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Study ID: 191622-112

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

Statistical Analysis Plan: 02 October 2018

**Allergan
Biostatistics
Analysis Plan**

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1. Introduction

This analysis plan details the analyses that will be performed for BOTOX® (Botulinum Toxin Type A) Study 191622-112, an open-label study designed to evaluate the long-term safety of repeated doses of BOTOX for the treatment of pediatric lower limb spasticity.

1.1 Primary Study Objectives and Design

The study objective is to evaluate the long-term safety of repeated doses of BOTOX for the treatment of pediatric lower limb spasticity.

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. 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 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.

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(s)).

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.

Approximately 350 patients will be enrolled. The sample size was determined empirically rather than by sample size calculation.

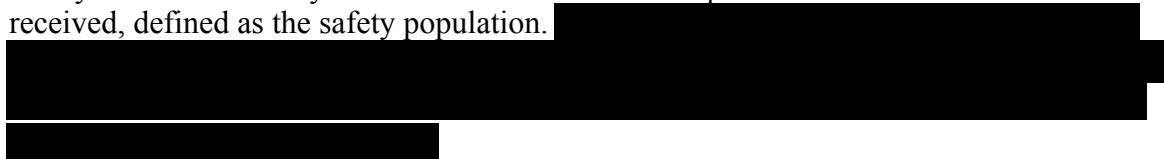
1.2 Secondary and Other Objectives

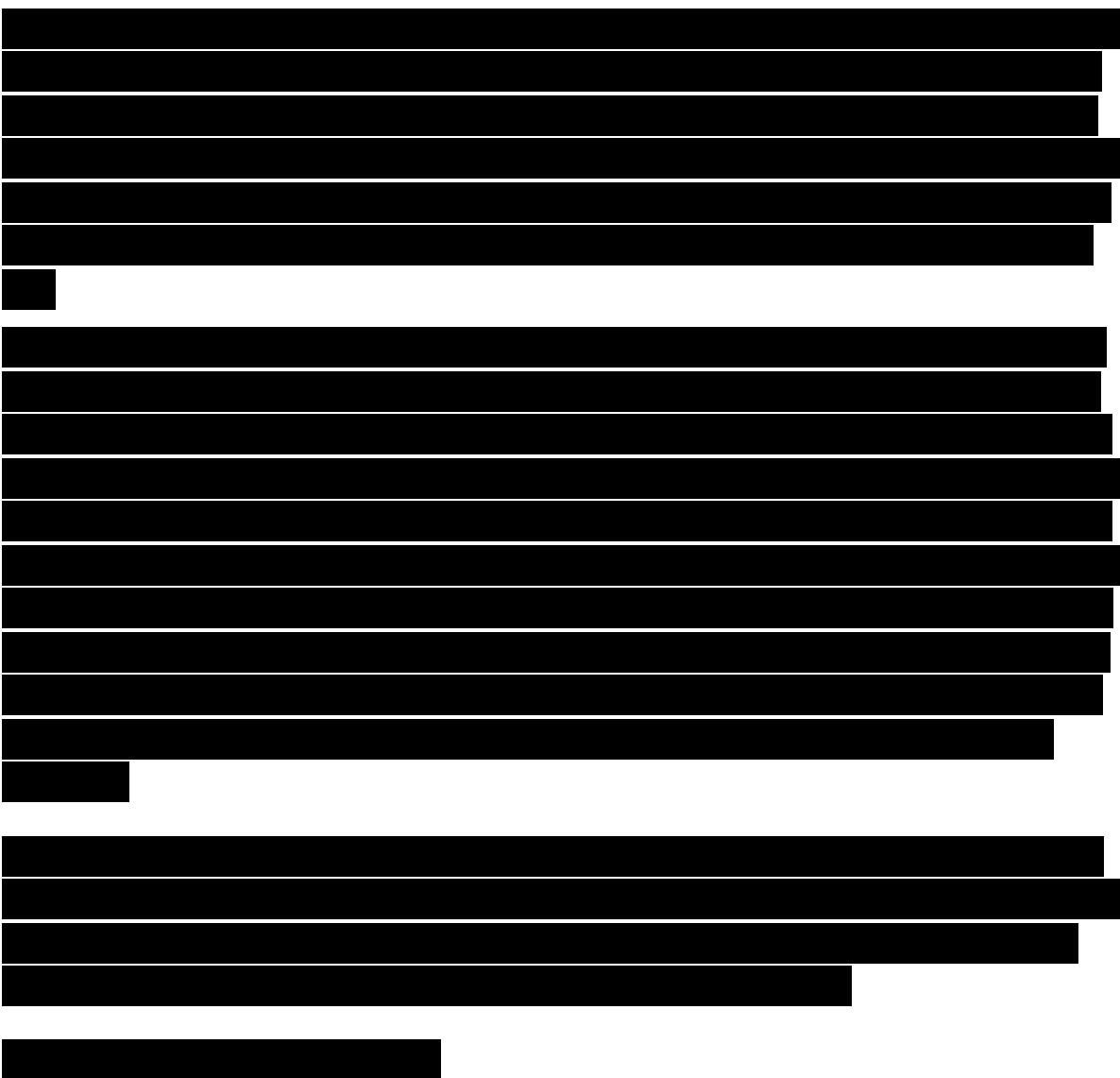
There are no secondary or other objectives for this study.

2. Analysis Populations and Data Conventions

2.1 Analysis Populations

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





2.3 Data Conventions

The data conventions and definitions listed in this section are to be applied to all analyses unless stated otherwise in a subsequent section of this Analysis Plan.

- Data will be analyzed according to the following treatment groups:
 - For rollover patients from Study 191622-111 under treatment group BTX 4 U/kg, BTX 8 U/kg, or Placebo, their corresponding treatment group will be

designated as BTX 4 U/kg/BTX, BTX 8 U/kg/BTX, Placebo/BTX, respectively.

- For de novo patients, , their treatment group will be designated as Placebo/BTX.
- Concurrent medication and prior medication will be calculated using the following convention: 1) If the stop date of taking medication is prior to first injection date, then it will be counted as prior medication; 2) If the start date of taking medication is after or on first injection date, then it will be counted as concomitant medication; 3) If the start date of taking medication is prior to first injection date and stop date is on or after last injection date, then it will be counted as both prior medication and concomitant medication.
- Concurrent procedures are defined as those taken on or after the first injection date.
- All data will be listed with the exceptions of commonly expected results such as physical examination, pregnancy tests results for females when not applicable, etc.
- Summary statistics of continuous variables will include the sample size (N), mean, standard deviation, median, minimum (Min), and maximum (Max).
- Summary statistics of categorical variables will include the sample size (N) and/or frequency counts and percentages.
- Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code all adverse events (AEs) and medical history.
- World Health Organization Drug Dictionary Enhanced (WHO DDE) preferred name and MedDRA will be used to code all medications.
- Metric systems will be used for all applicable measures including (kg), height (cm), and clinical laboratory data (SI: Standard International units).
- Baseline is defined as the last non-missing observation prior to receiving the first treatment for de novo patients and the same baseline in study 191622-111 for the rollover patients. For some measurements not measured in study 191622-111, the last non-missing observation prior to receiving the first treatment in study 191622-112 will be used. Change from baseline is calculated as follow-up minus baseline value.

- Missing values will not be imputed.
- Study days from the treatment day of a certain treatment cycle will be calculated as:

Study days = visit date – most recent treatment day visit date + 1.

- The study day of an event that has occurred before first treatment day will be calculated as:

Study day = date of event – treatment 1 visit date.

- Partial dates occurring when calculation of study day is germane to the study outcome will be handled as follows:

If the year is missing then the date is treated as missing.

If either the month or the day is missing, then the closest to baseline possible will be used. That is, an event occurring the year before baseline would use December and/or the last day of the month. An event occurring the year after baseline would use January and/or the first day of the month.

All partial dates will be listed “as is” in the data listings.

- All adverse events (AEs) with missing onset dates will be identified and the missing dates will be imputed as follows for analysis. These imputations are only for assigning adverse events to a particular study phase; calculations such as days to onset will not use these imputations. All partial dates will be listed “as is” in the data listings.
 - (a) For AE onset date: If day and month are missing but year is available (..../yy) then the imputed day and month will be 01/01/yy or the injection date if they have the same year, whichever is later. If day is missing but the month and year are available (mm..../yy), then the imputed day will be mm/01/yy or the injection date if they have the same month and year, whichever is later.
 - (b) For AE stop date: If day and month are missing but year is available (./.yy) then the imputed day and month will be 12/31/yy or the study exit date if they have the same year, whichever is earlier. If day is missing but the month and year are available (mm./.yy), then the imputed day will be the last day of the month mm in the year yy or the study exit date if they have the same month and year, whichever is earlier.

- (c) If the AE onset or stop month, day, and year are missing (..../..), then the study entry date will be used as the AE onset date and the exit date will be used as the AE stop date.
- Data from unscheduled visits or re-test visits will be treated the same way as scheduled visits, i.e., the dates of such visits will be used in the categorization of visit window. The algorithm handling multiple visits within a visit window will also be applied to unscheduled visits and re-test visits.
- There is no data pooling for efficacy analyses considering all are descriptive evaluations.
- The mean change from baseline for a given treatment group will be calculated by taking the sum of all individual changes from baseline divided by the number of patients with observations in that treatment group. As a consequence, patients without the particular follow-up data will not be taken into account, except if there is a missing value replacement method used.



3. Disposition and Exit Status

3.1 Disposition and Exit Status

A patient disposition and exit status table will be done for the mITT population. A cumulative frequency table showing patient disposition (enrolled, completed, and discontinued) in the study with sub-categorization by reason of premature discontinuation for each treatment group and overall patients will be generated.

4. Demographics and Other Baseline Characteristics

4.1 Demographics

Demographics data will be analyzed using the mITT population. Age, race, sex will be summarized using frequency tabulations and/or summary statistics, both by treatment group and overall patients. Race will be classified as White and non-White (black, Asian, Hispanic, and other). In addition, race will be displayed as collected in the CRF (White, black, Asian, Hispanic, and other). Age will also be summarized by ≤ 6 and > 6 years of age groups.

4.2 Concomitant Medications

Using the mITT population, the number and percent of patients who take concomitant medication (as defined in Section 2.3) will be presented by treatment group and overall patients for the base preferred (drug) name according to the World Health Organization Drug Dictionary Enhanced (WHO DDE) with the same active ingredients by the primary system organ class (SOC) and preferred term of the MedDRA code.

5. Efficacy Analyses

5.1 Collection of Primary Efficacy Measurement(s) and Derivation of Primary Efficacy Variable(s)

No primary efficacy variable is identified.

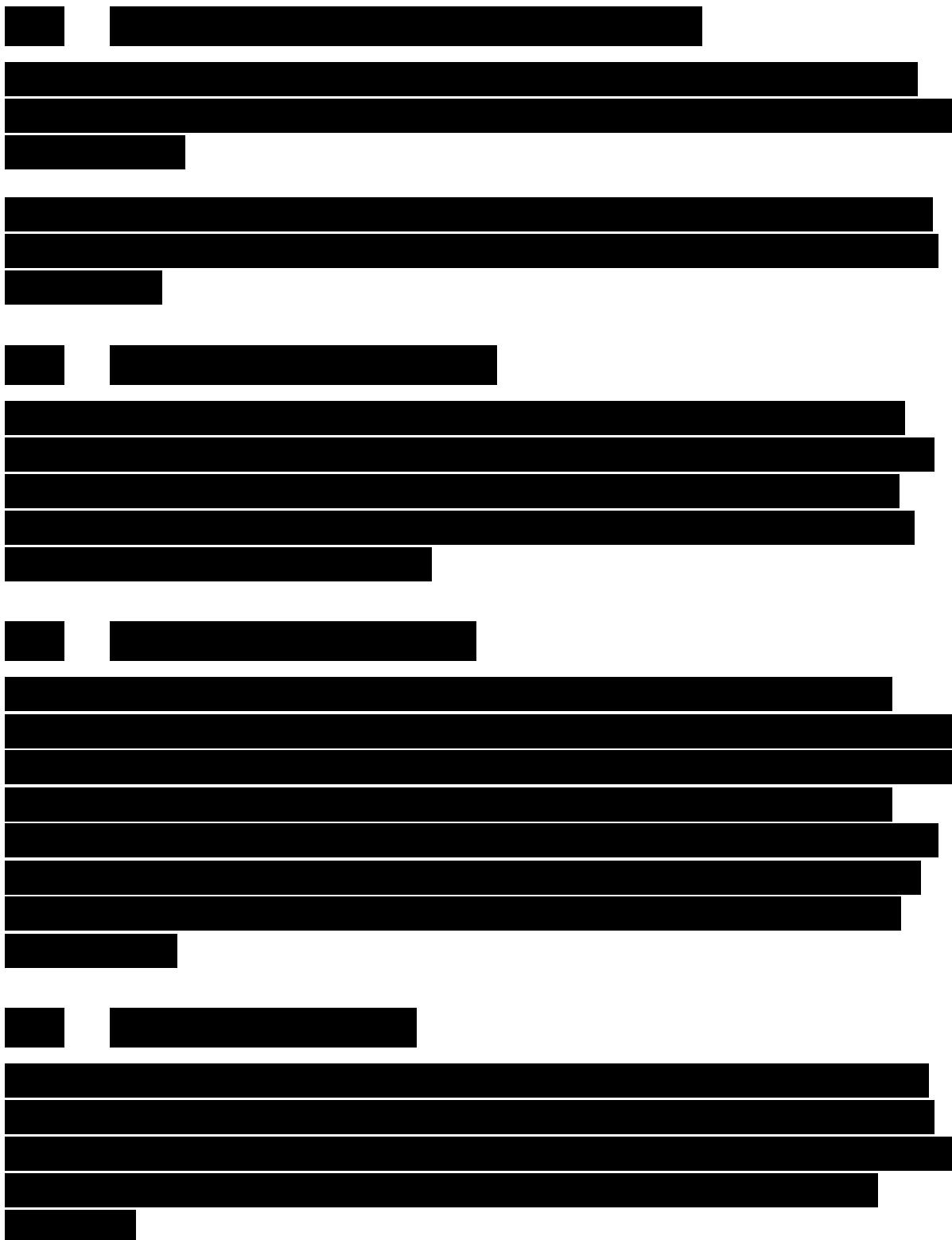
5.2 Primary Efficacy Analyses

Not applicable.

5.3 Secondary Efficacy Analyses

Not applicable.

[REDACTED]



[REDACTED] [REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

6. Safety Analyses

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

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

6.2 Treatment Emergent Adverse Events

Adverse events are collected for the period prior to the first treatment (which are referred to as pre-treatment AEs as cited in Section [Error! Reference source not found.](#)) and for the period on or after the first treatment.

An overall treatment-emergent adverse event (TEAE) is an adverse event with onset on or after the initiation of the first treatment or an adverse event with onset prior to the first treatment that worsened in severity or became serious on or after the initiation of the first treatment.

A treatment cycle treatment-emergent adverse event (TEAE) is an adverse event with onset on or after the initiation of the cycle treatment but before the initiation of the next cycle treatment or an adverse event with onset prior to the cycle treatment that worsened in severity or became serious on or after the initiation of the cycle treatment but before the initiation of the next cycle treatment.

An AE that stops during certain treatment cycle and recurs in the subsequent treatment cycle(s) is considered as a TEAE in the subsequent treatment cycle(s) if it fulfills the TEAE definition above.

The number and percentage of patients reporting each event will be summarized by treatment cycle and overall as follows:

- i. By primary SOC and preferred term. At each level of summarization (overall, primary SOC, and preferred term) a patient will be counted once if he/she reports 1 or more experiences at that level.
- ii. By primary SOC, preferred term and severity. For a given adverse event of a patient, if more than 1 severity grade was reported, the worst severity grade will be included in the tabulation.

An overall summary of TEAE will be presented. In addition, individual patient data listings (including adverse event listings that include the investigator verbatim terms and MedDRA lower level terms) will be provided.

Furthermore, the assessment of possible distant spread of toxin will be performed using the list of 39 MedDRA preferred terms (version 19.0 or its updated version as appropriate during the time of data analysis).

MedDRA Preferred Terms Evaluated for Possible Distant Spread of Toxin

Cardiac Disorders

Bradycardia

Eye Disorders

Accommodation disorder
Diplopia
Extraocular muscles paresis
Eyelid function disorder
Eyelid ptosis
Pupillary reflex impaired
Vision blurred

Gastrointestinal Disorders

Constipation
Dry mouth
Dysphagia
Ileus paralytic

Infections and Infestations

Botulism

Musculoskeletal and Connective Tissue Disorders

Muscular weakness

Nervous System Disorders

Bulbar palsy
Cranial nerve palsies multiple
Cranial nerve paralysis
Dysarthria
Facial paralysis
Facial paresis
Hyporeflexia
Hypotonia
Paralysis
Paresis cranial nerve
Peripheral nerve palsy
Peripheral paralysis
Speech disorder
Vocal cord paralysis
Vocal cord paresis

Renal and Urinary Disorders

Urinary retention

Respiratory, Thoracic and Mediastinal Disorders

Aspiration
Diaphragmatic paralysis
Dysphonia
Dyspnoea
Pneumonia aspiration
Respiratory arrest
Respiratory depression
Respiratory failure

Reproductive System and Breast Disorders

Pelvic floor muscle weakness





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7. 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.

8. Pharmacokinetic Data Analyses

There will be no pharmacokinetic data to be analyzed from this study.

9. Health Outcomes Data Analyses

There will be no health outcomes data to be analyzed from this study.

10. Data Collected but not Analyzed

The date and signature of investigator and system required variables of electronic data capture (EDC) and IVRS/IWRS will not be analyzed.

11. Deviations from Protocol

There is no deviations from the protocol amendment 3.

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