NCT01603615

Study ID: 191622-105

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Open-label Study

Protocol Amendment 4 Date: 01 August 2016

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STUDY TITLE

BOTOX® Treatment in Pediatric Upper Limb Spasticity: Open-label Study

Protocol Number:	191622-105 Amendment 4
EudraCT Number:	2012-000043-27
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

[redacted]

Approval Date: 01-Aug-2016

[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

Table of Contents

[redacted]

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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 long-term safety of repeated doses of BOTOX for the treatment of pediatric upper limb spasticity

Clinical Hypothesis: Repeated doses of BOTOX (up to 8 U/kg in the upper limb alone and up to 10 U/kg in a combination of upper and lower limbs) have an acceptable safety profile for treating pediatric upper limb spasticity (with or without treatment in the lower limb)

Study Design

Structure: Multicenter, open-label study

Duration: Approximately 60 weeks

Study Treatment Groups: BOTOX

Controls: None

Dosage/Dose Regimen (BOTOX doses are expressed per body weight):

There will be up to 5 treatments in the study.

For the first treatment cycle, *de novo* patients (who did not participate in Allergan Study 191622-101) are to receive at least 6 U/kg and not to exceed 8 U/kg or 300 U in the affected upper limb (referred to as the study upper limb). Patients with clinically significant lower limb spasticity may be eligible to receive BOTOX treatment in affected lower limb(s). The combined upper and lower limb dose should not exceed 8 U/kg or 300 U, whichever is lower.

Rollover patients (who participated in Allergan Study 191622-101), during the first treatment cycle may receive up to a maximum of 8 U/kg (not to exceed 300 U) in the same upper limb that was treated in Study 191622-101 (referred to as the study upper limb). Patients with clinically significant lower limb spasticity may be eligible to receive BOTOX treatment in affected lower limb(s) up to a maximum of 8 U/kg (not to exceed 300 U). The combined upper and lower limb dose should not exceed 8 U/kg or 300 U, whichever is lower, during the first cycle.

For treatment cycles 2 through 5, the maximum dose for the study upper limb only remains the same as in treatment cycle 1; the maximum dose for combined upper and lower limbs or for both lower limbs only for triplegic patients can be increased to 10 U/kg (not to exceed 340 U).

If a patient meets the retreatment criteria, including no indication of an unacceptable safety risk, and it is considered clinically appropriate by the investigator, the patient should receive at least 6 U/kg in the study upper limb every 12 to 14 weeks, with the total dose not to exceed the maximum specified for each treatment cycle.

Randomization/Stratification:

No randomization or stratification will be performed for this open-label study.

[redacted]

[redacted]

Study Population Characteristics

Patients who successfully completed Study 191622-101 without major protocol deviations (eg, noncompliance to protocol-required procedures) and have not experienced an adverse event that, in the investigator's opinion, may indicate an unacceptable safety risk for additional BOTOX treatments may be eligible for enrollment in this study (referred to as rollover patients). Patients who became pregnant during Study 191622-101 cannot be enrolled in this study.

Additionally, *de novo* patients (who did not participate in Study 191622-101) who meet the inclusion criteria and do not meet the exclusion criteria may be enrolled in this study.

Number of Patients:

Approximately 213 patients will be enrolled.

Condition/Disease:

Medically stable monoplegic, hemiplegic, or triplegic pediatric patients with upper limb spasticity involving the elbow and/or wrist flexor muscles with single-arm sparing (only 1 arm requiring treatment for spasticity during the study) due to cerebral palsy or stroke

[redacted]

<u>*De novo* patients</u>:

- 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

[redacted]

[redacted]

Key Exclusion Criteria (all patients except where noted otherwise):

[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 [redacted]

[redacted]

- Botulinum toxin therapy of any serotype for any condition within 3 months prior to the day 1 visit (de novo patients only)

[redacted]

- History of surgical intervention of the study upper limb within 12 months prior to the day 1 visit (de novo patients only) or planned surgical intervention of any limb(s) during the study

[redacted]

[redacted]

Response Measures

Safety measures:

- Adverse events

[redacted]

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 all treated patients who have at least 1 MAS-B score recorded after day 1.

Safety variables such as the incidence of adverse events [redacted]

Sample Size Calculation:

Approximately 213 patients will be enrolled. The sample size was determined empirically.

[redacted]

[redacted]

[redacted]

[redacted]

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 the 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 Pediatric 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 of BOTOX treatment in pediatric cerebral palsy patients with upper limb spasticity.

The doses selected for this study are supported by Allergan clinical trial experience, clinical expert advice, published literature including consensus guidelines for botulinum toxin type A treatment of pediatric spasticity, and nonclinical toxicology data. The pharmacodynamic effect of BOTOX is influenced by adjunctive procedures or therapies, such as casting, PT or OT, and other pharmacologic treatments. In addition, in response to the neuromuscular blockade of the agonist muscles, the corresponding antagonist muscles could become overactive and necessitate the change of dose or the selection of muscles to be injected in subsequent treatment cycles.

In clinical practice, the total dose of BOTOX required for management of the impaired limb depends on a variety of factors, including goals of treatment as defined by the patient/family and physician, number of muscles to be injected, degree of increased muscle tone, desired degree of muscle relaxation to be achieved, and size/dimensions of the muscle(s). Allergan has consulted with clinical experts in the field of pediatric spasticity who have recommended doses ranging from 3 to 8 U/kg in a single upper limb as doses within this range are likely to be efficacious in reducing spasticity and would allow for individualization of the treatment paradigm based on individual patient presentation.

The doses in this study are supported by the dose ranges described in the published literature. All of the randomized, controlled studies in upper limb pediatric spasticity published to date utilized 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 do not commonly require treatment and are not eligible for injection in the present study. In a study conducted by Pieber et al (2011) doses up to 12 U/kg were used but the dosing details are not provided in the publication.

The doses in the present study are further supported by 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, were 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 proposed 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 maximum doses (U/kg) in the current study. The international consensus statement published in 2010 recommended 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 (Fehlings et al, 2010).

The doses selected for this study are 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.

In addition to the upper limb injection, this study also allows for injection of affected muscles of the lower limb at doses up to 8 U/kg (not to exceed 300 U) if only the lower limb is injected or at doses up to 10 U/kg (not to exceed 340 U) if both upper and lower limbs, or both lower limbs only in triplegic patients, are injected in treatment cycles 2 through 5 to optimize individual treatment. Based on the consensus guidelines, the maximum total body dose of 10 U/kg is an acceptable dose for multilevel treatment.

Based on the above dose considerations, repeated doses of at least 6 U/kg (maximum 8 U/kg, not to exceed 300 U) for the upper limb and up to 8 U/kg (maximum 300 U) for the lower limb(s) (not to exceed a maximum total body dose of 10 U/kg or 340 U for upper and lower limbs combined or for both lower limbs only in triplegic patients) are considered to be appropriate.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the long-term safety of repeated doses of BOTOX for the treatment of pediatric upper limb spasticity.

2.2 Clinical Hypothesis

Repeated doses of BOTOX (up to 8 U/kg in the upper limb alone and up to 10 U/kg in a combination of upper and lower limbs) have an acceptable safety profile for treating pediatric upper limb spasticity (with or without treatment in the lower limb).

3. Study Design

This is a multicenter, open-label study evaluating the safety of repeated treatments of BOTOX in pediatric upper limb spasticity. Patients who successfully completed Allergan Study 191622-101 without major protocol deviations (eg, noncompliance to protocol-required procedures) may be eligible for enrollment in this study (rollover patients) if they meet the inclusion criteria and do not meet the exclusion criteria.

Additionally, *de novo* patients (who did not participate in Allergan Study 191622-101) who meet the inclusion criteria and do not meet the exclusion criteria may be enrolled in this study. Depending on the number of rollover patients from Study 191622-101 and the dropout rate for the present study, enrollment of *de novo* patients may be limited.

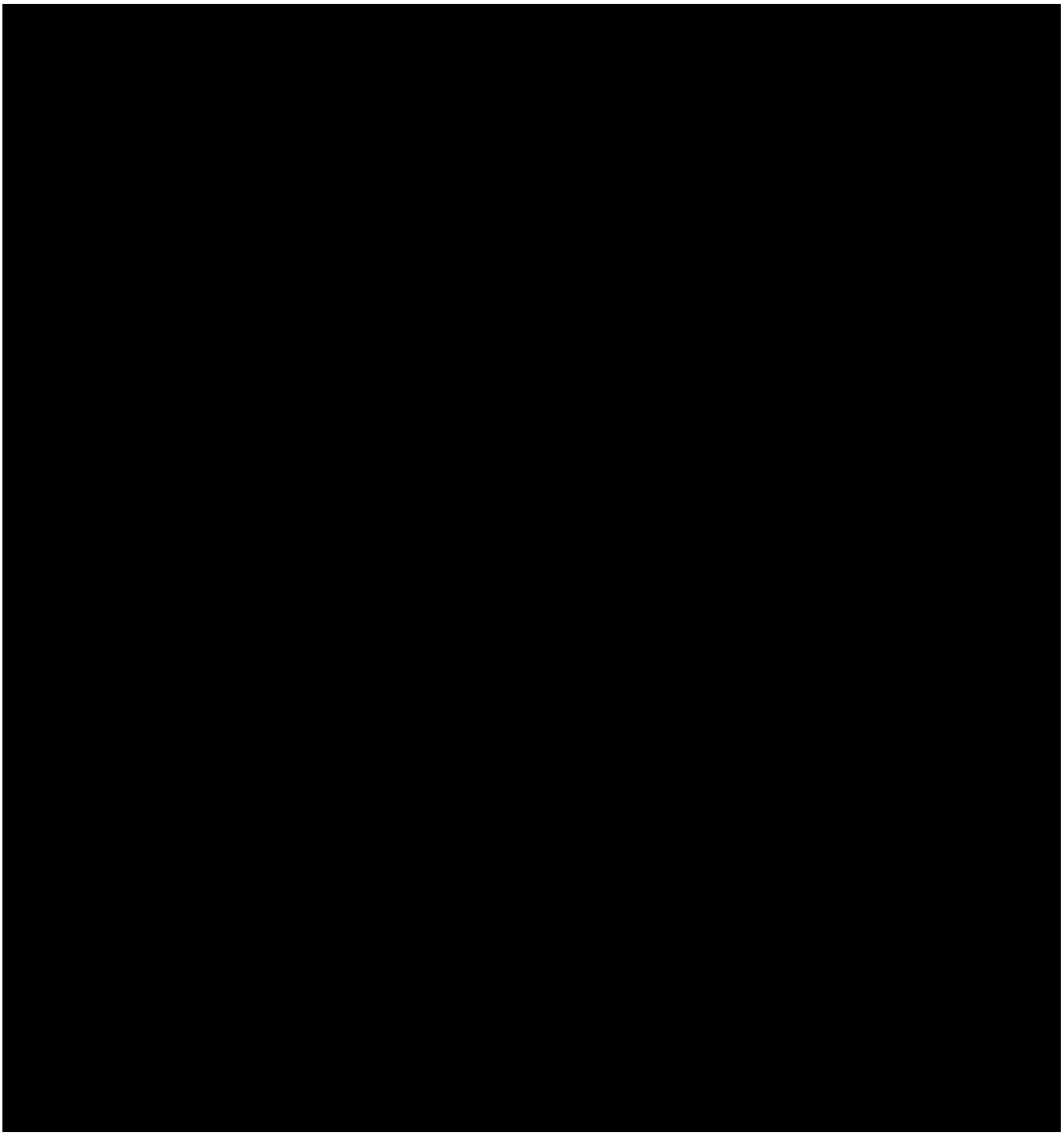
The study duration will be approximately 60 weeks. The total number of clinic visits will depend on the number and timing of treatments received by the patient. There will be a total of approximately 12 clinic visits for *de novo* patients, approximately 11 clinic visits for rollover patients who transitioned from Study 191622-101, and up to 5 telephone follow-up visits for all patients. Qualified rollover patients do not have to be re-screened for the current study; the exit visit from Study 191622-101 becomes the day 1 visit for this study after the patient signs the Study 191622-105 informed consent and assent (as applicable). These visits allow up to 5 treatment cycles with 12 weeks between treatments.

The timing of study visits and treatments is shown in Figure 1 and Figure 2. See Section 5.4 for a detailed description of the treatment regimen and Section 8 for a detailed description of the study visits. For this study, visits based on day 1 are referred to by “study week” and visits based on treatment are referred to by “treatment cycle week.”

If the patient does not meet the retreatment criteria during the 12-week window, he or she may be treated any time up to study week 48 (the last opportunity for retreatment) but should be evaluated at least every 6 weeks (calculated from the latest treatment visit date) until he or she meets the retreatment criteria or until study week 48. The exit visit will be study week 48

unless the patient receives treatment after study week 36, in which case the exit visit will be 12 weeks after the last treatment.

[redacted]



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 adverse events data throughout the entire duration of the study to ensure the safety of the study participants. The SDRC may elect to review additional safety parameters (eg, laboratory 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 213 patients will be enrolled.

4.2 Study Population Characteristics

Medically stable monoplegic, hemiplegic, or triplegic children with upper limb spasticity 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.

Patients who successfully completed Allergan Study 191622-101 without major protocol deviations (eg, noncompliance to protocol-required procedures) and have not experienced an adverse event that, in the investigator's opinion, may indicate an unacceptable safety risk for additional BOTOX treatments may be eligible for enrollment in this study. Patients who became pregnant during Study 191622-101 cannot be enrolled in this study.

Additionally, *de novo* patients (who did not participate in Study 191622-101) who meet the inclusion criteria and do not meet the exclusion criteria may be enrolled in this study.

4.3 Inclusion Criteria

[redacted]

The following are inclusion criteria for de novo patients:

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

[redacted]

[redacted]

[redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study for both rollover patients and de novo patients unless otherwise specified:

[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

[redacted]

11. Uncontrolled epilepsy [redacted]

[redacted]

17. Botulinum toxin therapy of any serotype for any condition within 3 months prior to the day 1 visit (*de novo* patients only)

[redacted]

[redacted]

20. History of surgical intervention of the study upper limb within 12 months prior to the day 1 visit (*de novo* patients only) or planned surgical intervention of any limb(s) during the study

[redacted]

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Concomitant anti-spastic medications or muscle relaxants will be permitted during the study. Patients who are already on concomitant anti-spastic medications or muscle relaxants (eg, benzodiazepines, baclofen [oral or pump], scopolamine [oral or patch], tizanidine, vigabatrin, or dantrolene) at the time of the day 1 visit will be encouraged to remain on a stable dose and regimen during the study; however, dose adjustments to their concomitant anti-spastic medications or muscle relaxants will be allowed as clinically indicated. Initiation and adjustment of anti-epileptics will be permitted during the study. If patient already has an intrathecal baclofen pump implanted, intrathecal baclofen therapy is permitted for both *de novo* and rollover patients during the study at the investigator's discretion.

Patients will also be permitted to use soft splints, casts and dynamic splints (UltraFlex®, DynaSplint®), and constraint therapy 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 (including OT and PT) considered necessary for the patient's welfare may be given at the discretion of the investigator. 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 their 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 representatives regarding the importance of maintaining their agreed-upon method of contraception. A urine pregnancy test is required prior to each study treatment for female patients of childbearing potential.

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 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)

Patients who enter the study on any of the above concomitant medications should remain on a stable dose throughout the study to the extent possible unless judged by the investigator to be clinically inappropriate.

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

- Botulinum toxin therapy of any serotype (outside of the study treatment)
- Phenol or alcohol injection to the study upper limb

- Planned surgery in any limb(s)

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 to be 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

OT/PT is an important element of the treatment approach in pediatric patients with spasticity. While no study-specific OT/PT will be required, patients should follow investigator's/therapist's recommendations regarding appropriate OT/PT. OT/PT should remain consistent, to the extent possible, throughout the entire duration of the study.

5. Study Treatments

5.1 Study Treatments and Formulations

The study treatment will be BOTOX. BOTOX [redacted] contains 100 U of *Clostridium botulinum* toxin type A, 0.5 mg of albumin (human), and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without preservative. The study medication will be reconstituted with 2 mL of 0.9% sodium chloride (preservative-free).

5.2 Methods for Blinding

This is an open-label study, and therefore no blinding of the study medication is required.

5.3 Method for Assignment to Treatment Groups

At the screening visit, after the *de novo* patient and/or legally authorized representative has signed the informed consent and minor assent (as applicable), the site will call the interactive voice response system (IVRS) or log on to the interactive web response system (IWRS) to obtain the patient number that will serve as the patient identification number on all study documents. At the study day 1 visit for both *de novo* and rollover patients, the site will access the IVRS/IWRS to enroll the patient. Rollover patients transitioning from Allergan

Study 191622-101 will maintain the same patient number that was assigned in that prior study.

Study medication will be labeled with medication kit numbers. At day 1 and at all retreatment visits when the patient qualifies for retreatment, sites will call the IVRS or log onto the IWRS to obtain specific study medication kit numbers for each 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 with the study source documents.

5.4 Treatment Regimen and Dosing

Each patient may receive up to 5 treatments during the course of study. Treatment cycle 1 for *de novo* patients requires identification and injection to the principal muscle group identified in the study upper limb. All other treatments for both rollover and *de novo* patients allow injections to upper limb only, lower limb(s) only, or a combination of upper and lower limbs.

If a patient meets the retreatment criteria, including no indication of an unacceptable safety risk, and it is considered to be clinically appropriate by the investigator, the patient should receive at least 6 U/kg in the study upper limb every 12 to 14 weeks, with the total dose not to exceed the maximum specified for each treatment cycle.

5.4.1 Treatment Cycle 1 for *De Novo* Patients

Each *de novo* patient will have either the elbow flexors or the wrist flexors designated as the principal muscle group for analysis purposes. [redacted]

During the first treatment cycle, *de novo* patients are to receive at least 6 U/kg of BOTOX in the study upper limb and all muscles in the principal muscle group must be injected. That is, if elbow is designated as the principal muscle group, biceps, brachialis and brachioradialis must be injected; if wrist is designated as the principal muscle group, flexor carpi ulnaris and flexor carpi radialis must be injected.

[redacted] The total dose injected during this cycle should be no more than 8 U/kg (not to exceed 300 U) in the upper limb only or in a combination of upper and lower limbs.

5.4.2 Treatment Cycle 1 for Rollover Patients

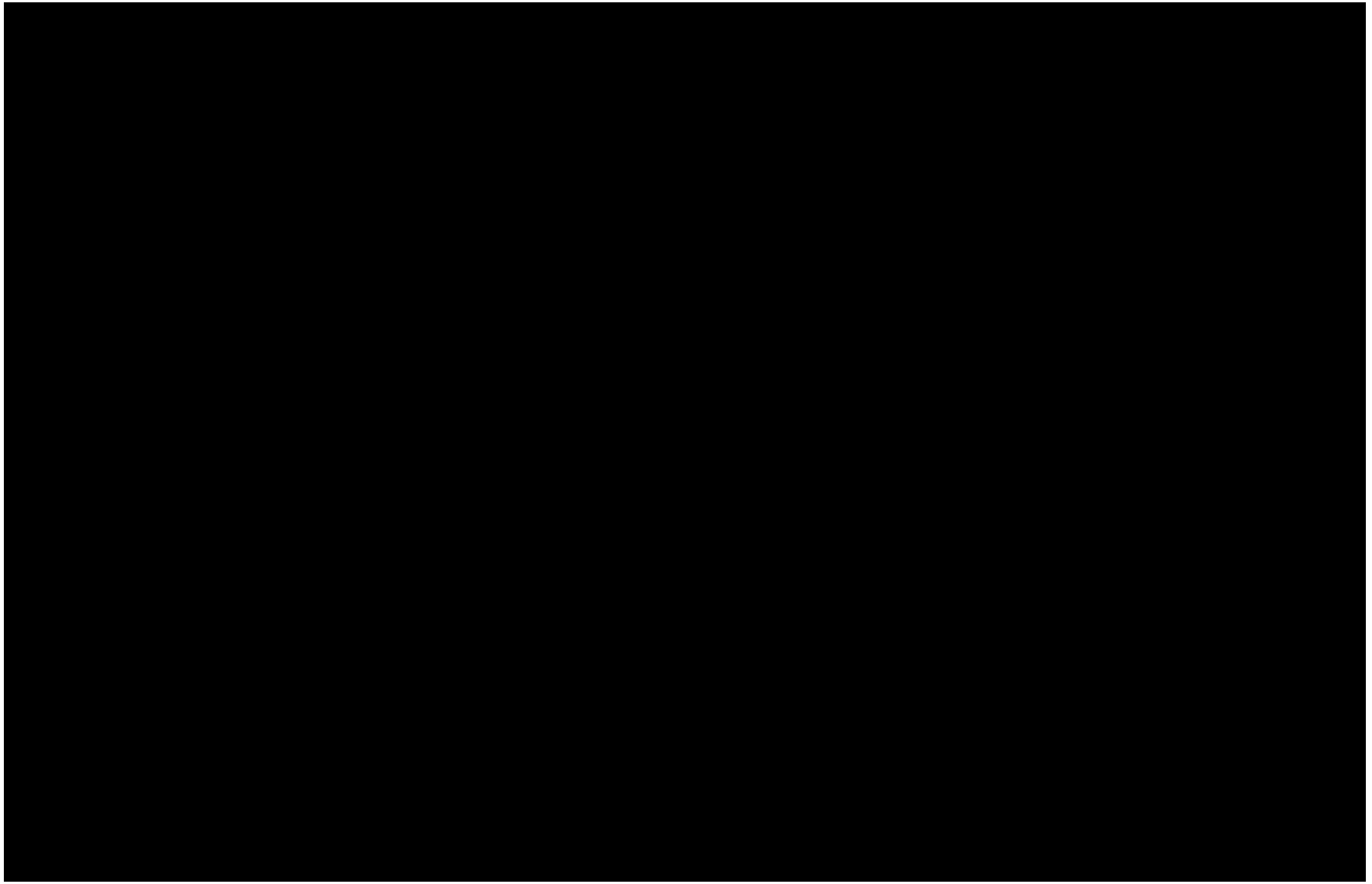
Patients transitioning from Study 191622-101 will be allowed to receive injections in the upper limb, the lower limb(s), or a combination of upper and lower limbs in all cycles, including treatment cycle 1. [redacted]

5.4.3 Treatment Cycles 2 Through 5 for All Patients (Rollover and *De Novo*)

For treatment cycles 2 through 5, the maximum dose for treatment only in the study upper limb remains the same as for treatment cycle 1; the maximum dose for combined upper and lower limbs or for both lower limbs only for triplegic patients can be increased to 10 U/kg (not to exceed 340 U). Dose limitations by the number of limbs affected are as follows:

- up to 8 U/kg (not to exceed 300 U) for each treatment session if administered only to the study upper limb or only to 1 lower limb,
- up to 10 U/kg (not to exceed 340 U) if administered to a combination of upper and lower limbs, or
- up to 10 U/kg (not to exceed 340 U) if administered to both lower limbs only (for triplegic patients only).

The dose for each muscle and the total dose will be determined by the investigator.



5.4.4 Treatment Regimen/Dosage Adjustment

For all patients enrolled, the dose should be calculated based on patient's body weight in kilograms measured on the day of each treatment/retreatment visit. For purposes of dose calculation only, the patient's weight will be rounded to the nearest whole kilogram. If the dose by body weight (U/kg x body weight) exceeds the per-muscle dose, the total maximum dose for the study upper limb or for the lower limb(s), or the total body maximum units, then the maximum dose ("not to exceed" units) should be used. The dose for each injection site should not exceed 50 U.

5.4.4.1 Retreatment Criteria

Patients may be retreated if they meet all of the following criteria on the day of retreatment prior to the injection:

a. [redacted]

b. At least 12 weeks since the last study treatment of BOTOX

c. Did not experience the following since previous treatment:

- adverse events of compromised respiratory function, aspiration, difficulty swallowing, or clinically significant excessive salivation. Patients who have experienced these adverse events must not receive any further study treatments.
- an adverse event or excessive weakness that, based on the investigator's clinical judgment, indicates an unacceptable safety risk for additional BOTOX treatments. Patients may be re-evaluated for retreatment once the adverse event or muscle weakness is resolved.
- [redacted]

d. A negative urine pregnancy test for female patients of childbearing potential

[redacted]

[redacted]

5.5 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.

[redacted]

5.6 Preparation of Study Medications/Treatments

BOTOX (100 U vial) will be reconstituted with 2 mL of preservative-free saline.

5.7 Treatment Administration

Muscle localization techniques such as e-stimulation, sonography, and/or electromyography (EMG) are recommended for this study. The study medication may be administered in conjunction with appropriate anesthesia according to each investigator's standard practice. Patients who are planning to undergo general anesthesia should be carefully examined by the investigator to ensure that they are suitable candidates for general anesthesia.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

[redacted]

6.1.1 Primary Efficacy Measure

No primary efficacy measure is identified.

6.2 Safety Measures

- Adverse events

[redacted]

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 the 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 refrigerator temperatures
- Syringe labels
- Goniometer
- Kilogram-only weight scale for selected sites (weight should 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, if applicable

6.5 Summary of Methods of Data Collection

An IVRS/IWRS will be used to assign patient numbers for *de novo* patients and to 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 conducted 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 lock will occur when all patients have completed the study. A detailed analysis plan will be generated prior to the database lock. All planned analyses will be performed after the database is locked.

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. [redacted]

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

[redacted]

[redacted] The applicable scores, and applicable changes from baseline to each follow-up office visit, as well as any applicable response status at each follow-up office visit, will be derived. For rollover patients from Allergan Study 191622-101, an additional set of variables using the original baseline values in the previous study will also be derived. In addition, the time interval from the injection in Study 191622-101 to the first injection in this study will be derived.

7.2.1 Efficacy Variables

[redacted]

7.2.2 Primary Efficacy Variable

No primary efficacy variable is identified.

7.3 Hypothesis and Methods of Analysis

There will be no hypothesis testing unless otherwise specified.

[redacted]

[redacted]

7.3.2 Safety Analyses

Safety variables including the incidence of adverse events, [redacted]

The incidence of adverse events will be tabulated by primary system organ class and the preferred term overall and for each treatment cycle. [redacted]

[redacted]

7.4 Subgroup Analyses

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

7.5 Sample Size Calculation

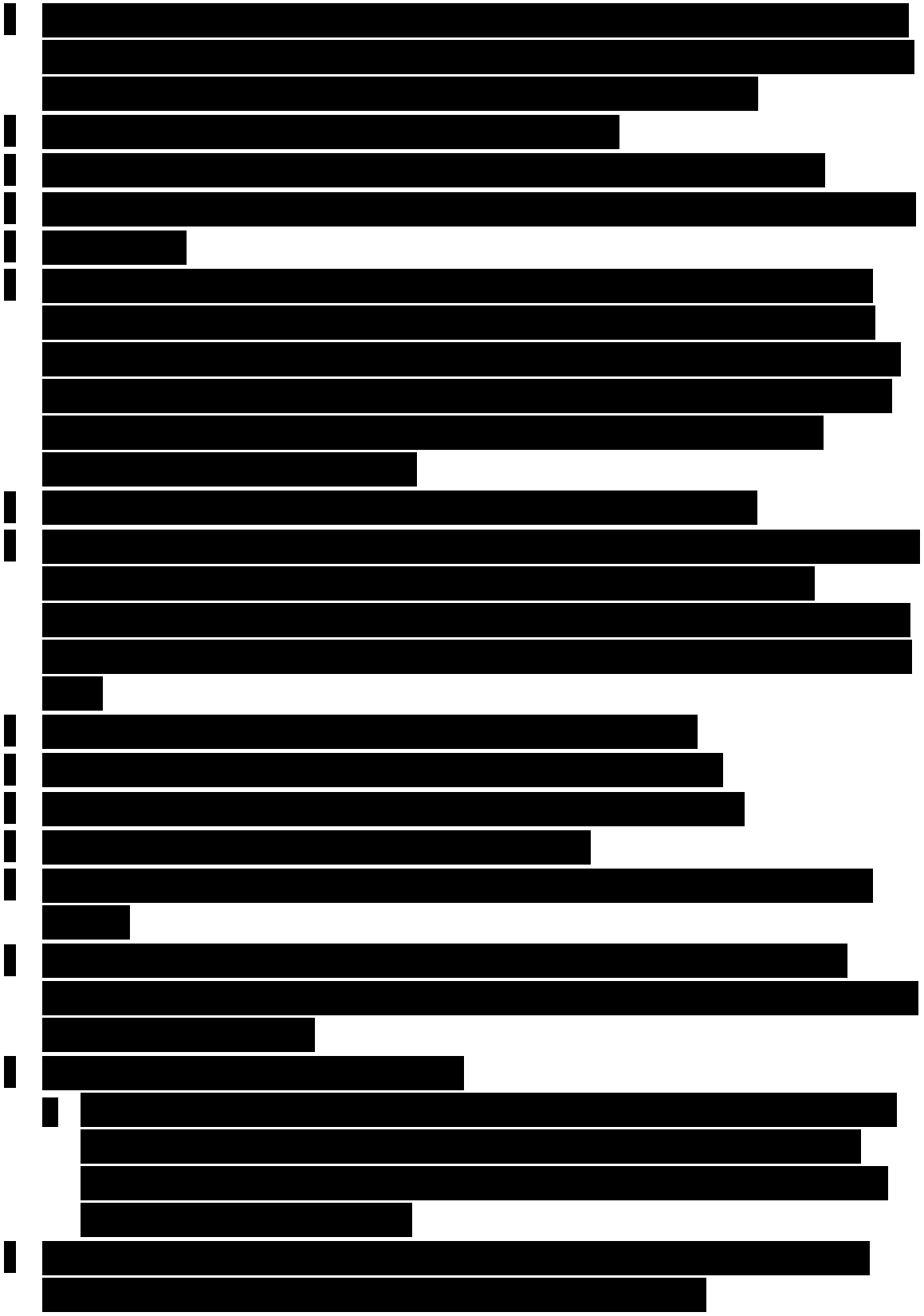
Approximately 213 patients will be enrolled. The sample size was determined empirically rather than by sample size calculation.

7.6 Interim Analyses

Periodic safety summaries will be provided to the SDRC for review. In addition, periodic safety and efficacy data summaries may be generated for the purpose of study monitoring. An interim safety analysis may be performed for regulatory filing, if needed.

[redacted]

[redacted]



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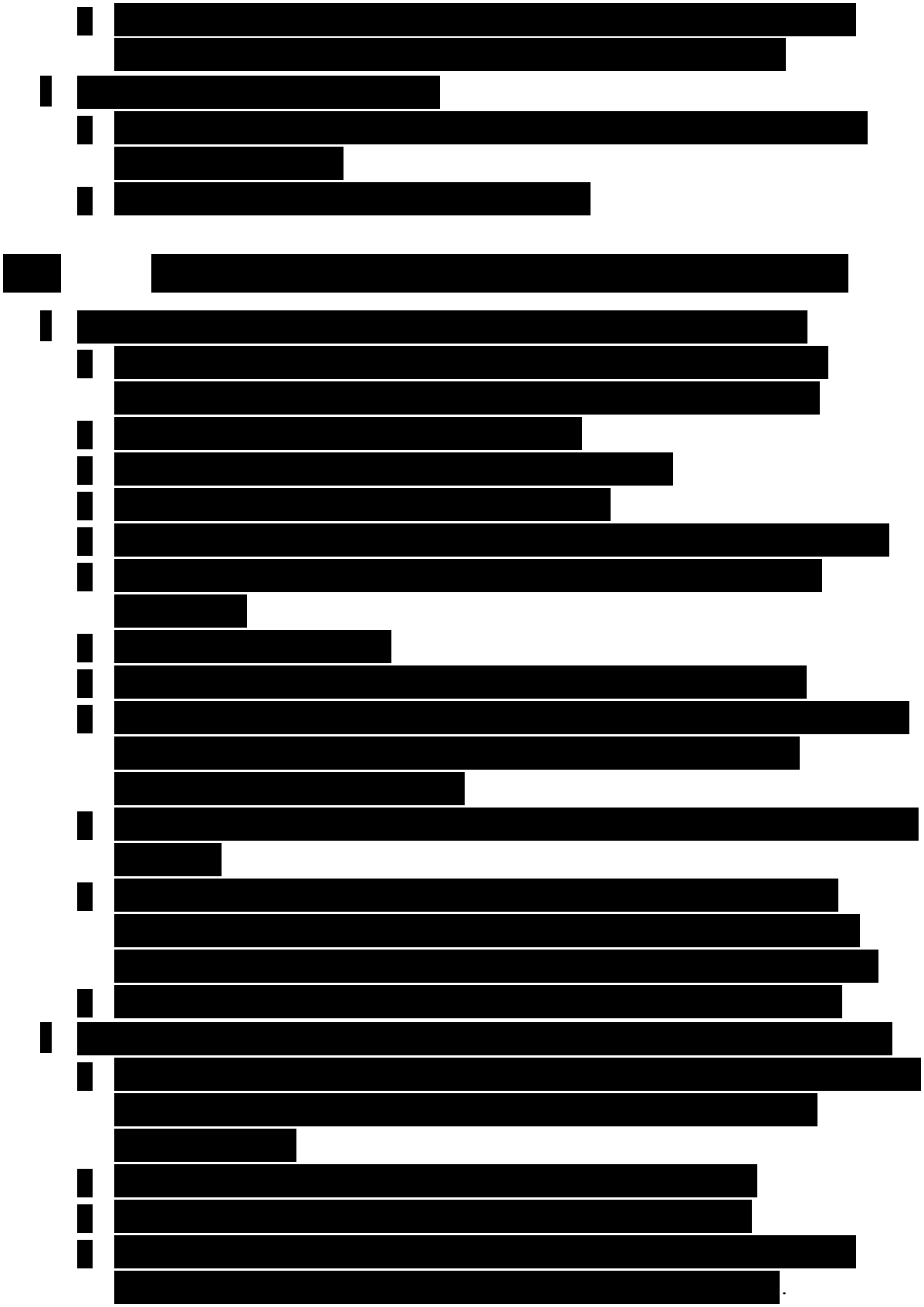

[redacted]

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.

8.5 Unscheduled Visits

Unscheduled visits can be performed at the discretion of the investigator, eg, for safety concerns or for retreatment evaluation (if at least 12 weeks since the last study treatment). If the patient is eligible and receives study treatment, this visit becomes a treatment visit. 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 postbaseline visit, patients/caregivers will be questioned on concomitant medication use and procedures or test 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. Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan and be clearly documented on the appropriate eCRF. Patients who wish to discontinue future treatments should be asked to consider returning for the study exit visit.

The last visit for the patient will be considered the study exit visit. Procedures identified in Table 1 and Table 2 for the exit/early termination visit will be performed if the study exit visit occurs earlier than study week 48.

8.8 Withdrawal Criteria

Patients will be withdrawn from the study if they:

- develop a medically significant hypersensitivity reaction to the study drug such as angioedema or anaphylaxis, or
- become pregnant during the study

Patients will continue to be followed up for safety until the issue is resolved or the condition is stabilized. Please see Section 4.5.1.1 for follow-up for patients who become pregnant during the study.

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.

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 (US 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 subject 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 should 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 and reason(s) why patient did not meet retreatment criteria. [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

[redacted]

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, and hematology 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

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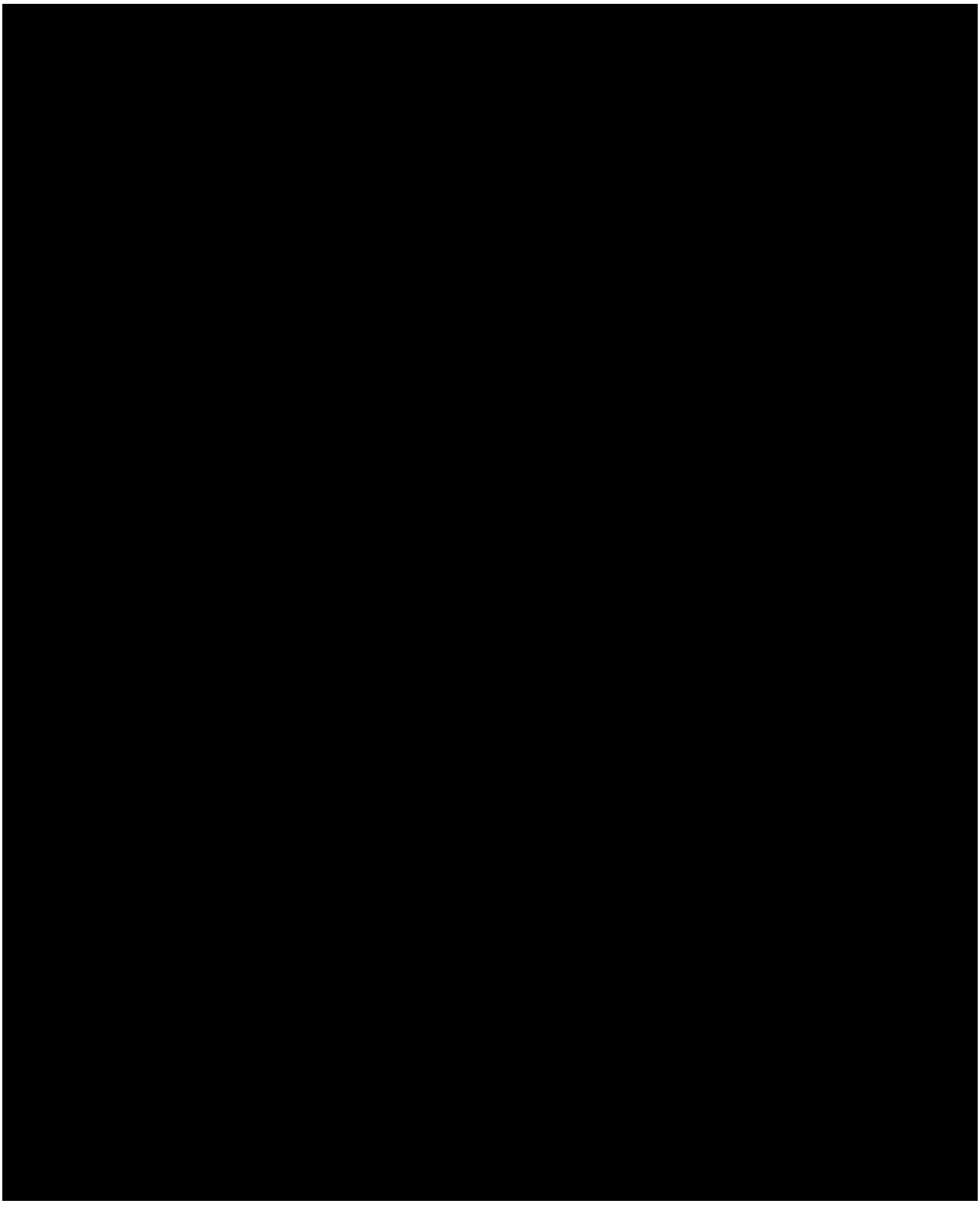

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12.2 Package Insert/Summary of Product Characteristics

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
[redacted]	[redacted]
BoNT-A	botulinum neurotoxin type A
BOTOX®	botulinum toxin type A purified neurotoxin complex (US Adopted Name, onabotulinumtoxinA)
CFR	Code of Federal Regulations (US)
[redacted]	[redacted]
CNS	central nervous system
[redacted]	[redacted]
D	day
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMG	electromyography
EU	European Union
[redacted]	[redacted]
GCP	Good Clinical Practices
[redacted]	[redacted]
[redacted]	[redacted]
HbA1c	glycosylated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
MACS	Manual Ability Classification System
[redacted]	[redacted]
[redacted]	[redacted]
NA	not applicable
No.	number
NOAEL	No-observable-adverse-effect level

OT	occupational therapy
PT	physical therapy
QUEST	Quality of Upper Extremity Skills Test
[redacted]	[redacted]
[redacted]	[redacted]
Scrn	screening
SDRC	Safety Data Review Committee
Tx	treatment
U	unit, corresponding to the median lethal dose (LD_{50}) in mice
US	United States
V1	slow velocity
V3	fast velocity
Wk	week

12.4 Protocol Amendment 1 Summary

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Open-label Study

Protocol 191622-105, Amendment 1

Date of Amendment: 30 March 2012

Amendment Summary

This summary includes changes made to Protocol 191622-105 (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
[redacted]	[redacted]	[redacted]
8.3.1, [redacted]	[redacted]	[redacted]
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.

Section(s)	Revision	Rationale
[redacted]	[redacted]	[redacted]

12.5 Protocol Amendment 2 Summary

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Open-label Study

Protocol 191622-105, Amendment 2

Date of Amendment: 7 December 2012

Amendment Summary

This summary includes changes made to Protocol 191622-105 Amendment 1 (e-signature date 02 April 2012) to provide clarifications 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. Underlining is used to identify wording that has been added and strikethrough for wording that has been deleted. Minor editorial and document formatting revisions have not been summarized.

Section(s)	Revision	Rationale
Summary	Changes corresponding to those identified below in the body were made to the Summary section.	For consistency within the protocol
[redacted]	[redacted]	[redacted]
1.4, Dose Justification 5.4, Treatment Regimen and Dosing Table 3	Added wording for a combination of only both lower limbs for triplegic patients	Allows a dose up to 10 U/kg and not to exceed 340 U to be injected during treatment cycles 2 to 5 when only both lower limbs are treated.
3, Study Design	Replaced details regarding dosing with a cross reference to Section 5.4, Treatment Regimen and Dosing	To consolidate dosing information in a clearly designated section.

Section(s)	Revision	Rationale
4.4, Exclusion Criteria	Changed #21 regarding history of fracture in the study upper limb within 12 months from "prior to the screening visit" to "prior to the day 1 visit."	For consistency with other criteria
4.5.2, Prohibited Medications/Treatments	Added to the wording that requires a patient to remain on a stable dose of anti-spastic medications: to the extent possible unless judged by the investigator to be clinically inappropriate.	For clarification
5.3, Method for Assignment to Treatment Groups	Added At the study day 1 visit for both *de novo* and rollover, the site will access the IVRS/IWRS to enroll the patient;	For clarification
5.4, Treatment Regimen and Dosing	At the beginning of 5.4, replaced similar wording that was in 5.4.2 and 5.4.3 with: If a patient meets the retreatment criteria, including no indication of an unacceptable safety risk, and it is considered to be clinically appropriate by the investigator, the patient should receive at least 6 U/kg in the study upper limb every 12 to 14 weeks, with the total dose not to exceed the maximum specified for each treatment cycle.	For clarification
5.4.3, Treatment Cycles 2 Through 5 for All Patients (Rollover and *De Novo*)	Revised description of dose limitations	For clarification

Section(s)	Revision	Rationale
[redacted]	[redacted]	[redacted]
5.4.4, Treatment Regimen/Dosage Adjustment	Added <u>For purposes of dose calculation, the patient's weight will be rounded to the nearest whole kilogram.</u>	For clarification
5.4.4.1, Retreatment Criteria	Revised to "Patients ~~should~~ <u>may</u> be retreated" if they meet the retreatment criteria.	For clarification
5.4.5, Retreatment Visits	Deleted sentence regarding dose (because that is specified in Section 5.4.3). Revised the last sentence to "…determine if the patient will be eligible for retreatment and if the above-mentioned dosing regimens are <u>clinically</u> appropriate for the patient or dose reduction <u>relative to the last injection received</u> is required.	For clarification
6.4, Other Study Supplies	For the calibrated temperature recorder, deleted mention of freezer temperatures.	Only refrigerator monitors are needed and will be supplied.
	In addition to ultrasound and/or e-stimulation, added EMG device for muscle localization, if applicable	For clarification
[redacted]	[redacted]	[redacted]

Section(s)	Revision	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
8.8, Withdrawal Criteria	Added that patients will be withdrawn from the study if they develop a medically significant hypersensitivity reaction to the study drug such as angioedema or anaphylaxis, or if a patient becomes pregnant during the study.	For clarification
[redacted]	[redacted]	[redacted]

Section(s)	Revision	Rationale
[redacted]	[redacted]	[redacted]

12.6 Protocol Amendment 3 Summary

Title: BOTOX® Treatment in Pediatric Upper Limb Spasticity: Open-label Study

Protocol 191622-105, Amendment 3

Date of Amendment: January 2014

Amendment Summary

This summary includes changes made to Protocol 191622-105 Amendment 2 (e-signature date 11 December 2012). [redacted]

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
[redacted]	[redacted]	[redacted]
3.1	Changed "members" to "participants" and removed "or investigator" from the examples given of ad hoc SDRC participants	Clarification
[redacted]	[redacted]	[redacted]
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 27 to exclude patients with significant suicidality from treatment	To avoid confounding the safety data

Section(s)	Revision	Rationale
[redacted]	[redacted]	[redacted]
4.5.1	Added a sentence on use of anti-epileptics	Clarification that anti-epileptics are permissible during the study
5.4.4.1	Amended bullet (c) of the retreatment criteria	To specify that patients who experience certain adverse events will not receive further study treatments
5.4.5	Revised paragraph regarding retreatment for patients with adverse events of compromised respiratory function, aspiration, difficulty swallowing, or clinically significant excessive salivation	To specify that patients who experience these adverse events will not receive further study treatments
6.4	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
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
9.3	Updated serious adverse event language	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 "<u>temporal, rectal</u>" to body temperature	As per common practices
[redacted]	[redacted]	[redacted]
12.1.13; 12.1.14	Amended "investigator" to "physician investigator"	Clarification

12.7 Protocol Amendment 4 Summary

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

Protocol 191622-105, Amendment 4

Date of Amendment: July 2016

Amendment Summary

This summary includes changes made to Protocol 191622-105 Amendment 3 (January 2014). This protocol was amended to decrease the sample size.

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 enroll in study was decreased from 350 to 213	Based on decreased number of completers from DBPC study due to adjusted treatment differences from upper limb studies.
Protocol Summary; 7.5 (sample size calculation)	Number of patients was revised from 350 to 213.	Based on decreased number of completers from DBPC study