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Study ID: 191622-112

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

Protocol Amendment 3 Date: 28 January 2014

BOTOX[®] (Botulinum Toxin Type A) Purified Neurotoxin Complex

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STUDY TITLE

BOTOX[®] Treatment in Pediatric Lower Limb Spasticity: Open-label Study

Protocol Number: 191622-112 Amendment 3

EudraCT Number: 2012-000084-24

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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Emergency Telephone Number(s): Refer to the Study Contacts Page.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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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.

BOTOX[®] (Botulinum Toxin Type A) Purified Neurotoxin Complex**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

Approval Date: 28-Jan-2014

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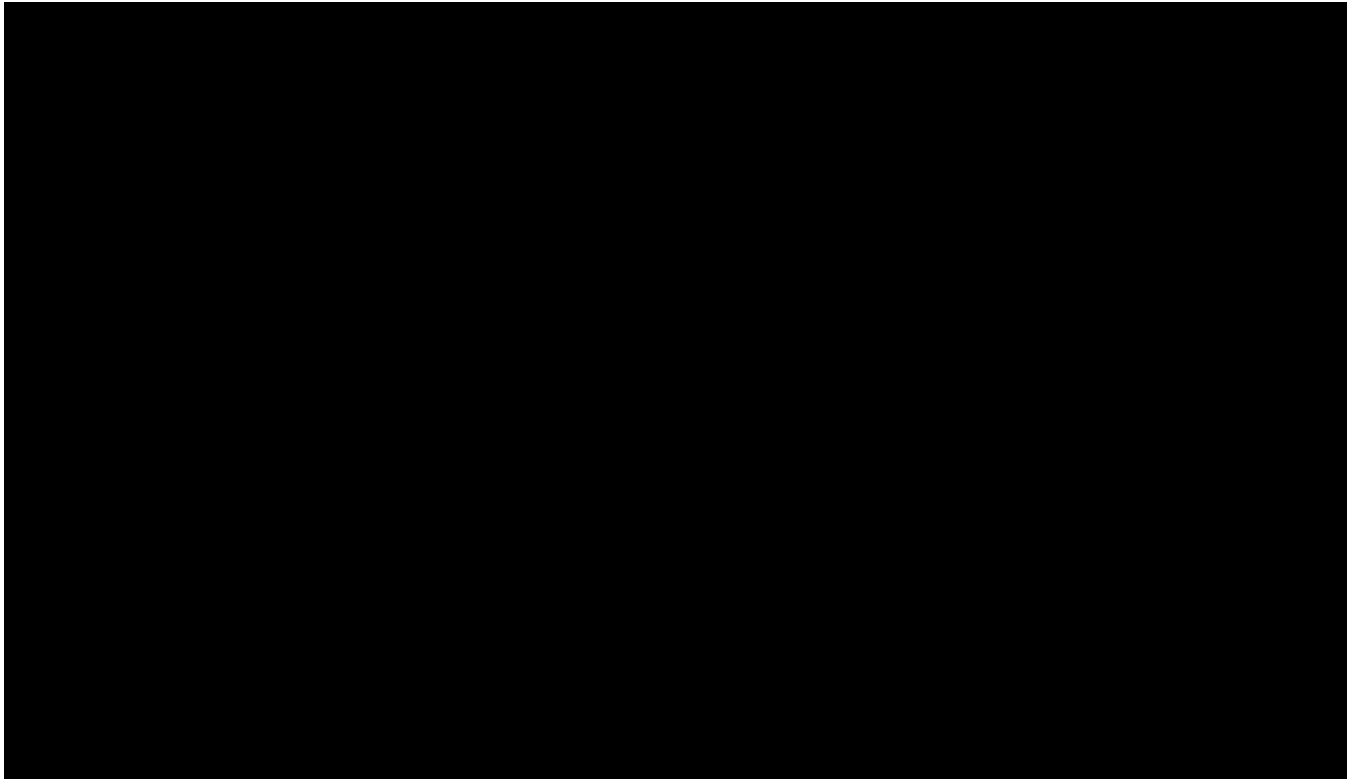
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Protocol Summary

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

Phase: 3

Study Objectives: To evaluate the long-term safety of repeated doses of BOTOX for the treatment of pediatric lower limb spasticity

Clinical Hypothesis: Repeated doses of BOTOX (up to 8 U/kg in the lower limb alone, up to 10 U/kg in a combination of both lower limbs, or up to 10 U/kg in a combination of upper and lower limbs) have an acceptable safety profile for treating pediatric lower limb spasticity (with or without treatment in the upper 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 191622-111) are to receive a total of 8 U/kg (not to exceed 300 U) either in a single affected lower limb or divided between both study limbs (referred to as the study lower limb or study lower limbs).

Rollover patients (who participated in Allergan Study 191622-111) during the first treatment cycle may receive up to a maximum of 8 U/kg (not to exceed 300 U) in the same lower limb that was treated in Study 191622-111 (referred to as the study lower limb). Patients with clinically significant upper limb spasticity may be eligible to receive BOTOX treatment in an affected upper limb up to a maximum of 8 U/kg (not to exceed 300 U). The combined lower and upper 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 a single lower limb or a single 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 diplegic 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 4 U/kg in the study lower limb(s) 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.

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Study Population Characteristics

Patients who successfully completed Study 191622-111 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 191622-111 cannot be enrolled in this study.

Additionally, *de novo* patients (who did not participate in Study 191622-111) who meet inclusion criteria and do not meet the exclusion criteria may be enrolled in this study.

Number of Patients:

Approximately 350 patients will be enrolled.

Condition/Disease:

Medically stable monoplegic, hemiplegic, or diplegic pediatric patients with cerebral palsy who have dynamic muscle contracture of the ankle plantar flexors associated with equinus foot position

*Key Inclusion Criteria:*Rollover patients:

- Eligible patients who successfully completed Allergan Study 191622-111 without major protocol deviations (eg, noncompliance to protocol-required procedures) and who, in the investigator's clinical judgment, did not experience an adverse event that may indicate an unacceptable safety risk for additional BOTOX treatments
- Stable medical condition in the investigator's opinion
- Written informed consent has been obtained from parent/legally authorized representative
- Written minor assent has been obtained in accordance with local laws and institutional review board (IRB)/independent ethics committee (IEC) requirements
- Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information for United States [US] sites and written Data Protection consent for European Union [EU] sites)
- Negative urine pregnancy test at day 1 visit (for females of childbearing potential, defined as females post menarche)

De novo patients:

- [REDACTED]
- Minimum weight of 10 kg at the screening and day 1 visits
- Monoplegic, hemiplegic, or diplegic patients with cerebral palsy with dynamic muscle contracture (spasticity confirmed by Hypertonia Assessment Tool [HAT]) of the ankle plantar flexors. Equinovarus and equinovalgus deformities are acceptable.

- [REDACTED]
- [REDACTED]
- [REDACTED]

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- [REDACTED]
- [REDACTED]
- [REDACTED]
- [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]
- [REDACTED]
- [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]
- [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 lower leg (the knee and below of the study limb[s]) within 12 months prior to the day 1 visit (*de novo* patients only) or planned surgical intervention of any limb(s) during the study

Response Measures

Safety measures:

- Adverse events

Response	Percentage
Yes, the U.S. should take action to address climate change	95%
No, the U.S. should not take action to address climate change	5%

Safety data will be analyzed on the basis of all treated patients based on treatment received, defined as the safety population. [REDACTED]

Safety variables such as the incidence of adverse events,

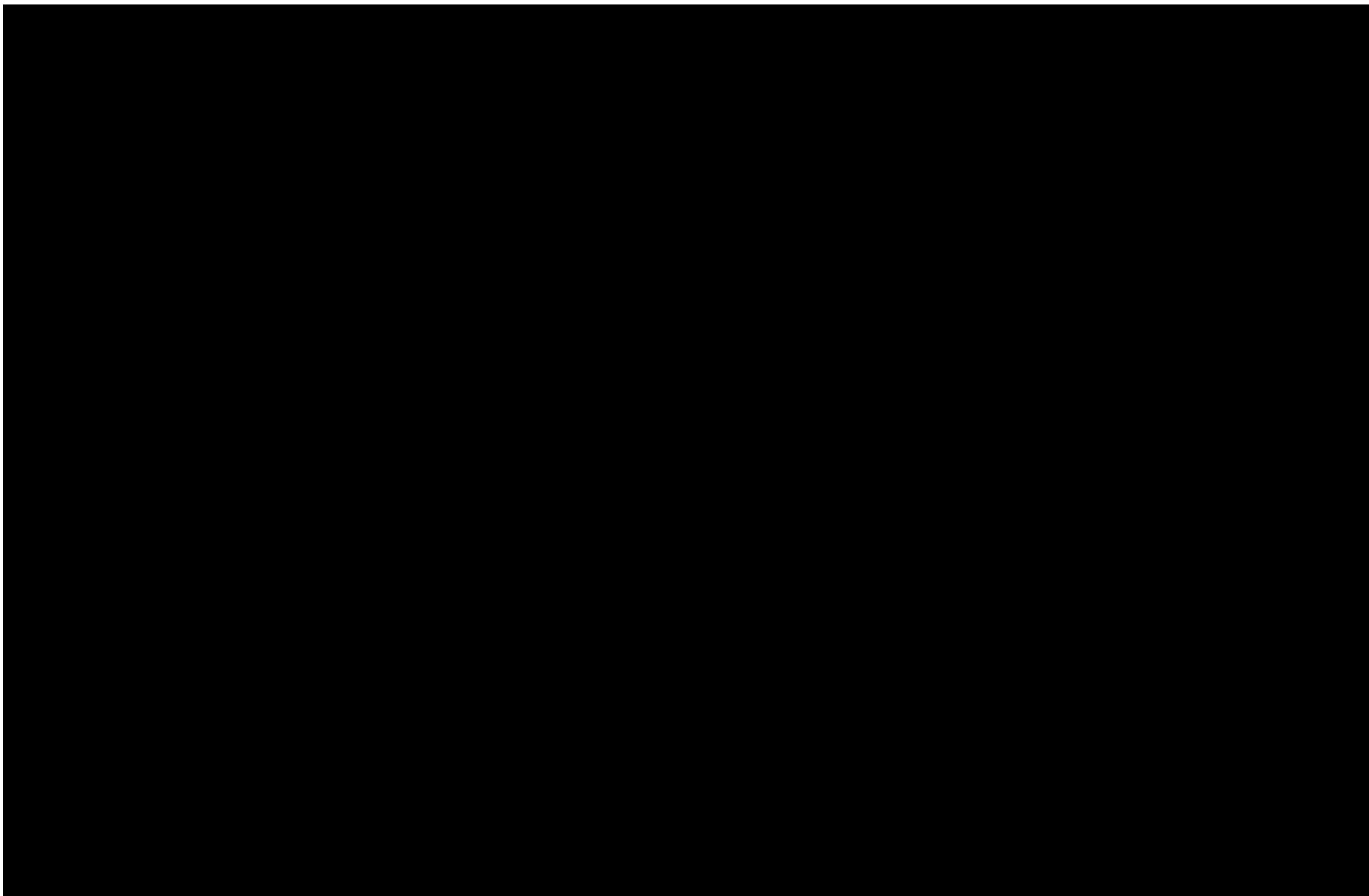
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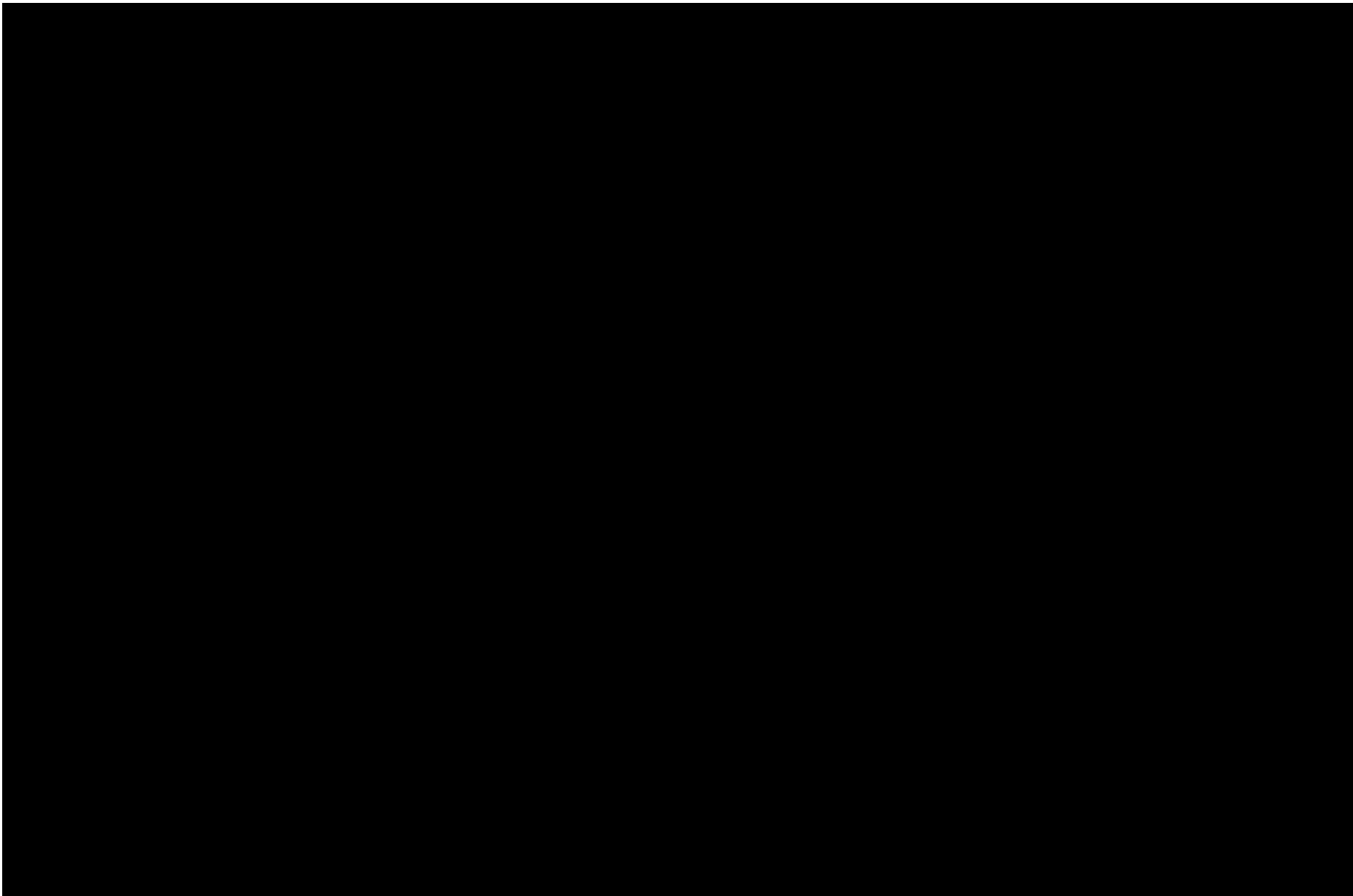
Sample Size Calculation:

Approximately 350 patients will be enrolled. The sample size was determined empirically.

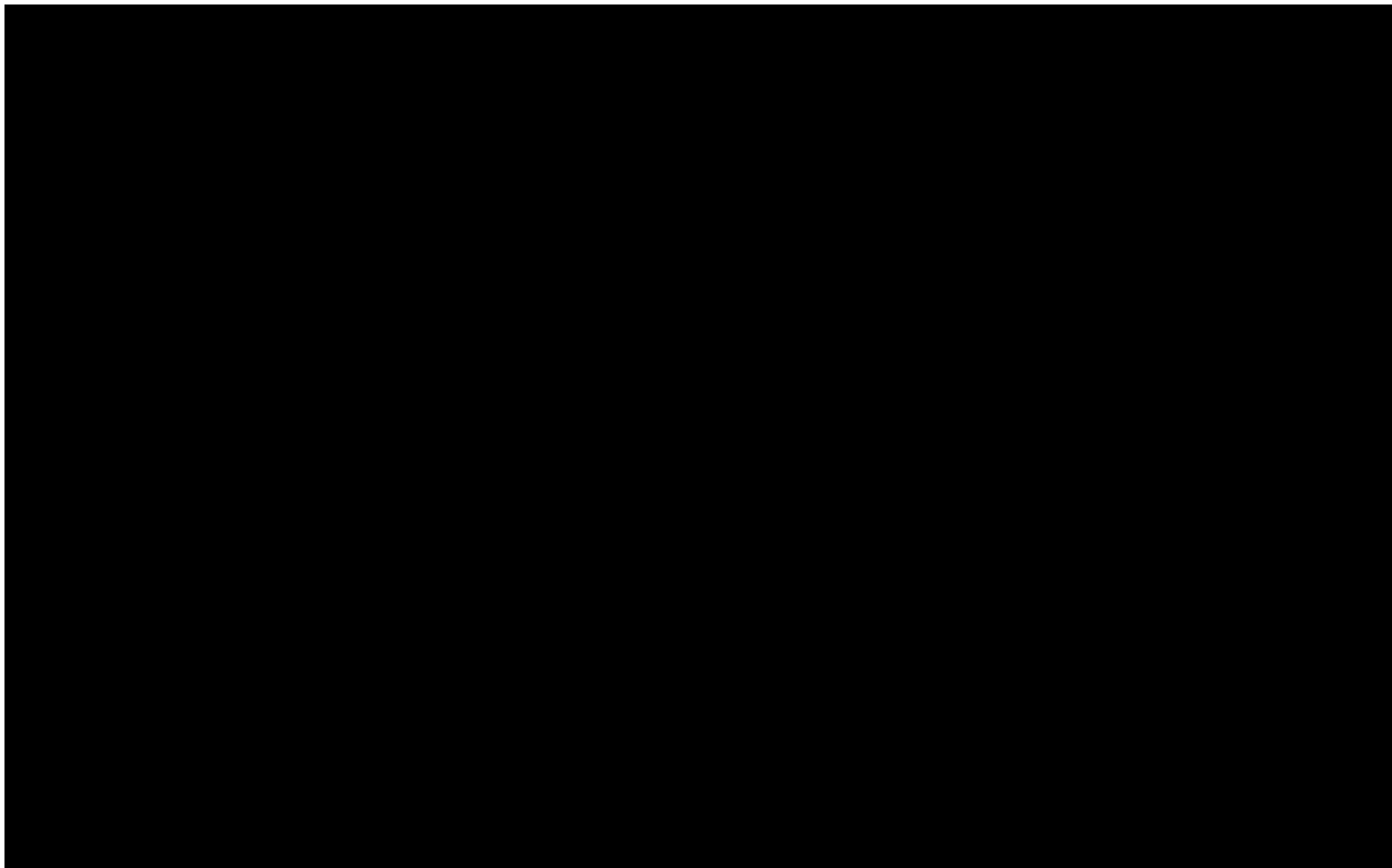
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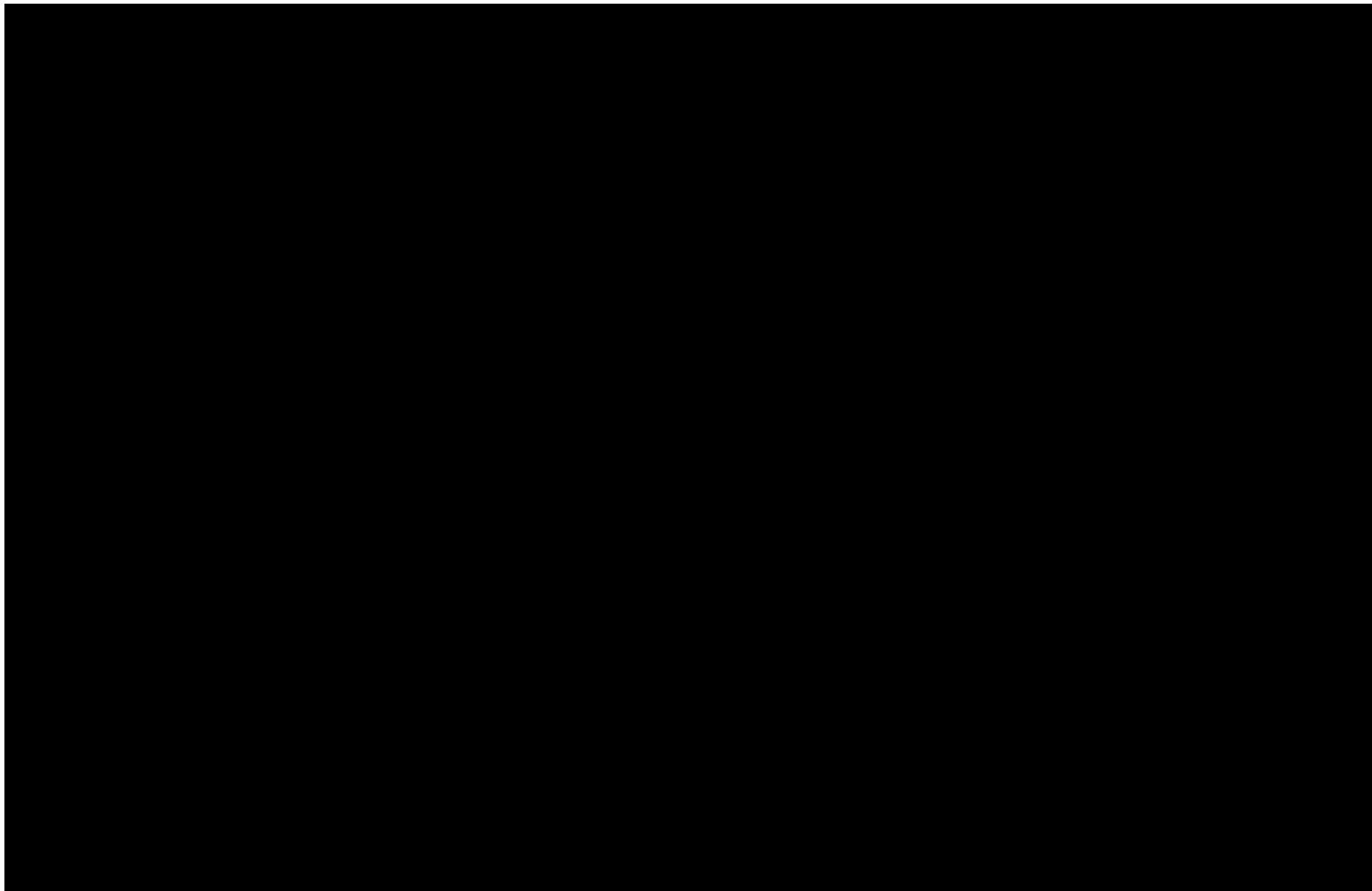
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1. Background and Clinical Rationale

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, presented in about 13% to 30% of patients with cerebral palsy, is characterized by spasticity of both legs with relative sparing of the arms (Odding et al, 2006; Stanley et al, 2000). 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

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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.

Equinus foot deformity is the most common (75%) form of spasticity in patients with cerebral palsy ([Cobeljic et al, 2009](#)). The increased muscle tone first presents as dynamic deformity and, if left untreated, transforms to fixed deformity as the child grows ([Detrembleur et al, 2002](#)). Early treatment to prevent the development of fixed contracture is therefore important in the management of spasticity in this population.

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 is 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

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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 and reduce pain 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

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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.

1.4 Dose Justification

The purpose of this study is to further investigate the safety of BOTOX treatment in pediatric patients with cerebral palsy who have dynamic muscle contracture of the ankle plantar flexors associated with equinus foot position.

The maximum lower limb dose in a single limb selected for this study corresponds to the maximum dose group (8 U/kg) from the efficacy Study 191622-111. This dose is supported by Allergan clinical trial experience in pediatric lower limb spasticity, clinical expert advice, published literature including consensus guidelines for botulinum toxin type A treatment of pediatric spasticity, and nonclinical toxicology data.

The doses for lower limb treatment used in the present study are supported by the dose ranges described in the consensus guidelines and published literature. The European consensus paper ([Heinen et al, 2010](#)) recommended a dose range of 1 to 20 U/kg with a maximum total dose of 400 U, regardless of location of injection. The American Academy of

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Neurology also 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 2010 International Consensus Paper for botulinum toxin treatment in lower limb spasticity for children with cerebral palsy recommends a dose range of 16 to 20 U/kg for patients with Gross Motor Function Classification System – Expanded and Revised (GMFCS-E&R) level I to IV without risk factors (Love et al, 2010). The higher dose ranges were based on studies allowing injections to multiple muscles (multi-level injections) across upper and lower extremities (Heinen et al, 2006; Molenaers et al, 2009).

Doses recommended for individual muscles are 3 to 6 U/kg for gastrocnemius, 2 to 3 U/kg for soleus, and 1 to 2 U/kg for tibialis posterior (Russman et al, 2008). In published double-blind studies in pediatric patients with lower limb spasticity, a dose of 2 to 8 U/kg was most commonly used for the gastrocnemius muscles. The maximum dose ranged from 200 to 600 U for both legs. Doses used in Study 191622-111 and the present study are consistent with the range of doses recommended by the consensus documents and reflect current clinical practice.

In addition, the safety of 10 U/kg for combined treatment of the lower limb and upper limb or both lower limbs in this study is also 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 dose considerations, doses of up to 8 U/kg (maximum 300 U) for one lower limb, up to 10 U/kg (maximum 340 U) for both lower limbs, and up to 8 U/kg (maximum 300 U) for the upper limb (not to exceed a maximum total body dose of 10 U/kg or 340 U for upper and lower limbs combined) 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 lower limb spasticity

2.2 Clinical Hypothesis

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

3. Study Design

This is a multicenter, open-label study evaluating the safety of repeated treatments of BOTOX in dynamic muscle contracture in pediatric patients with lower limb spasticity due to cerebral palsy. Patients who successfully completed Allergan Study 191622-111 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 191622-111) who meet inclusion criteria and do not meet the exclusion criteria may be enrolled in this study. Depending on the number of rollover patients from Study 191622-111 and the dropout rate for the present study, enrollment of *de novo* patients may be limited.

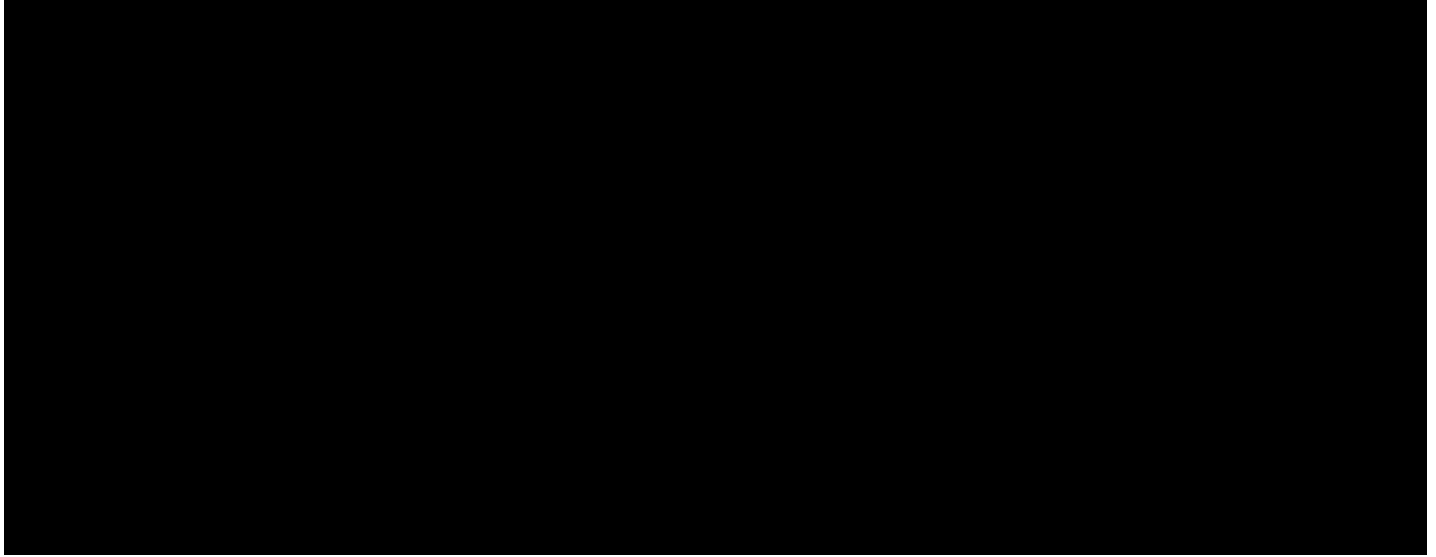
The study duration will be approximately 60 weeks. The total number of clinic visits will depend on the number and timing of treatments received by the patient. There will be a total of approximately 12 clinic visits for *de novo* patients, approximately 11 clinic visits for rollover patients who transitioned from Study 191622-111, 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 191622-111 becomes the day 1 visit for this study after the patient signs the Study 191622-112 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- to 14-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

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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.



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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 350 patients will be enrolled.

4.2 Study Population Characteristics

The study population is medically stable monoplegic, hemiplegic, or diplegic pediatric patients with cerebral palsy who have dynamic muscle contracture of the ankle plantar flexors associated with equinus foot position.

Patients who successfully completed Allergan Study 191622-111 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 191622-111 cannot be enrolled in this study.

Additionally, *de novo* patients (who did not participate in Study 191622-111) who meet inclusion criteria and do not meet exclusion criteria may be enrolled in this study.

4.3 Inclusion Criteria

██████████

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 day 1 visit
2. Minimum weight of 10 kg at the screening and day 1 visits

[illegible]

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:

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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]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

13. Uncontrolled epilepsy [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

22. History of surgical intervention of the lower leg (the knee and below of the study limb[s]) within 12 months prior to the day1 visit (*de novo* patients only) or planned surgical intervention of any limb(s) during the study

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[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, oral baclofen, scopolamine [oral or patch], tizanidine, vigabatrin, or

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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[®]) 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 the participation in the study. The method of contraception must be documented in the patient's medical record

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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 lower 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 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

PT/OT is an important element of the treatment approach in pediatric patients with spasticity. While no study-specific PT/OT will be required, patients should follow investigator's/therapist's recommendations regarding appropriate PT/OT. PT/OT 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. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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 191622-111 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 where the patient qualifies for reinjection, 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. The dose for each muscle and total dose will be calculated. [REDACTED]

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 4 U/kg in the study lower limb(s) 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

During the first treatment cycle, *de novo* patients are to receive a total of 8 U/kg (not to exceed 300 U) either in a single study lower limb or divided between both study lower limbs only for diplegic patients.

5.4.2 Treatment Cycle 1 for Rollover Patients

Patients transitioning from Study 191622-111 will be allowed to receive injections in the upper limb, the lower limb, 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 a single lower limb or 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 diplegic patients can be increased to 10 U/kg (not to exceed 340 U). Dose limitations by the number of limbs affected are as follows:

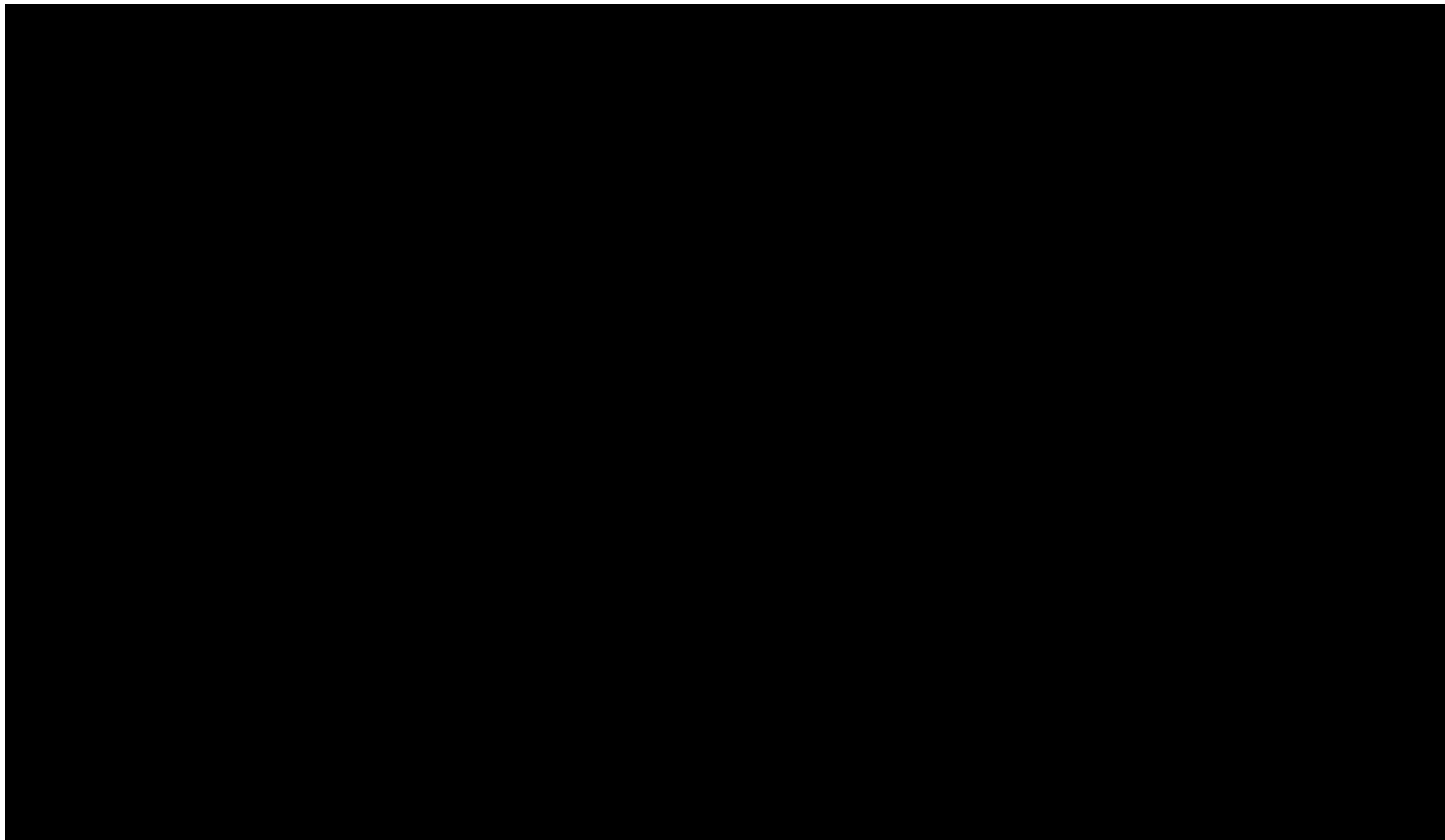
- up to 8 U/kg (not to exceed 300 U) for each treatment session if administered only to one lower limb or only to one upper limb or

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- up to 10 U/kg (not to exceed 340 U) if administered to both lower limbs for diplegic patients or
- up to 10 U/kg (not to exceed 340 U) if administered to a combination of upper and lower limbs

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

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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, 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 lower limb(s) or upper limb, 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 reinjected if they meet all of the following criteria on the day of retreatment prior to the injection:

[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]

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[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

Muscles localization techniques such as e-stimulation, sonography, and/or electromyography (EMG) are recommended for this study. Motor endplate targeting injection techniques are recommended ([Van Campenhout and Molenaers, 2011](#)).

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.

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6. Response Measures and Summary of Data Collection Methods

[REDACTED]

[REDACTED]

- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
[REDACTED]
- | [REDACTED]
[REDACTED]
- | [REDACTED]
[REDACTED]
- | [REDACTED]

6.1.1 Primary Efficacy Measure

No primary efficacy measure is identified.

[REDACTED]

[REDACTED]

- Adverse events

- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
[REDACTED]
- | [REDACTED]

6.2 Examination Procedures, Tests, Equipment, and Techniques

The procedures are described in Attachment 12.1.

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- | Row | Bar Length (approx. % of total width) |
|-----|---------------------------------------|
| 1 | 85 |
| 2 | 95 |
| 3 | 60 |
| 4 | 25 |
| 5 | 80 |
| 6 | 20 |
| 7 | 100 |
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| 9 | 98 |
| 10 | 25 |

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- | Row | Relative Length (approximate) |
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| 1 | 85% |
| 2 | 95% |
| 3 | 55% |
| 4 | 100% |
| 5 | 90% |
| 6 | 25% |
| 7 | 75% |
| 8 | 50% |
| 9 | 95% |
| 10 | 15% |

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

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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. [REDACTED]

A central laboratory will be used for the analysis of all blood samples. Blood samples for immunogenicity tests will be shipped by the central laboratory, analyzed by a specialty laboratory using validated assays, and the data will be transferred to Allergan or enter to the eCRF.

7. Statistical Procedures

The database lock will occur when all patients have completed the study and all data except immunogenicity data have been cleaned. 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, applicable changes from baseline to

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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 191622-111, an additional set of variables using the original baseline values in the previous study will also derived. In addition, the time interval from the injection in Study 191622-111 to the first injection in this study will be derived.

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2.2 Primary Efficacy Variable(s)

No primary efficacy variable is identified.

7.3 Hypothesis and Methods of Analysis

There will be no hypothesis testing unless otherwise specified.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

7.3.2 Safety Analyses

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

[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]

[REDACTED]

[REDACTED]

[REDACTED]

7.5 Sample Size Calculation

7.6 Interim Analyses

[REDACTED]

[REDACTED]

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[REDACTED]

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- | Row | Bar 1 Length (approx. %) | Bar 2 Length (approx. %) | Bar 3 Length (approx. %) |
|-----|--------------------------|--------------------------|--------------------------|
| 1 | 100 | 75 | |
| 2 | 85 | | |
| 3 | 70 | | |
| 4 | 60 | | |
| 5 | 90 | | |
| 6 | 100 | 100 | 95 |
| 7 | 10 | | |
| 8 | 95 | 100 | |
| 9 | 10 | | |
| 10 | 100 | 100 | |
| 11 | 85 | | |
| 12 | 55 | | |

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[REDACTED]

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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 and at the discretion of the investigator eg, for safety concerns or for retreatment evaluation (if time since the last study treatment has been at least 12 weeks). 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 post baseline 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.

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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 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.

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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:

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- 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 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 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]
[REDACTED]
- For sites performing the Edinburgh Visual Gait score, the videotape

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- The results of laboratory tests performed by the site (eg, results of hematology, serum chemistry, HbA1c, urine pregnancy, and immunogenicity 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 eCRFs) 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.

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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

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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. Samples for immunogenicity will be sent to the central laboratory for temporary storage and will then be sent to a specialty laboratory for analysis. Allergan shall have full ownership rights to any biological specimens/samples derived from the study. Approximately 14 mL of blood is estimated to be collected at a given visit for children 15 kg and above (7 mL for hematology and chemistry and 7 mL for immunogenicity testing). Approximately 7 mL of blood will be collected at a given visit for children under 15 kg in weight. 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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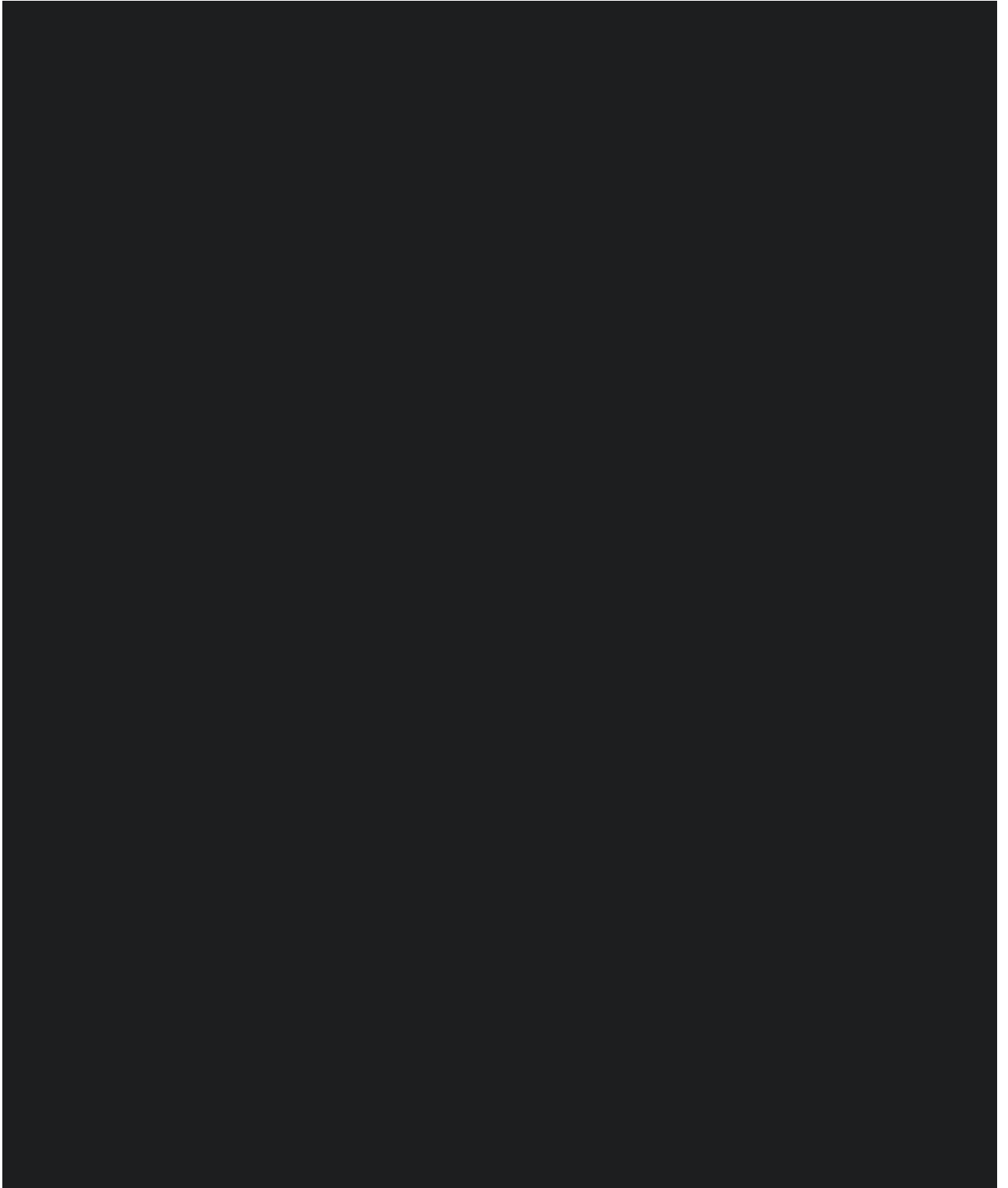
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Approval Date: 28-Jan-2014

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Service	Percentage
Online banking	78%
Mobile banking	65%
ATM services	52%
Branch services	41%
Other services	33%

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Category	Percentage
1	10%
2	80%
3	10%
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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.

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12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
AFO	ankle foot orthosis
[REDACTED]	[REDACTED]
BoNT-A	botulinum neurotoxin type A
BOTOX [®]	Botulinum Toxin Type A Purified Neurotoxin Complex (US adopted name onabotulinumtoxinA), referred to as BOTOX
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
ELISA	enzyme-linked immunosorbent assay
EMG	electromyography
EU	European Union
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
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
[REDACTED]	[REDACTED]
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NA	not applicable
No.	number

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NOAEL	No-observable-adverse-effect level
OT	occupational therapy
PT	physical therapy
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 Lower Limb Spasticity: Open-label Study

Protocol 191622-112, Amendment 1

Date of Amendment: 30 March 2012

Amendment Summary

This summary includes changes made to Protocol 191622-112 (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]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
10.7, Handling of Biological Specimens	Revised approximate volume of blood collection for hematology and chemistry regardless of weight from 5 to 7 mL and total for children 15 kg and above from 12 to 14 mL.	Based on the revised central laboratory (Covance) requirements.

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

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12.5 Protocol Amendment 2 Summary

Title: BOTOX[®] Treatment in Pediatric Lower Limb Spasticity: Open-label Study

Protocol 191622-112, Amendment 2

Date of Amendment: 29 November 2012

Amendment Summary

This summary includes changes made to Protocol 191622-112 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
Tables 1 and 2, Schedules [REDACTED]	[REDACTED]	[REDACTED]
1.4, Dose Justification 2.2, Clinical Hypothesis 5.4, Treatment Regimen and Dosing Table 3	Added wording for a combination of both lower limbs for diplegic 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 both lower limbs are treated

Approval Date: 28-Jan-2014

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Section(s)	Revision	Rationale
1.4, Dose Justification	Second paragraph: The <u>maximum lower limb dose in a single limb doses</u> selected <u>for</u> in this study corresponds to the <u>maximum high</u> dose group (8 U/kg) from the efficacy Study 191622-111. <u>This dose is</u> These doses are supported by Allergan clinical trial experience in pediatric lower limb spasticity, clinical expert advice, published literature including consensus guidelines for botulinum toxin type A treatment of pediatric spasticity, and nonclinical toxicology data.	For clarification
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
4.4, Exclusion Criteria	Changed #23 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: <u>to the extent possible unless judged by the investigator to be clinically inappropriate.</u>	For clarification
5.3, Method for Assignment to Treatment Groups	Added <u>At the study day 1 visit for both <i>de novo</i> and rollover, the site will access the IVRS/IWRS to enroll the patient;</u>	For clarification

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Section(s)	Revision	Rationale
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: <u>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 4 U/kg in the study lower limb(s) every 12 to 14 weeks, with the total dose not to exceed the maximum specified for each treatment cycle.</u>	For clarification
5.4.1, Treatment Cycle 1 for <i>De Novo</i> Patients	Specified that a total of 8 U/kg is to be injected either in the single study lower limb or divided between both study lower limbs only for diplegic patients.	For clarification
5.4.3, Treatment Cycles 2 Through 5 for All Patients (Rollover and <i>de novo</i>)	Revised description of dose limitations	For clarification
Table 3	Revised title to be more specific (Maximum Per-muscle, Per-limb, and Total Body Dose), added row for total maximum dose for both lower limbs, and added footnote to indicate that only 1 upper limb is to be injected.	For clarification
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 reinjected" if they meet the retreatment criteria.	For clarification

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

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Section(s)	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
8.7, Early Discontinuation of Patients	Revised study week 42 to study week 48.	Correction
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]

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

12.6 Protocol Amendment 3 Summary

Title: BOTOX[®] Treatment in Pediatric Lower Limb Spasticity: Open-label Study

Protocol 191622-112, Amendment 3

Date of Amendment: January 2014

Amendment Summary

This summary includes changes made to Protocol 191622-112 Amendment 2 (e-signature date 28 November 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 13a regarding seizure frequency for exclusion	Clarification
	Modified Exclusion Criterion 14 regarding vulnerable respiratory state	Clarification
	Added Exclusion Criterion 29 to exclude patients with significant suicidality from treatment	To avoid confounding the safety data

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Section(s)	Revision	Rationale
Protocol Summary; [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	Added a sentence on use of anti-epileptics	Clarification that anti-epileptics are permissible during the study
5.4.1.1	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	Removed: "Non-frost-free -20°C freezer for storage of serum neutralizing antibody samples"	Correction
[REDACTED]	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]
[REDACTED]	[REDACTED]	[REDACTED]
9.3	Updated serious adverse event language	Per new Allergan protocol template
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

ALLERGAN

Protocol 191622-112 Amd 3

