 1 visit: prolonged seizures or repetitive seizure activity requiring administration of a rescue benzodiazepine (oral, rectal, etc) more than once a month, seizures lasting more than 10 minutes, status epilepticus, or epilepsy with autonomic involvement

12. [redacted]

13. [redacted]

16. [redacted]

17. Botulinum toxin therapy of any serotype for any condition within 6 months prior to the day 1 visit

18. [redacted]

21. History of surgical intervention of the study limb (except for tendon lengthening more than 12 months prior to the day 1 visit) or planned surgical intervention of any limb(s) during the study.

22. [redacted]

23. Previous casting within 6 months prior to the day 1 visit or splinting with a dynamic splint (eg, Dynasplint® or UltraFlex®) within 3 months prior to the day 1 visit for spasticity of the study limb or the affected lower limb(s), or planned casting or splinting with a dynamic splint (eg, Dynasplint or UltraFlex) for spasticity of the study limb or affected lower limb(s) during the study

24. [redacted]

29. [redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Patients who are already on stable concomitant anti-spastic medications, or muscle relaxants (eg, benzodiazepines, baclofen [oral or pump], scopolamine [oral or patch], tizanidine, vigabatrin, or dantrolene) prior to the day 1 visit and otherwise eligible for the study will be permitted to continue taking their medications at the same dose and regimen during the study. Patients who are on oral concomitant anti-spastic medications, anti-epileptics, or muscle relaxants should be instructed to take their medications at approximately the same time each day during the study, especially on the days of office visits. Efforts should be made to keep the same interval from the time of the medication to the time of the spasticity assessments during the office visits throughout the study. Patients who are on baclofen pumps must be on a continuous infusion with a stable dose and their baclofen treatment regimen must not include bolus infusions. Patients using scopolamine patches must not wear their patches at least 2 days prior to an office visit (except for the screening and week -2 visits).

Patients will be permitted to initiate the use of soft splints during the study at the investigator's discretion. However, patients should be asked not to wear the splint for at least 30 minutes before a spasticity measure at the office visits.

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, those medications should be administered in dosages that remain constant throughout the course of the trial. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

4.5.1.1 Acceptable Contraceptive Methods and Definition of Females of Childbearing Potential

At the time of screening, if a female patient is approaching puberty but is not yet of childbearing potential, then the patient and/or her legally authorized representative must be advised that if she becomes of childbearing potential (defined as females post menarche) during the study, she and/or her legally authorized representative must notify the site of this change. A urine pregnancy test must be performed at the patient's next scheduled visit. Upon receiving this notification, the site personnel must advise the patient and/or her legally authorized representative of the protocol requirement that any female of childbearing potential must use a reliable method of contraception, as described below.

For females of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, implantable contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation or removal of both ovaries), vasectomized partner, or sexual abstinence.

The investigator and each patient (and/or her legally authorized representative) will determine the appropriate method of contraception for the patient during the participation in the study. The method of contraception must be documented in the patient's medical record and electronic case report forms (eCRFs). At each study visit, the investigator must counsel female patients of childbearing potential and/or their legally authorized representative regarding the importance of maintaining their agreed-upon method of contraception.

If a female patient of childbearing potential becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient

will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with BOTOX or placebo and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

4.5.2 Prohibited Medications/Treatments

Patients should not be permitted to initiate the following therapy during the study:

- Anti-spastic medications or muscle relaxants (eg, benzodiazepines, vigabatrin, baclofen [oral or pump], scopolamine [oral or patch], tizanidine, or dantrolene)
- Anti-epileptic medication

Patients who enter the study on any of the above concomitant medications should remain on a stable dose throughout the study.

In addition, the following treatments or therapy are not permitted during the study:

- Botulinum toxin therapy of any serotype (except for the study treatment)
- Phenol or alcohol injection to any limb(s)
- Planned surgery in any limb(s)
- General anesthesia (drug-induced depression of consciousness) or deep sedation/analgesia (drug-induced loss of consciousness) as defined in "Practice guidelines for sedation and analgesia by non-anesthesiologists" (American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists, 2002) is prohibited regardless of the medication used. Minimal sedation (anxiolysis) or moderate sedation/analgesia (conscious sedation) in addition to local anesthesia is allowed for injection of the study medication.
- Casts or dynamic splints (UltraFlex, DynaSplint) for spasticity in the study limb or the affected lower limb(s)
- Occupational/physical therapy modalities such as ultrasound, transcutaneous electrical nerve stimulation, electrical stimulation, or acupuncture
- Constraint-induced movement therapy will not be permitted during the study.

Co-administration of aminoglycosides or other agents that could interfere with neuromuscular transmission (eg, curare-like agents) should only be used with caution as the effects of toxin theoretically could be potentiated.

The decision to administer a prohibited medication/treatment is done with the safety of the patient as the primary consideration. Patients may stay in the study even if a prohibited medication is administered. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

4.5.3 Special Diet or Activities

Protocol-specific, standardized OT will be provided to all enrolled patients. For the purposes of this protocol, OT is defined as "physical interventions performed by a licensed therapist (or equivalent per local regulations) to facilitate functional improvement in the upper extremities."

Patients will initiate their protocol-specified standardized OT approximately 2 weeks prior to the day 1 (randomization) visit. Patients who are on concurrent OT at the time of screening must modify their existing OT to comply with the protocol-specified standardized OT. After randomization, patients will be required to follow the same standardized OT protocol for the entire duration of the study.

The standardized OT protocol will consist of weekly sessions of approximately 1 hour that will include the following modalities:

- Elongation (approximately 20 minutes)
- Strengthening (approximately 20 minutes)
- Task-oriented functional therapy (approximately 20 minutes)

For each of the 3 modalities, the specific duration and activity options will depend on the patient's age, affected muscles, level of ability based on the MACS, and individual treatment goals (refer to the Standardized OT Reference Manual for further details).

Standardized OT scheduled on the day of an office visit should not be performed prior to any efficacy assessments. The last OT session should be scheduled during week 11.

If applicable, patients who are undergoing or will undergo school-based therapy as per relevant local legislation will be allowed to receive school-based therapy during the study in addition to the protocol-specified standardized OT; however, the school-based therapy should remain constant throughout the study if possible. Patients undergoing PT for lower limb spasticity at study entry should continue the same regimen during the study.

5. Study Treatments

5.1 Study Treatments and Formulations

The study treatment will consist of BOTOX or placebo and standardized OT. To maintain the blinding of the study, an Independent Drug Reconstitutor (IDR) will be assigned at each site for study drug preparation. A Pharmacy Manual will be provided with detailed information.

[redacted]

5.2 Control Treatment

Each vial of BOTOX placebo [redacted] contains 0.9 mg of sodium chloride in a sterile, vacuum-dried form without preservative.

5.3 Methods for Masking/Blinding

Patients and all site personnel with the exception of the IDR will be blinded to the study medication and dose administered. The IDR must not be involved in any study procedures other than study drug preparation and accountability (eg, proper drug storage).

The **physician investigator** will be responsible for identifying the muscles and doses to be injected.

Following randomization, to ensure that the injector remains blinded to the treatment group assignment, the **IDR** will be responsible for preparing the study medication according to the specific dilution requirements depending on the randomization assignment. A dosing summary will be provided to the IDR by the investigator or other site personnel for preparation of the study medication and injection syringes for each eligible muscle to be injected.

The study drug will be diluted according to the schedule below (Table 2) and in accordance with the randomization assignment received from the interactive voice response system/interactive web response system (IVRS/IWRS).

Table 2 Dilution of Study Drug

Treatment Group	Placebo	BOTOX 3 U/kg[a]	BOTOX 6 U/kg[a]
Volume of preservative-free saline used for dilution	2 mL	4 mL	2 mL
BOTOX units	0 U/mL	25 U/mL	50 U/mL

[a] Per 100 unit (U) vial

This dilution requirement will ensure that the same volume is injected into each of the muscles irrespective of the BOTOX dose group assignment. The randomization assignment documentation received from the IVRS/IWRS must be placed in the pharmacy file in a secure location with limited access to prevent inadvertent unblinding of other study personnel.

5.4 Treatment Allocation Ratio and Stratification

A centralized randomization scheme stratified by age group, principal muscle group, and baseline MAS-B will be prepared by Allergan. Patients will be randomized to 1 of the 3 treatment groups in a 1:1:1 ratio within each combination of strata. Randomization will be dispensed by the IVRS/IWRS. The stratification categories are as follows:

- Age (≤ 6 years and > 6 years)
- Designated principal muscle group (elbow flexors and wrist flexors)
- Baseline (day 1) MAS-B score of the principal muscle group (MAS-B = 2 and MAS-B > 2)

5.5 Method for Assignment to Treatment Groups/Randomization

At the screening visit, after the patient and/or legally authorized representative has signed the informed consent and minor assent (as applicable), the site will call the IVRS or log onto the IWRS to obtain the patient number that will serve as the patient identification number on all study documents. The automated IVRS/IWRS will be used to manage the randomization and treatment assignment based on the randomization scheme prepared by Allergan Biostatistics. At the study day 1 visit, the site will access the IVRS/IWRS to randomize the patient/assign treatment. Following enrollment, patient distribution will be monitored by the system as follows:

1. Principal muscle group – to ensure that at least 40% of the patients enrolled have elbow flexors spasticity and 40% have wrist/finger flexors spasticity. If necessary, one or both of the following modifications may be implemented:

a. For patients with the same MAS-B score for the elbow and the wrist at baseline (day 1), the wrist will be selected instead of the elbow

b. Enrollment may be limited to patients with one of the principal muscle groups (eg, wrist) if the majority of the patients enrolled have the other muscle group (eg, elbow) designated as the principal muscle group

2. Baseline (day 1) MAS-B score – to ensure that approximately 30% of the patients enrolled have a baseline MAS-B of 3 or greater in the principal muscle group. If necessary, enrollment of patients with baseline MAS-B = 2 will be closed and enrollment will continue for patients with baseline MAS-B > 2.

The study will also aim to enroll approximately 20% botulinum toxin-naïve patients in the subgroup ≤ 6 years of age and at least some botulinum toxin-naïve patients in the subgroup > 6 years of age. This will also be monitored by the IVRS/IWRS.

Study medication will be labeled with medication kit numbers. At the time of randomization, sites will call the IVRS or log onto the IWRS to obtain the specific study medication kit numbers for each randomized patient. Sites will dispense study medication according to the IVRS/IWRS instructions. Sites will receive an IVRS/IWRS confirmation notification for each transaction. All notifications must be maintained in the pharmacy file in a secure location to prevent inadvertent unblinding of other study personnel.

5.6 Treatment Regimen and Dosing

This study will include 1 treatment of the study limb.

The volume and corresponding dose for each identified muscle and the total dose will be calculated for each of the 3 potential treatment assignments to maintain blinding. A dosing summary will be provided to the IDR who will prepare the study medication according to the randomization assignment.

5.6.1 Treatment Regimen/Dosage Adjustments

For all patients enrolled, the muscles and dose for each muscle to be injected are listed in Table 3 according to the randomization assignment. For patients who weigh 40 kg or more, the maximum per-muscle dose must be used. For patients who weigh less than 40 kg, the dose for each muscle should be calculated using the patient's body weight in kilograms measured at the day 1 visit multiplied by the U/kg assigned to the muscle according to the randomization assignment. For purposes of dose calculation only, the patient's weight will

be rounded to the nearest whole kilogram. If the calculated unit (U/kg x body weight) is higher than the "not to exceed" dose for that muscle, the dose must be reduced to the "not to exceed" dose. No other dose adjustment is allowed in this study except for reducing the calculated dose to the maximum per-muscle ("not to exceed") dose level.

The dose for each muscle must be evenly distributed across the number of injection sites specified for each muscle. The total dose across all injections must not exceed the maximum doses of 3 U/kg (not to exceed 100 U) or 6 U/kg (not to exceed 200 U) for the BOTOX groups. The dose volume will be the same for all treatment groups, including the placebo group.

In addition to BOTOX or placebo, patients will receive standardized OT consisting of approximately 1-hour weekly sessions from week -2 through week 11.

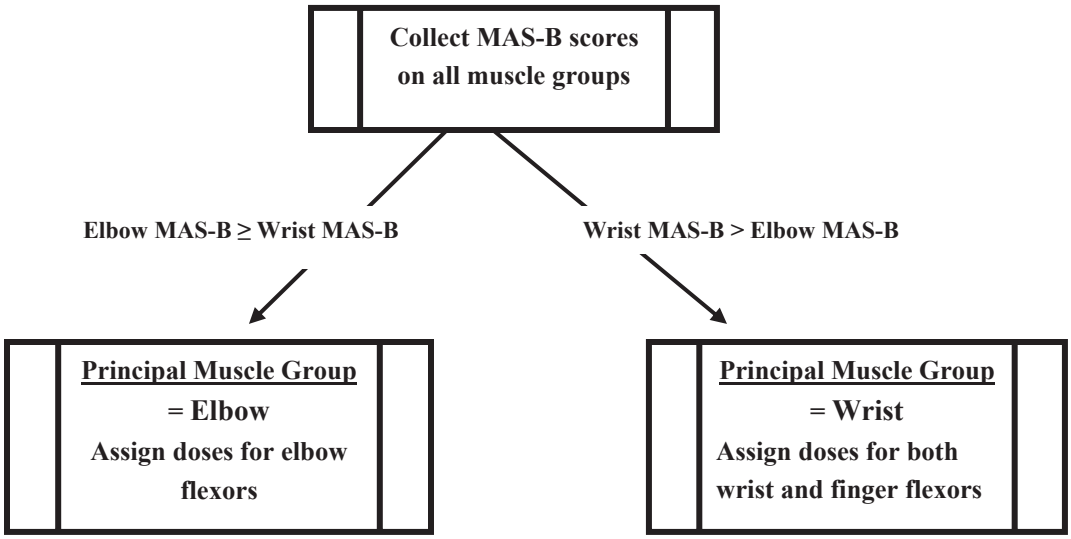
5.6.2 Determination of Principal Muscle Group for Injection

Each patient will have either the elbow flexors or the wrist flexors designated as the principal muscle group for analysis purposes (see Figure 1). The principal muscle group must have a MAS-B score of 2 or greater. If wrist flexors are identified as the principal muscle group then the wrist must have a MAS-B of 2 or greater but finger flexors need only have MAS-B of 1+.

If both the wrist and elbow flexors meet the minimum MAS-B score of 2 at baseline (day 1), then the muscle group with the higher MAS-B score will be designated as the principal muscle group. If both the wrist and elbow flexors have exactly the same MAS-B score, then the elbow flexors will be designated as the principal muscle group. Note that the last algorithm in the case of equal MAS-B score in wrist and elbow may be changed based on enrollment activity (see Section 5.5).

All muscles specified for the principal muscle group must be injected. If the elbow flexors are designated as the principal muscle group, then the biceps, brachialis, and brachioradialis must all be injected exactly according to the dose requirements specified in Table 3. If the wrist flexors are designated as the principal muscle group, both the wrist and finger flexors, which also contribute to spasticity at the wrist level, will be injected; ie, flexor carpi ulnaris and flexor carpi radialis, flexor digitorum superficialis, and flexor digitorum profundus must all be injected exactly according to the dose requirements specified in Table 3.

Figure 1 Determination of Muscle Group(s) for Injection



MAS-B = Modified Ashworth Scale – Bohannon

[redacted]

5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patients, in accordance with the conditions specified in this protocol. To prevent possible unblinding, access to study medication during the reconstitution process is prohibited for staff involved in the care and evaluation of study patients or the handling of study data throughout the study.

The lyophilized vials of study medication must be stored immediately upon receipt in a [redacted] Reconstituted study medication must be stored in the vial [redacted] If not used [redacted], study medication may not be used. Refer to the Pharmacy Manual for additional instructions.

5.8 Preparation of Study Medications/Treatments

To ensure that the same volume is injected into each of the muscles irrespective of the treatment group assignment, BOTOX (100 U vial) and placebo will be reconstituted by the IDR according to Table 2.

5.9 Treatment Administration

Patients will be injected according to the protocol-required dosing regimen.

Muscles will be injected using muscle localization techniques such as e-stimulation, sonography, and/or electromyography (EMG). Muscle localization using palpation alone is not permitted.

The study medication may be administered in conjunction with appropriate local anesthesia according to each investigator's standard practice and must be documented in the patient's medical record and appropriate eCRF. General anesthesia (drug-induced depression of consciousness) or deep sedation/analgesia (drug-induced loss of consciousness) as defined in "Practice guidelines for sedation and analgesia by non-anesthesiologists" (American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists, 2002) is prohibited regardless of the medication used. Minimal sedation (anxiolysis) or moderate sedation/analgesia (conscious sedation) in addition to local anesthesia is allowed.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measures

- MAS-B of the principal muscle group (elbow or wrist)
- CGI by Physician (for US FDA only)

6.1.2 Secondary Efficacy Measures

- CGI by Physician (for non-US FDA analyses)
- MAS-B of the finger flexor muscle group
- Goal Attainment Scale (GAS) by Physician
- Modified Tardieu Scale (MTS) of the principal muscle group

6.2 Safety Measures

- Adverse events
- Physical examination
- Urine pregnancy tests (for all females of childbearing potential)
- Hematology and serum chemistry
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)
- Body weight
- C-SSRS (for patients ≥ 6 years of age at day 1)

6.3 Examination Procedures, Tests, Equipment, and Techniques

The procedures are described in Attachment 12.1.

6.4 Other Study Supplies

The following study supplies will be provided by Allergan or a vendor contracted by Allergan:

- Laboratory kits for the collection and shipment of hematology, biochemistry, and urine samples (including pregnancy kits) will be provided by a vendor (eg, central laboratory) contracted by Allergan.
- Calibrated temperature recorder for monitoring drug storage refrigerator temperatures
- Syringe labels
- Goniometer
- Kilogram-only weight scale for selected sites (weight must be measured and collected in kilograms only)

The study sites will be responsible for providing the following supplies/equipment:

- Needles and syringes for study drug reconstitution and injection
- Sterile saline (0.9% without preservative) for study drug reconstitution
- Surgical gloves for study drug reconstitution
- [redacted]
- Access to a computer with internet connection (high-speed connection for eCRF completion)
- Standard 12-lead ECG
- Weight scale with height measure (if not supplied by Allergan)
- Centrifuge for processing lab samples
- Ultrasound and/or e-stimulation or EMG device for muscle localization techniques

6.5 Summary of Methods of Data Collection

An IVRS/IWRS will be used to screen, randomize, and manage study medication inventory. Data will be collected using eCRFs via a validated electronic data capture system (EDC). Source documents will be used and stored at the sites, and may include a patient's medical records, hospital charts, clinical charts, patient chart, copy of the EDC file, as well as the results of diagnostic tests such as laboratory tests, ultrasounds, x-rays, and ECGs. A central laboratory will be used for the analysis of all blood samples. For patients ≥ 6 years of age at day 1, the C-SSRS will be collected as a clinical interview and the scores will be collected from the designated site staff using an electronic data collection method (eg, electronic tablet).

7. Statistical Procedures

The database will be locked when all patients have completed the study. A detailed analysis plan will be generated prior to the final database lock. All planned analyses will be performed after the database has been locked and randomization data released.

7.1 Analysis Populations

Safety data will be analyzed on the basis of all treated patients based on the treatment received, defined as the safety population. Efficacy data, demographics, and background information will be analyzed on the basis of the modified intent-to-treat (mITT) population, defined as all randomized patients with a valid MAS-B baseline score of the principle muscle group and at least one post-baseline measurement at weeks 2, 4, or 6 for the MAS-B of the principle muscle group and the CGI by Physician.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

At each scheduled office visit at weeks 2, 4, 6, 8, and 12, the patient's spasticity of the designated principal muscle group will be evaluated using the MAS-B. MAS-B scores of 0, 1, 1+, 2, 3, or 4 will be coded as grades of 0, 1, 2, 3, 4, or 5, respectively. The MAS-B grade change from baseline to each post-randomization office visit and the primary endpoint, average change at weeks 4 and 6 using the multiple imputation (MI) method, will be derived for each patient. Additionally, a responder status will be determined according to whether or not a patient has at least a 1-grade reduction from baseline on the MAS-B.

The secondary efficacy measure, CGI by Physician (for US FDA, CGI by Physician is a co-primary measure), will be measured at weeks 2, 4, 6, 8, and 12. CGI is a 9-point scale from -4 (very marked worsening) to +4 (very marked improvement). Each assessment is evaluated relative to the patient's baseline status obtained at day 1. The average of scores at weeks 4 and 6 using the MI method for missing values will be derived for CGI by Physician. Additionally, a responder status will be determined according to whether or not a patient has at least +1 score of CGI by Physician. The secondary efficacy measures of MAS-B of the finger flexor muscle group, GAS, and MTS will also be collected at scheduled office visits according to the Schedule of Visits and Procedures in Table 1. The difference between slow (R2) and fast (R1) range of motion (R2 - R1; see Attachment 12.1.11 for a detailed description of the MTS) and respective change from baseline to each posttreatment office visit on the MTS will be derived. The MI method is only intended for MAS-B scores of the principle muscle group and the CGI by Physician. Missing values for other variables will not be imputed.

7.2.1 Primary Efficacy Variables

The primary efficacy variable is the grade change from baseline in MAS-B of the principal muscle group. The primary efficacy endpoint will be the average grade change from baseline in the MAS-B of the principal muscle group at weeks 4 and 6. For US FDA only, the average grade change from baseline in the MAS-B of the principal muscle group and the average CGI by Physician are co-primary efficacy variables. Grade change from baseline in the MAS-B of the principal muscle group and the CGI by Physician will be analyzed as co-primary endpoints for the average of weeks 4 and 6 (see Section 7.7).

7.2.2 Secondary Efficacy Variables

The secondary efficacy variables are CGI by Physician (for non-US FDA analyses), the grade change of MAS-B of the finger flexors, GAS by Physician, and MTS. The secondary efficacy variables of CGI by Physician and the MAS-B change from baseline for finger flexors will be evaluated at weeks 2, 4, 6, 8, and 12. The MAS-B change from baseline for finger flexors will be analyzed using the subgroup of patients with wrist identified as the principal muscle group. Functional goals (active and passive) using GAS by Physician will be evaluated separately relative to baseline at weeks 8 and 12, and MTS including the difference between slow (R2) and fast (R1) range of motion (R2 - R1) as well as respective change from baseline on the MTS of the principal muscle group at weeks 2, 4, 6, 8, and 12. Additionally changes from baseline for each R1 and R2 at each assessment point will be evaluated. In addition to each timepoint, the average of the weeks 4 and 6 MAS-B change from baseline of the finger flexors and CGI by Physician will be analyzed.

[redacted]

7.3 Hypothesis and Methods of Analysis

7.3.1 Primary Efficacy Analyses

The primary efficacy analyses will be based on the mITT population. The primary analysis will be conducted for the average change from baseline in MAS-B score for the principal muscle group at weeks 4 and 6 using the MI method for missing values. The statistical null hypothesis is that both higher dose (6 U/kg) and lower dose (3 U/kg) have the same mean as placebo. The alternative hypothesis is that at least one study dose has a different mean than placebo. The hypothesis will be tested based on the least square (LS) mean differences from an analysis of covariance (ANCOVA) at a significance level of 0.05. The primary variable will be summarized by treatment group. The difference of LS means of each dose group and the placebo group from the ANCOVA model will be used to test the null hypothesis. The ANCOVA will be performed using the following model statement:

Primary variable = baseline MAS-B + age group + principal muscle group + treatment group + study center + 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). Baseline MAS-B grade is a continuous variable included as a covariate. Two tests will be performed based on the pairwise comparisons: 6 U/kg versus placebo and 3 U/kg versus placebo, each at a 0.05 significance level.

To control the type I error rate for the primary endpoint of the average change from baseline in MAS-B score of the principal muscle group at weeks 4 and 6, a gatekeeping approach will be used for this variable (Dmitrienko et al, 2005). Specifically, for the average of the grade change from baseline in MAS-B at weeks 4 and 6, the LS mean difference of 6 U/kg versus placebo from the ANCOVA will be tested first. If the test is not statistically significant at the level of 0.05, the test of the LS mean difference of 3 U/kg versus placebo will not be considered statistically significant regardless of its p value. Otherwise if the test for 6 U/kg versus placebo is statistically significant, then the test for 3 U/kg versus placebo will be evaluated based on its p value.

For sensitivity analysis purposes to supplement the primary analyses, Mixed Model Repeated Measures (MMRM) with an unstructured covariance matrix will be conducted. The model will include baseline MAS-B 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. A summary of the percentage of missing MAS-B scores by visit will also be provided. Additional sensitivity analyses for the MAS-B changes from baseline at each assessment timepoint will also be performed using ANCOVA with the same model as specified above, and linear contrasts will be used to estimate the treatment differences between each study dose and placebo. The sensitivity analyses will be conducted using observed data.

In addition, the frequency distribution of the grade changes from baseline in the MAS-B, as well as the percentage of responders (with at least a 1-grade reduction in MAS-B), will be summarized by treatment group at each posttreatment office visit. A logistic regression analysis will also be performed on the responder status at each posttreatment visit with a covariate of baseline MAS-B and factors of age group, principal muscle group, treatment group, study center, and previous botulinum toxin exposure, if applicable. The additional analyses will be conducted using observed cases unless stated otherwise.

For US FDA only, CGI by Physician will be a co-primary variable (see Section 7.7 for description of analyses).

7.3.2 Secondary Efficacy Analyses

The observed cases will be used for secondary efficacy analyses unless stated otherwise. CGI by Physician will be rated at study weeks 2, 4, 6, 8, and 12. CGI by Physician will be summarized and analyzed by ANCOVA as the average of values at weeks 4 and 6 using the MI method for missing values, as well as at each assessment timepoint using observed cases. The frequency distribution of the CGI scores, as well as the percentage of responders (CGI score of at least +1), will be summarized by treatment group at each posttreatment timepoint. A logistic regression analysis will also be performed on the responder status at each posttreatment timepoint with factors age group, principal muscle group, treatment group, study center, and previous botulinum toxin exposure, if applicable.

The average grade change from baseline for weeks 4 and 6 in the MAS-B for finger flexor muscle groups will be summarized by treatment group and analyzed by ANCOVA using the subgroup of patients with wrist identified as the principal muscle group. The grade change from baseline in the MAS-B for finger flexor muscle groups at each timepoint will also be summarized by treatment group and analyzed by ANCOVA using the same subgroup. The ratings for each of the 2 goals using GAS at weeks 8 and 12 will be summarized by treatment group and analyzed by ANCOVA as specified in Section 7.3.1 to assess the treatment differences. For MTS, the difference between slow and fast motion (R2 - R1) and the individual R2 and R1 values in degrees for the principal muscle group, as well as the respective changes from baseline, will be summarized by treatment group and analyzed by ANCOVA.

[redacted]

[redacted]

[redacted]

[redacted]

7.3.4 Safety Analyses

Safety variables, including the incidence of adverse events, the incidence of suicide-related events using the C-SSRS (for patients ≥ 6 years of age at day 1), laboratory test values and changes from baseline, as well as vital signs and their change from baseline, will be summarized by treatment group using the safety population. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events and medical history. The incidence of adverse events (both pre-treatment events and treatment-emergent events) will be tabulated by primary system organ class and preferred term for each treatment group. Possible distant spread of toxin adverse events will be assessed using a standardized methodology.

Descriptive statistics will be presented for vital signs and numeric laboratory tests and the respective changes from baseline. All laboratory values will be presented by descriptive statistics. In addition, laboratory values outside the normal reference ranges for each patient at each applicable visit will be identified and evaluated against baseline via shift table analysis. Potentially clinically significant abnormal values may be identified or summarized descriptively.

7.4 Subgroup Analyses

Among the efficacy variables, the primary and selected secondary efficacy variables will be summarized by baseline MAS-B score (2 and > 2), age (≤ 6 years and > 6 years), designated principal muscle group, and previous exposure to botulinum toxin.

The analyses of adverse events will be presented by type of anesthesia, previous exposure to botulinum toxin, and age group, if appropriate.

7.5 Sample Size Calculation

Approximately 224 patients will be enrolled to ensure that at least 213 patients (71 per treatment group) will complete the study.

Using a 2-sample t-test, a significance level of 0.05, and the assumptions in Table 4, the power for MAS-B change from baseline is 86% (PASS, Hintze, 2008). The calculation is based on assumptions for the 6 U/kg group and the placebo group. Since there are 2 co-primary endpoints for the US FDA analysis, for the 6 U/kg group the power for CGI by Physician is calculated to be 94%, and the overall power for the US FDA co-primary endpoints will be at least 81%. The assumptions for MAS-B and CGI treatment differences were based on completed Studies 191622-008, BTOX-133/134/8051, BTOX-418/422-8051, BTX108509 and 112958, with standard deviation assumptions based on observed masked data from this ongoing study. The conservative overall power is calculated assuming that the MAS-B and CGI are independent. Note that the improvements in MAS-B were generally positively correlated with CGI scores based on completed adult spasticity studies.

Table 4 Sample Size Assumptions and Power Calculations

Endpoint	Average difference between 6 U/kg BOTOX group and placebo group at Weeks 4 and 6	Standard Deviation	Power
MAS-B Change from Baseline	-0.5	0.98	86%
CGI by Physician (Co-primary for US FDA Analysis)	0.6	1.02	94%
Overall Power			81%

CGI = Clinical Global Impression of Overall Change; MAS-B = Modified Ashworth Scale - Bohannon

7.6 Interim Analyses

There is no planned interim analysis.

7.7 Additional Analysis/Inference for US FDA

Analyses are as described in all preceding sections except for the items described below.

7.7.1 Primary Efficacy Analyses

There are 2 co-primary endpoints: the average grade change from baseline in the MAS-B of the principal muscle group at weeks 4 and 6 and the average CGI by Physician at weeks 4 and 6. For both co-primary endpoints, the statistical null hypothesis is that both the higher dose (6 U/kg) and the lower dose (3 U/kg) have the same mean as placebo. The alternative hypothesis is that at least one study dose has a different mean than placebo. In addition to the primary statistical analyses cited in Section 7.3.1 for the average grade change from baseline in MAS-B score of the principal muscle group at weeks 4 and 6, the average CGI by Physician at weeks 4 and 6 will be analyzed using the same statistical method (with the same ANCOVA model and the MI method).

The Hochberg procedure (Hochberg and Tamhane, 1987) will be used to control the family-wise type I error rate. With 2 doses and 2 co-primary endpoints in each dose, the maximum p value for the 2 co-primary endpoints in each dose will be used in the Hochberg procedure. We first define 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).

p1 and p2 will be sorted in an increasing order to get $p(1) \leq p(2)$. The following decision rule will then be applied:

Step 1: If $p(2) \leq 0.05$, both doses are considered efficacious; otherwise go to step 2.

Step 2: If $p(1) \leq 0.025$, its corresponding dose is considered efficacious; otherwise go to step 3.

Step 3: Neither dose is considered efficacious.

For sensitivity analysis purposes to supplement the co-primary analyses, MMRM with unstructured covariance matrices will be conducted for the co-primary endpoints of MAS-B and CGI. The models will include a covariate of baseline MAS-B and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure. A summary of the percentages of missing MAS-B and CGI scores by visit will also be provided. Additional sensitivity analyses for the MAS-B

changes from baseline and CGI scores at each assessment time point will also be performed using ANCOVA with the same model as specified for the primary analysis, and linear contrasts will be used to estimate the treatment differences between each study dose and placebo. The sensitivity analyses will be conducted using observed data.

8. Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the schedule visits and procedures.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient/legally authorized representative and a patient wishing to participate or his/her legally authorized representative must give informed consent and, when applicable, minor assent prior to any study-related procedures or change in treatment. The patient/legally authorized representative must also give authorization (US only), data protection consent (Europe only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Further information is provided in Section 10.1.

Each patient who provides informed consent and/or assent will be assigned a patient number that will be used on patient documentation throughout the study.

8.2 Procedures for Final Study Entry

At visit 3 (randomization) patients must meet all of the inclusion criteria and must not meet any of the exclusion criteria. Also, all females of childbearing potential must have a negative urine pregnancy test.

The patient is considered to have entered this study at the time of randomization to treatment on day 1. See Section 5.5 for the method for assignment to treatment groups/randomization.

8.3 Visits and Associated Procedures

Ideally, the CGI by Physician should be performed prior to administering the MAS-B and MTS to reduce the likelihood of the CGI being influenced by the spasticity evaluations. An alternative is to have different evaluators rate the CGI and perform the spasticity assessments (MAS-B and MTS). Whenever possible each procedure should be performed by the same evaluator for an individual patient throughout the trial. Study personnel should avoid reviewing or discussing the MAS-B, MTS, or CGI scores from previous visits when they are completing these assessments.

[redacted]

In addition to the procedures outlined below, patients are to complete approximately 1-hour weekly standardized OT sessions (see Section 4.5.3) from week -2 through week 11.

8.3.1 Visit 1: 2 to 4 Weeks Before Day 1 (Screening)

- Obtain written informed consent and minor assent and data protection from the patient and/or legally authorized representative prior to performing any study-related procedures.
- Obtain patient identification number from the IVRS/IWRS.
- Obtain demographic information, including date of birth. Ensure that the patient will be ≥ 2 years and ≤ 16 years and 11 months (prior to 17th birthday) on projected day 1, randomization visit.
- Obtain medical and surgical history, ensuring that the patient has upper limb monoplegic, hemiplegic, or triplegic spasticity with single-arm sparing resulting from cerebral palsy, or is post-stroke with the stroke onset prior to age 2 and at least 12 months prior to the day 1 visit. Include details on histories of dysphagia, drooling, aspiration pneumonia, seizure, and epilepsy.
- Obtain past (in the last 3 months) and current concomitant medication use (including prescription, non-prescription, and herbal medications) and procedures. Previous use of botulinum toxin, phenol, and alcohol injections should be included.
- Perform C-SSRS (for patients ≥ 6 years of age at day 1).
- Perform physical examination, including measurement of height and weight.
- Obtain vital signs (blood pressure, pulse rate, respiratory rate, and body temperature).
- Perform ECG.
- Collect blood sample for hematology, serum chemistry, and HbA1c analysis after informed consent is signed. Fasting blood samples should be collected unless the

patient is not able to fast for approximately 8 hours. Patients who are willing to fast and did not come to the visit in a fasting state may return prior to the day 1 visit for blood sample collection as long as the laboratory results can be received and reviewed at or before the day 1 visit.

- Perform urine pregnancy test for all females of childbearing potential.
- Discuss choice of contraceptive method with female patients of childbearing potential and/or their caregivers and document method of contraception in the source documentation and the eCRF. Counsel such female patients/caregivers regarding the importance of maintaining their agreed upon method of contraception throughout the study.
- Ascertain spasticity only in the study upper limb using the HAT.
- Assess dystonia only in the study upper limb using the BAD scale.
- Assess manual ability only in the study upper limb using the MACS.
- Assess gross motor function using the GMFCS-E&R.
- Assess spasticity in the elbow, wrist, and finger in the study limb using the MAS-B.
- Perform MTS in the elbow, wrist, and finger in the study limb. Passive range of motion for the elbow, wrist, and finger for can be performed during the MTS assessment in order to verify inclusion criteria.
- Evaluate inclusion and exclusion criteria.
    - For patients who are not eligible for the study (screen failures), depending on the reason(s) for screen failure, collect detailed information regarding spasticity, contracture, respiratory condition or functions associated with increased risk of aspiration, seizure, and epilepsy.
- Query patient for any adverse event that has occurred and any related medication used or procedure performed since signing the informed consent.
- Instruct patient/caregiver to initiate approximately 1-hour weekly standardized OT session with the therapist at week -2 and schedule through the last session at week 11.
- Schedule the next visit, if applicable.

8.3.2 Visit 2: Week -2 (OT Start) – Visit with the Occupational Therapist

- Establish with each patient/caregiver 2 goals for the GAS (1 functional active and 1 functional passive) and define each level of patient-specific goal achievement for each of the 2 goals using the GAS by Physician.

- With the patient/caregiver, review protocol-specified standardized weekly OT and develop a patient-tailored OT plan.
- If patient reports adverse events to the therapist, the therapist should inform the Study Coordinator for further follow-up regarding adverse events and related medication used or procedures performed.
- Schedule the next weekly OT session.

8.3.3 Visit 3: Day 1 (Randomization/Treatment)

- **The following procedures must be performed prior to the study treatment:**
  - [redacted]
  - Note any update to medical and surgical history, if needed. Query patient/caregiver for any adverse events prior to study treatment.
  - Perform C-SSRS (for patients ≥ 6 years of age at day 1).
  - For patients who are not eligible for the study (screen failures), depending on the reason(s) for screen failure, collect detailed information regarding spasticity, contracture, respiratory condition or functions associated with increased risk of aspiration, seizure, and epilepsy.
  - Obtain any update to concomitant medication use.
  - Obtain any information on new medical procedures or tests since the last visit.
  - Obtain vital signs (blood pressure, pulse rate, respiratory rate, and body temperature).
  - Obtain weight in kilograms.
  - Review the results of the screening safety laboratory tests.
  - Perform urine pregnancy test for all females of childbearing potential.
  - Assess spasticity in the elbow, wrist, and finger in the study limb using the MAS-B.
  - Perform MTS in the elbow, wrist, and finger in the study limb. Passive range of motion for the elbow, wrist, and finger can be performed during the MTS assessment in order to verify inclusion criteria.
  - Confirm the 2 goals selected and the definitions of patient-specific goal achievement using the GAS by Physician.

  - [redacted]
  - If applicable, counsel female patients and/or caregivers of childbearing potential regarding the importance of maintaining their agreed upon method of contraception throughout the study.
  - Confirm patient continues to meet study inclusion and exclusion criteria.
  - Identify principal muscle group and calculate the dose for study treatment using the dose calculation worksheet and dose verification eCRF.
  - Access the IVRS/IWRS to randomize the patient and obtain a study medication kit number.
- Inform IDR that patient is qualified for the study treatment and send blinded dosing summary to the IDR for study drug preparation.
- Inject assigned study treatment as per protocol (see Section 5.9).
- Query patient/caregiver for any adverse events and related medication used or procedure performed.
- Remind patient/caregiver of the importance of the weekly OT session.
- Schedule the next visit.

8.3.4 Visits 4, 5, 6, and 7: Weeks 2, 4, 6, and 8 (Follow-up Visits)

- [redacted]
- [redacted]
- [redacted]
- Query patient/caregiver for any adverse events.
- Perform C-SSRS (for patients ≥ 6 years of age at day 1).
- Obtain any update to concomitant medication use.
- Obtain any information on new medical procedures or tests since the last visit.
- Rate the CGI by Physician before performing the spasticity assessments (MAS-B and MTS).
- Assess spasticity in the elbow, wrist, and finger in the study limb using the MAS-B.
- Perform MTS on the elbow, wrist, and finger in the study limb.
- Only at visit 7/week 8, evaluate the patient's performance for each of the 2 goals using the GAS by Physician.

- [redacted]
- Remind patient/caregiver of the importance of the weekly OT session.
- Schedule the next visit.

8.3.5 Visit 8: Week 12 or Early Termination (Exit Visit)

- [redacted]
- Query patient/caregiver for any adverse events.
- Perform C-SSRS (for patients ≥ 6 years of age at day 1).
- Obtain any update to concomitant medication use.
- Obtain any information on new medical procedures or tests since the last visit.
- Perform physical examination, including measurement of weight.
- Obtain vital signs (blood pressure, pulse rate, respiratory rate, and body temperature).
- Collect blood sample for hematology, serum chemistry, and hemoglobin A1c analysis for all patients. Fasting blood samples should be collected unless the patient is not able to fast for approximately 8 hours.
- Perform urine pregnancy test for all females of childbearing potential.
- Rate the CGI by Physician before performing the spasticity assessments (MAS-B and MTS).
- Assess spasticity in elbow, wrist, and finger in the study limb using the MAS-B.
- Perform MTS on the elbow, wrist, and finger in the study limb.
- Evaluate the patient's performance for each of the 2 goals using the GAS by Physician.
- [redacted]
- Any adverse event that is marked "ongoing" at the exit visit must be followed-up as appropriate.
- Enter patient exit status in the IVRS/IWRS.
- If the patient/legally authorized representative agrees to participate in the follow-on Study 191622-105, have the patient/legally authorized representative sign the consent/assent/privacy form and proceed with the day 1 visit for that study.

8.4 Instructions for the Patients

Patients/caregivers will be instructed to strictly follow the study visit schedule and report any changes in condition to the investigative site.

Patients/caregivers will be instructed to complete the approximately 1-hour weekly standardized OT sessions (see Section 4.5.3) from week -2 through week 11.

8.5 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the investigator. Additional examinations may be performed as necessary to ensure the safety and well being of patients during the study. eCRFs will be completed for each unscheduled visit.

8.6 Compliance With Protocol

At each post-baseline visit, patients/caregivers will be questioned on concomitant medication use and procedures or tests since the last visit to ensure protocol compliance.

8.7 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time or may be withdrawn at the discretion of the investigator and Allergan due to clinically significant findings including, but not limited to, adverse events and clinical laboratory abnormalities. Allergan will be notified of early patient discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate eCRF.

The last visit for the patient will be considered the study exit visit. Procedures for week 12 will be performed if the study exit visit occurs earlier than week 12.

8.8 Withdrawal Criteria

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. The investigator and Allergan also have the right to withdraw a patient from the study at any time for any reason. Patients who withdraw from the study will not be replaced.

8.9 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Adverse events will be assessed and documented, as appropriate, throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient/caregiver a general, non-directed question such as “How have you been feeling since the last visit?” Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Note: Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked "ongoing" at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study drug must be immediately reported no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan or its designee as listed on the Allergan Study Contacts Page and recorded on the serious adverse event form. All patients with a serious adverse

event must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. Provide Allergan with a complete, written case history (adverse event report form) which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unmasking of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unmasking study medication. The investigator must inform the sponsor (Allergan Medical Safety Physician) of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel calling into the IVRS/IWRS system via password-protected access. The reason for breaking the code must be recorded in the patient's source documents.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Human Subjects

10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

Written parental/legally authorized representative informed consent in addition to a separate written minor consent and/or assent (in accordance with any applicable state and local laws/regulations) are required for each minor study patient prior to study enrollment or any study-related procedures in the study.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (21 CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards

to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization (US sites only), data protection consent (European sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ["EU Directive"]).

In accordance with HIPAA requirements, additional purposes of this study include the following:

- to publish anonymous patient data from the study, and
- to create and maintain a data repository

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- Patient's name
- Patient's contact information
- The date that the patient entered the study, patient number, and medication kit number
- The study title and/or the protocol number of the study and the name of Allergan
- A statement that informed consent and/or assent, if applicable was obtained (including the date). A statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date).
- A statement that patient meets all the inclusion criteria and does not meet any of the exclusion criteria. If a patient does not qualify for the study, a screen failure reason must be noted.
- Dates of all patient visits
- Medical and surgical history
- Documentation of results of all procedures conducted during the course of the trial, including the dose determination process. [redacted]
- The results of laboratory tests performed by the site (eg, results of hematology, serum chemistry, HbA1c, and urine pregnancy tests).
- All concurrent medications (list all prescription, non-prescription and herbal medications being taken 3 months prior to or at the time of enrollment). At each subsequent visit, changes to the list of medications and concurrent procedures should be recorded.
- Occurrence and status of any adverse events
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded in each patient's eCRF and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the eCRF) to ensure that the observations and findings are recorded in the eCRFs correctly and completely. The eCRFs are to be completed in a timely manner.

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study-related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and electronic copies of eCRFs must be maintained on file.

For countries falling within the scope of the ICH guidelines, the Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

The investigational materials will be packaged and labeled in identically appearing vials. The study treatment will be identified as an investigational compound. The study number and kit number will be identified on the unit label.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, and the number of units returned to

Allergan or Allergan designee during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be reconstituted and administered only by appropriately qualified persons to patients in the study. The medication is to be used in accordance with the protocol under the direct supervision of an investigator.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.6 Monitoring by the Sponsor

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Laboratory specimens for blood chemistry panel, hematology, and HbA1c will be sent to a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] certification) to be assayed using validated methods. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.

Approximately 7 mL of blood is estimated to be collected at a given visit. Please refer to the Laboratory Manual for details regarding specimen sample collection, processing, storage, and shipping procedures.

10.8 Publications

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As

this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

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12. Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

Further details are provided in the Study Procedure Manual.

12.1.1 Physical Examination

The investigator physician will examine the patient for any detectable abnormalities of the following body systems: general appearance, head/eyes/ears/nose/throat, lungs, heart/cardiovascular, abdomen, neurologic, extremities, back (including spinal deformity), musculoskeletal, lymphatic, skin, and other. Weight in kilograms and height (height measured at screening visit only) should be measured consistently throughout the study using a ruler and calibrated scale; patients should wear similar clothing and remove items such as splints, orthotics, braces, shoes, heavy clothes, and wet diapers for each weight measurement.

12.1.2 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate will be taken after patients have been at rest (seated) for at least 2 minutes. Blood pressure will be recorded in mm Hg. Pulse rate and respiratory rate will be measured in beats or breaths per minutes, respectively, by counting over 30 seconds and multiplying by 2.

Oral, axillary, temporal, rectal, or tympanic body temperature may be taken. The same route should be used throughout the study. If oral temperature is taken, the patient should not have any oral intake for at least 5 minutes prior to the measurement.

12.1.3 Electrocardiogram

A standard 12-lead ECG will be performed at screening to ensure that a patient does not have a clinically significant condition that may indicate an unacceptable safety risk for study participation.

12.1.4 Hematology and Serum Chemistry

During screening, patients will need to have a blood sample for laboratory evaluations collected after informed consent is signed. Another blood sample will be collected at the study exit visit. Blood specimens will be collected using standard laboratory instructions and procedures provided by the central laboratory. Fasting blood samples should be collected unless the patient is not able to fast for approximately 8 hours. Patients who are willing to fast and did not come to the screening visit in a fasting state may return prior to the day 1

visit for blood sample collection as long as the laboratory results can be received and reviewed at or before the day 1 visit. The blood specimens will be analyzed for the following:

Hematology	hemoglobin	hematocrit	red blood cells
	white blood cells	neutrophils	bands
	lymphocytes	monocytes	basophils
	eosinophils	platelets	
Electrolytes	sodium	potassium	bicarbonate
	chloride	phosphorus	calcium
Chemistry	glucose	creatinine	urea nitrogen
	total bilirubin	alkaline phosphatase (total plus bone and liver fractions)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
	alanine aminotransferase (serum glutamic pyruvic transaminase)	albumin	
Other	HbA1c	25 hydroxyl vitamin D	Parathyroid hormone if alkaline phosphatase bone fraction is abnormal

Reference ranges for alkaline phosphatase and glucose are shown in Table 5.

Table 5 Reference Ranges for Alkaline Phosphatase and Glucose

Parameter	Age (Years)	Range
Alkaline phosphatase		
Female	1 to 3	125 to 320 U/L
	4 to 6	150 to 370 U/L
	7 to 9	150 to 440 U/L
	10 to 11	150 to 530 U/L
	12 to 13	110 to 525 U/L
	14 to 15	55 to 305 U/L
	16 to 19	40 to 120 U/L
Male	1 to 3	125 to 320 U/L
	4 to 6	150 to 370 U/L
	7 to 9	150 to 440 U/L
	10 to 11	150 to 470 U/L
	12 to 13	160 to 500 U/L
	14 to 15	130 to 530 U/L
	16 to 19	60 to 270 U/L
Bone-specific alkaline phosphatase (ostase)		
Female	1 to 6	0 to 189 U/L
	7 to 9	0 to 246 U/L
	10 to 13	0 to 340 U/L
	14 to 15	0 to 91 U/L
	≥ 16	0 to 55 U/L
Male	1 to 6	0 to 208 U/L
	7 to 9	0 to 264 U/L
	10 to 15	0 to 340 U/L
	16 to 19	0 to 165 U/L
Glucose	All ages	70 to 100 mg/dL, 3.9 to 5.6 mmol/L

Note: Reference ranges were received from Covance Laboratory as of 16 January 2012.

12.1.5 Pregnancy Test

Females of childbearing potential will have urine pregnancy tests performed at screening, day 1 (randomization) prior to injection, and the exit visit. Pregnancy test kits will be provided by Allergan or an Allergan contracted central laboratory and will be administered according to the instructions provided with the tests. A female of childbearing potential is defined as a female who is post menarche.

12.1.6 Barry-Albright Dystonia (BAD) Scale

The BAD scale (Barry et al, 1999) is used to assess the level of dystonia, which is a comorbid condition in patients with cerebral palsy. This scale contains a 5-point, criterion-based, ordinal scale assessing dystonia in 8 body regions: eyes, mouth, neck, trunk, and the 4 extremities.

In this study, the investigator will only assess the patient's dystonia level in the study limb identified for this study using the BAD scale at the screening visit. Patients with dystonia defined as level 3 or greater by the BAD for the study limb will not be eligible from the study.

Below is the specific scoring description for the upper extremities:

Signs of dystonia of the upper extremities include sustained muscle contractions causing abnormal posturing of the upper extremities.

0 Absence of upper extremity dystonia

1 Slight. Dystonia less than 10% of the time and does not interfere with normal positioning and/or functional activities

2 Mild. Dystonia less than 50% of the time and does not interfere with normal positioning and/or functional activities

3 Moderate. Dystonia more than 50% of the time and/or dystonia that interferes with normal positioning and/or upper extremity function

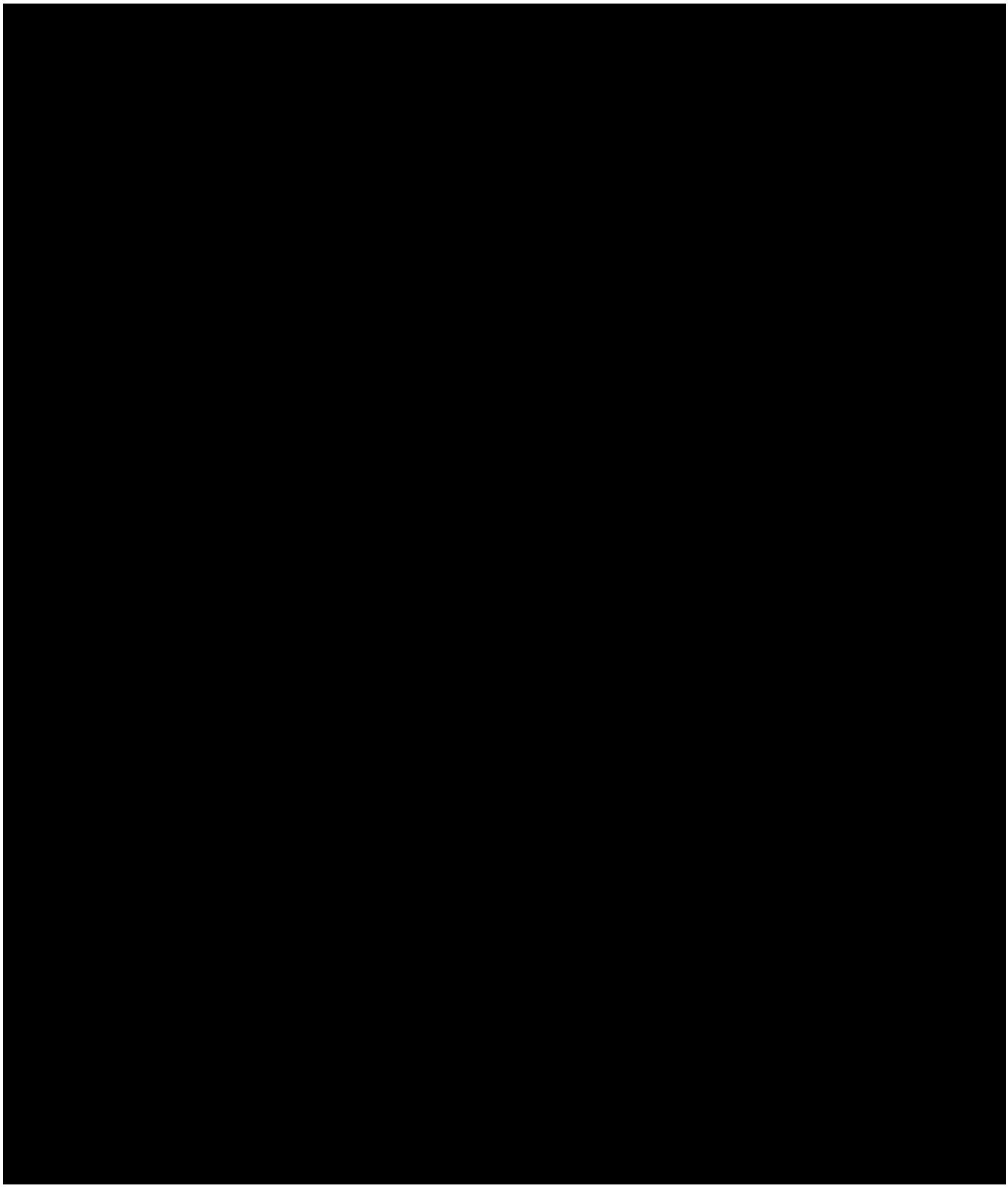
4 Severe. Dystonia more than 50% of the time and/or dystonia that prevents normal positioning and/or upper extremity function (eg, arms restrained in wheelchair to prevent injury)

* Unable to assess upper extremity movements

12.1.7 Hypertonia Assessment Tool (HAT)

The HAT is a clinical assessment tool developed to differentiate subtypes of hypertonia in the pediatric population. This scale contains 7 items and each item can be scored as 0 (negative) or 1 (positive). The results determine if a patient has spasticity, dystonia, rigidity, or mixed tone (Jethwa et al, 2010).

For this study, HAT will be performed on the study upper limb to ensure the presence of spasticity.



12.1.8 The Manual Ability Classification System (MACS)

The MACS provides a functional description of how a child with cerebral palsy uses his or her hands when handling objects in daily activities. This measure focuses on typical manual performances, not the maximal capacity (Eliasson et al, 2006); and is a description of function of both hands together. MACS should be conducted by asking someone who is familiar with the child, not by performing an assessment. The child's level of manual ability can be depicted by one of the following levels:

I. Handles objects easily and successfully

II. Handles most objects but with somewhat reduced quality and/or speed of achievement

III. Handles objects with difficulty; needs help to prepare and/or modify activities

IV. Handles a limited selection of easily managed objects in adapted situations

V. Does not handle objects and has severely limited ability to perform even simple actions

While this scale is developed specifically for patients with cerebral palsy, it will be applied to the post-stroke patients in this study for screening purposes. Investigators will review patient's manual ability at the screening visit. Patients with MACS level I-IV will be eligible for the study.

12.1.9 Gross Motor Function Classification System – Expanded and Revised (GMFCS–E&R)

The GMFCS-E&R for cerebral palsy is based on self-initiated movement (Palisano et al, 2007). The emphasis of this scale is on sitting, transfers, and mobility, and focuses on determining which level best represents the child's present ability and limitations in gross motor function. Instead of reflecting what the child can do best (capability), this scale focuses on his or her usual performance in home, school, and community settings.

Five levels are included in this scale:

Level I	Walks without limitations
Level II	Walks with limitations
Level III	Walks using a hand-held mobility device
Level IV	Self-mobility with limitations; may use powered mobility
Level V	Transported in a manual wheelchair

Detailed descriptions are provided for each level of classification by age groups (before 2nd birthdays, between 2nd and 4th birthdays, between 4th and 6th birthdays, between 6th and 12th birthdays, and between 12th and 18th birthdays). While this scale is developed specifically for patients with cerebral palsy, it will also be applied to the post-stroke patients in this study for screening purposes. The investigator will assess the patient's motor function using GMFCS-E&R at the screening visit. Patients with GMFCS-E&R levels I to IV will be eligible for the study.

12.1.10 Modified Ashworth Scale - Bohannon (MAS-B)

The MAS-B will be used to evaluate spasticity based on grading the resistance encountered in a specific muscle group by means of passively moving a limb through its range of motion at a study-specified velocity. The resistance encountered to passive stretch is graded from 0 = no increase in muscle tone to 4 = affected part(s) rigid in flexion or extension (Bohannon and Smith, 1987). The same investigator should perform this measure at each visit, if possible.

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

Please refer to the Study Procedure Manual for detailed instructions on performing the MAS-B on the elbow, wrist, and finger muscle groups.

12.1.11 Modified Tardieu Scale (MTS)

The MTS will be used to determine the passive range of movement at different movement velocities, V1 (as slow as possible) and V3 (as fast as possible), with the relative difference between a slow and a fast velocity passive stretch determining the dynamic component of the muscle contracture (Love et al, 2001).

At each visit, the same investigator (when possible) will measure 2 joint angles by goniometer: the R1 angle, which is the "angle of catch" after a fast velocity (V3) stretch, and the R2 angle, which is defined as the passive joint range of movement following a slow velocity (V1) stretch. The R2 – R1 value indicates the level of dynamic contracture in the joint. Measurements of R1 and R2 should be done at approximately the same time of day at each visit using a constant position for the affected study upper limb being evaluated. The R1 angle should be measured prior to the R2 angle.

Please refer to the Study Procedure Manual for detailed instructions on performing the MTS on the elbow, wrist, and finger muscle groups.

12.1.12 Goal Attainment Scale (GAS) by Physician

The GAS by Physician will be used to measure functional goal attainment relative to the effect of the study intervention. Goals should be specific, measurable, achievable and realistic, resource sensitive, and timed (SMART). At week -2, two goals will be selected by the patient and family in consultation with the physician investigator and/or treating therapist relative to the upper limb impairment due to spasticity. These goals will be confirmed at the day 1 visit. Two functional goals will be established for each patient: a functional active goal and a functional passive goal. After the functional goals (active and passive) are set, they should remain the same throughout the study. It is crucial to define all the levels of the goal. Goal achievement will be assessed by the physician investigator taking into consideration input from the treating therapist, caregiver, and/or patient.

The following scale will be used to evaluate the level of achievement of the 2 goals:

-3	Worse than start
-2	Equal to start: the patient's initial condition; no change
-1	Less than expected: slight improvement, but below the defined therapeutic goal
0	Expected goal: attains the defined therapeutic goal
+1	Somewhat more than expected: improvement slightly exceeds the defined therapeutic goal
+2	Much more than expected: improvements clearly exceed the defined therapeutic goal

[redacted]

12.1.15 Clinical Global Impression of Overall Change (CGI) by Physician

Ideally, the CGI by Physician should be performed prior to administering the MAS-B and MTS to reduce the likelihood of the CGI being influenced by the spasticity evaluations. An alternative is to have different evaluators rate the CGI and perform the spasticity assessments (MAS-B and MTS). Whenever possible each procedure should be performed by the same evaluator for an individual patient throughout the trial. Study personnel should avoid reviewing or discussing the MAS-B, MTS, or CGI scores from previous visits when they are completing these assessments.

Each assessment should be evaluated relative to the patient's condition prior to entering the study. The physician investigator should make an assessment of the change (improvement or worsening) from baseline (day 1) taking into account the patient's clinical condition and severity of side effects. The investigator should choose a score that indicates his/her assessment about any therapeutic effects from the study intervention. Several factors can be considered when assigning a score including but not limited to assessment of any specific benefit/detriment to the patient, adverse events, risk/benefit of the study intervention, any effects on the patient's social and/or psychological status.

"How is the subject doing in his/her life since he/she received the study medication?":

-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

[redacted]

[redacted]

12.1.18 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al, 2011) is a semistructured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior over a specified time period (eg, prior year, since last visit). The measurement of suicidal ideation is based on 5 "yes" or "no" questions (plus a description if answered "yes") arranged in order of increasing severity. If the patient answers "yes" to either question 1 or 2, the intensity of ideation will then assessed in 5 additional questions relating to the frequency, duration, controllability, deterrents, and reasons for the most severe ideation. Suicidal behavior is then assessed by asking further questions to categorize the behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. The interview is used in full only if the initial questions are positive; this assessment is completed at all scheduled clinic visits at which other clinical assessments are to be carried out.

If any item(s) on the C-SSRS are answered with "yes", a physician investigator must review patient's responses in order to:

a. at screening and baseline determine patient's study eligibility and potential need for referral to a mental health professional, and

b. during the study evaluate patient's need for appropriate medical management such as referral to a mental health professional

A significant risk of suicide is defined as a "yes" in answer to: a) questions 4 or 5 on the suicidal ideation section; or b) any questions on any item in the suicidal behavior section.

This must be reported as a serious adverse event and followed up accordingly (see Sections 9.1.2 and 9.3 of the study protocol). Additionally, if a patient responds "yes" to any of the suicidal ideation questions 1 to 3, the investigator should apply clinical judgment to determine the need for reporting as an adverse event or serious adverse event and the need for any referral.

The C-SSRS is available in several versions designed for use in clinical trials. Appropriate versions of the scale will be used in this trial.

12.2 Package Insert/Summary of Product Characteristics

The appropriate package insert or Summary of Product Characteristics will be supplied to investigators in countries where the product is marketed.

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
ANCOVA	analysis of covariance
BAD	Barry-Albright Dystonia scale
BoNT-A	botulinum neurotoxin type A
BOTOX®	botulinum toxin type A purified neurotoxin complex (US Adopted Name, onabotulinumtoxinA)
CFR	Code of Federal Regulations (US)
CGI	Clinical Global Impression of Overall Change
CNS	central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMG	electromyography
EU	European Union
FDA	Food and Drug Administration
GAS	Global Attainment Scale
GCP	Good Clinical Practices
GMFCS-E&R	Gross Motor Function Classification System Expanded and Revised
HAT	Hypertonia Assessment Tool
HbA1c	glycosylated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information
ICH	International Conference on Harmonisation
IDR	Independent Drug Reconstitutor
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LS	least square
MACS	Manual Ability Classification System
MAS-B	Modified Ashworth Scale – Bohannon
Max	maximum

MI	multiple imputation
MMRM	Mixed Model Repeated Measures
mITT	modified intent-to-treat
MTS	Modified Tardieu Scale
NA	not applicable
No.	number
NOAEL	no-observable-adverse-effect level
OT	occupational therapy
PASS	power analysis and sample size
PT	physical therapy
[redacted]	[redacted]
R1	fast range of motion (R1 angle is the “angle of catch” after a fast velocity [V3] stretch)
R2	slow range of motion (R2 angle is the passive joint range of movement following a slow velocity [V1] stretch
SDRC	Safety Data Review Committee
U	unit, corresponding to the median lethal dose (LD_{50}) in mice
US	United States
V1	slow velocity
V3	fast velocity

12.4 Protocol Amendment 1 Summary

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Double-blind Study

Protocol 191622-101, Amendment 1

Date of Amendment: 30 March 2012

Amendment Summary

This summary includes changes made to Protocol 191622-101 (02 December 2011) to provide clarifications, updated information, and corrections.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section(s)	Revision	Rationale
Title page	Added EudraCT number and changed Allergan Medical Safety Physician.	Updated information.
4.4, Exclusion Criteria	Deleted number 12 and renumbered remaining criteria accordingly.	Number 12 duplicated 11b.
5.6.1, Treatment Regimen	In second paragraph, corrected 150 U to 100 U in "…maximum doses of 3 U/kg (not to exceed 100 U)…"	Corrected typographical error.
7.3.1, Primary Efficacy Analyses	Added wording to specify that if a pairwise comparison in MAS-B is not statistically significant, the corresponding pairwise comparison in CGI will not be considered statistically significant regardless of the actual p value.	Additional details added for clarification.
7.7, Additional Analysis/Inference for US FDA	Section 7.7 added to the protocol to clarify when dose effectiveness will be concluded.	Clarification added to address comments by US FDA during Special Protocol Assessment review.

Section(s)	Revision	Rationale
Table 1 (schedule), Footnote "i"; 8.3, Visits and Associated Procedures; and 12.1.16, CGI by Physician	Revised to clarify the ideal order of CGI and spasticity assessments.	Emphasis on these points was increased to reduce potential bias in CGI and spasticity assessments.
10.7, Handling of Biological Specimens	Revised approximate volume of blood collection for hematology and chemistry from 5 to 7 mL	Based on the revised central laboratory (Covance) requirements.
12.1.4, Hematology and Serum Chemistry	Revised reference ranges for alkaline phosphatase in Table 4.	Corrected values based on revised reference ranges provided by central laboratory (Covance).
12.1.17, Patient-reported Onset of Spasticity Symptom Relief	Revised the question from "have you noticed any treatment effect…" to "have you noticed any effect…"	Revised based on central IRB requirement to minimize potential bias in response.

12.5 Protocol Amendment 2 Summary

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Double-blind Study

Protocol 191622-101, Amendment 2

Date of Amendment: January 2014

Amendment Summary

This summary includes changes made to Protocol 191622-101 Amendment 1 (e-signature date 02 April 2012). This protocol was amended 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.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section(s)	Revision	Rationale
Title page	Referred to the Study Contacts Page for emergency telephone numbers; updated page 2	Per new Allergan protocol template
Protocol Summary	Amended Visit Schedule description to state there will be "approximately" 13 weekly OT sessions	Clarification
Protocol Summary; 2.2	Added distinction between US FDA and non US FDA clinical hypotheses and analyses	Clarification
Protocol Summary; Table 1; 6.2; 6.5; 7.3.4; 8.3.1; 8.3.3; 8.3.4; 8.3.5; 11; 12.1.18; 12.3	Specified that the C-SSRS is to be performed as a safety measure for patients ≥ 6 years of age at day 1, and provided description of scale, data handling, and reference information	As requested by US FDA's Division of Neurology Products
Protocol Summary; Table 1; 6.1.3; 7.2.3; 7.3.3; 8.3.4; 8.3.5; 12.1.17	Added patient-reported benefit of injection	To collect patient-reported data on benefit of injection

Section(s)	Revision	Rationale
Protocol Summary; 4.4	Modified Exclusion Criterion 11a regarding seizure frequency for exclusion	Clarification
	Modified Exclusion Criterion 12 regarding vulnerable respiratory state	Clarification
	Added Exclusion Criterion 29 to exclude patients with significant risk of suicide from treatment	To avoid confounding the safety data
Table 1	Added "Review safety lab results" to visit 3	In agreement with Section 8.3.3
	Added "Access IVRS/IWRS" and clarified in new footnote (k) how and when IVRS/IWRS is used	Clarification
3.1	Changed "members" to "participants" and removed "or investigator" from the examples given of ad hoc SDRC participants	Clarification
4.5.2	Added the statement that patients may stay in the study even if a prohibited medication is administered	Clarification
4.5.3	Moved and amended sentence regarding school-based therapy	Clarification that school-based therapy, if relevant per local legislation, is permitted during the study
5.3	Amended first paragraph regarding IDR	To clarify responsibilities of the IDR
5.5	Inserted sentence in first paragraph regarding IVRS/IWRS	To clarify that the site will access the system on day 1
Protocol Summary; 5.6.1; 8.3; 8.3.1	Amended to "approximately" 1-hour OT sessions	Clarification
5.6.1	Amended the first paragraph regarding patient's weight and dose calculation	To clarify that patient's weight in kilograms will be rounded to the nearest kilogram for dose calculation only
6.1.1; 6.1.2; 7.2; 7.2.1; 7.2.2	Made the distinction between US FDA measures and non-US FDA measures	Clarification
6.4	Corrected second bullet by removing "freezer" from the equipment needing temperature monitoring	Correction
	Added bullet that Allergan will supply a kilogram-only weight scale for selected sites, and that the site will supply it only if it is not already supplied by Allergan	To ensure that patient's weight is collected in kilograms only

Section(s)	Revision	Rationale
	Corrected last bullet by adding "or EMG" to the devices for muscle localization techniques	Correction
7.2.2; 7.2.3; 7.3.2; 7.3.3	Clarified that MAS-B and MTS for finger flexors will be analyzed for the subgroup of patients with wrist identified as the principal muscle group	Clarification
7.3.1	The original multiple testing procedure (Fisher's Protected Testing procedure) was changed to a gatekeeping procedure	To control type I error rate
	Pairwise comparison for high dose versus low dose was removed	To incorporate US FDA recommendation
	Overall test for among-group comparison was removed	Gatekeeping procedure for the 2 pairwise comparisons is sufficient to control type I error rate
	CGI by Physician was removed for non-US FDA primary analyses	Clarification
7.3.1; 11	Removed Saville citation and reference	No longer applicable due to the multiple testing procedure change
7.3.2	CGI by Physician was added for non-US FDA analyses as a secondary measure	Clarification
7.4	Removed subgroup efficacy analyses by type of anesthesia	The distribution and number of patients in each type of anesthesia will not produce meaningful efficacy results.
Protocol summary; 7.5	Revised sample size calculation to base the calculation on 2-sample t-test	Since the overall test for among group comparison was removed
7.7	Added separate sections (7.7.1 and 7.7.2) to specify the primary and secondary efficacy analyses for FDA and added a table for efficacy claim	Clarification and to incorporate US FDA recommendation
8.3.1; 12.1.4	Amended sentence to remove time frame for blood sample collection	Clarification
Table 1; 8.3.1; 8.3.3	Removed passive range of motion bullet to indicate that assessment of passive range of motion can be performed as part of the MTS using the angle of slow stretch (R2)	Clarification
8.3.3	Added bullets for review of screening laboratory results and accessing IVRS/IWRS to randomize patients	Clarification of day 1 procedures
	Added "in kilograms" to weight measurement	Clarification

Section(s)	Revision	Rationale
8.3.4	[redacted]	Clarification of visit 8 procedures
8.3.5	Added [redacted] use of IVRS/IWRS	Clarification of visit 8 procedures
9.3	Updated serious adverse event reporting procedure	Per new Allergan protocol template
12.1.1	Amended second sentence regarding weight measurements	Clarification on requirements for weight measurements and that weight must be measured in kilograms
12.1.2	Added “temporal, rectal” to body temperature	As per common practices
12.1.10	Deleted “physician”	To clarify that other qualified site personnel can perform the MAS-B
	Revised MAS-B description to say “study-specified” instead of “non-study-specified” velocity	To clarify that we do instruct the sites on a specific velocity
12.1.11	Merged sections 12.1.11 and 12.1.12 to indicate that assessment of passive range of motion can be performed as part of the MTS using slow stretch (V1)	Clarification
12.1.12, 12.1.15	Amended “investigator” to “physician investigator”	Clarification

12.6 Protocol Amendment 3 Summary (October 2015)

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Double-blind Study

Protocol 191622-101, Amendment 3

Date of Amendment: October 2015

Amendment Summary

This summary includes changes made to Protocol 191622-101 Amendment 2 (January 2014). This protocol was amended to decrease the sample size and to incorporate changes in statistical procedures.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section(s)	Revision	Rationale
Title page	Updated Allergan Medical Safety Physician and Allergan signatory information	Change in staff
Protocol Summary, 4.1 (Number of Patients)	Estimated number of patients to complete study was decreased from 351 to 213	Recalculated sample size based on adjusted treatment differences from upper limb studies
Protocol Summary; 7.5 (Sample Size Calculation)	Number of patients and sample size calculations were revised	Recalculated sample size based on adjusted treatment differences from upper limb studies
7.2 (Collection and Derivation of Primary and Secondary Efficacy Assessments)	Added sensitivity analyses (MMRM and summary of percentage of missing data for the primary variables)	To supplement primary analysis using observed data, not imputed data for primary analysis
7.3 (Hypothesis and Methods of Analysis)	Statistical analysis method (ANOVA) was changed to ANCOVA (added study center and previous botulinum toxin exposure as factors) and changed baseline MAS-B to continuous variable	To obtain more consistent results and increase model power
7.7 (Additional Analysis/Inference for US FDA)	Multiple testing procedure (gatekeeping procedure) was changed to Hochberg procedure for the co-primary analysis for US FDA	To control type I error rate

12.7 Protocol Amendment 3 Summary (January 2016)

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Double-blind Study

Protocol 191622-101, Amendment 3

Date of Amendment: January 2016

Amendment Summary

This summary includes changes made to Protocol 191622-101 Amendment 3 (October 2015). This protocol was amended to incorporate FDA recommendations.

Following is a summary of content-oriented changes that were made to each section of the protocol and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section(s)	Revision	Rationale
Title page	Updated Allergan Medical Safety Physician and Allergan signatory information	Personnel changes
Protocol Summary, 7.1 (Analysis Populations), 7.3 (Hypothesis and Methods of Analysis)	The intent-to-treat (ITT) population was replaced with the mITT population, which is defined as all randomized patients with a valid MAS-B baseline score of the principle muscle group and at least one post-baseline measurement at weeks 2, 4, or 6 for the MAS-B of the principle muscle group and the CGI by Physician.	Revised based on FDA recommendation
Protocol Summary, 7.5 (Sample Size Calculation)	The sample size assumptions and power calculations tables (Protocol Summary and Table 4) are now in agreement	Correction
7.2 (Collection and Derivation of Primary and Secondary Efficacy Assessments), 7.3 (Hypothesis and Methods of Analysis), 7.7 (Additional Analysis/Inference for US FDA)	The primary MAS-B analysis and FDA co-primary MAS-B and CGI analyses were changed to use the MI method for missing values instead of observed cases; sensitivity analyses using last observation carried forward (LOCF) were removed.	Based on FDA feedback on handling missing data for the primary analysis

Section(s)	Revision	Rationale
7.3 (Hypothesis and Methods of Analysis)	Text describing sensitivity analyses was edited to spell out the covariate and factors in the MMRM model; factors for logistic regression were updated to match the primary analysis model; analyses of co-primary endpoints for US FDA were moved to Section 7.7	For clarification
7.7 (Additional Analysis/Inference for US FDA)	Sensitivity analyses using MMRM and ANCOVA to support the co-primary analysis for US FDA are now described in this section	For clarification