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Study ID: 1789-202-008

Title: BOTOX® (onabotulinumtoxinA) Treatment of Masseter Muscle Prominence: A Phase 2b, Multicenter, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study

Statistical Analysis Plan Date: August 5, 2019
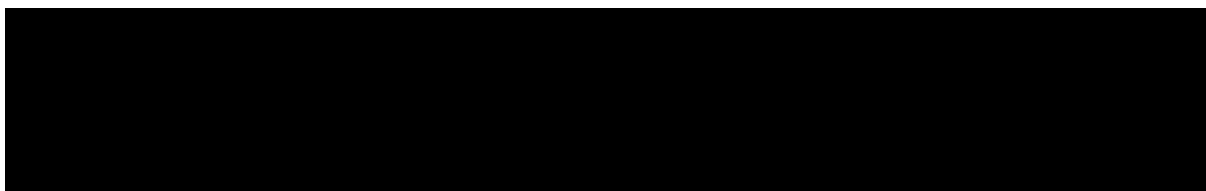
1.0   TITLE PAGE

1789-202-008

BOTOX® (onabotulinumtoxinA) Treatment of Masseter Muscle Prominence:

A Phase 2b, Multicenter, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study

STATISTICAL ANALYSIS PLAN - Clinical Study Report

Final: 05 Aug 2019

2.0   TABLE OF CONTENTS

3.0   LIST OF ABBREVIATIONS

|	
AE	adverse event
AOI	area of interest
ANCOVA	analysis of covariance
CMH	Cochran-Mantel-Haenszel
CRF	case report form
████	██████████████████████████
mITT	modified Intent-to-Treat
MMP	masseter muscle prominence
MMPS	Masseter Muscle Prominence – Investigator Assessment
MMPS-P	Masseter Muscle Prominence – Participant Assessment
MedDRA	Medical Dictionary for Regulatory Activities
PCS	potentially clinically significant
PDSOT	possible distant spread of toxin
PID	patient ID
████	█████████████████████████████
PSAC	Participant Self-Assessment of Change
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

4.0   INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the approved protocol of Study 1789-202-008 (dated 12 Feb 2019). Specifications of tables, figures, and data listings are contained in a separate document.

Study 1789-202-008 is a Phase 2b, 6-month, double-blind, randomized, placebo-controlled, single-treatment trial to assess the safety and efficacy of BOTOX treatment for MMP.

Approximately 150 participants were planned to be randomly assigned (1:1:1) to receive a single treatment of BOTOX 48 U (n=50), BOTOX 72 U (n=50), or placebo (n=50) on Day 1. Randomization will be stratified at each investigator site by the participant's baseline MMPS Grade (4 or 5). Up to 8 scheduled visits are planned: screening (Day -14 to Day -1), randomization/baseline (Day 1), follow-up (Days 30, 60, 90, 120, 150, and 180). On Day 180, final study exit assessments will be collected.
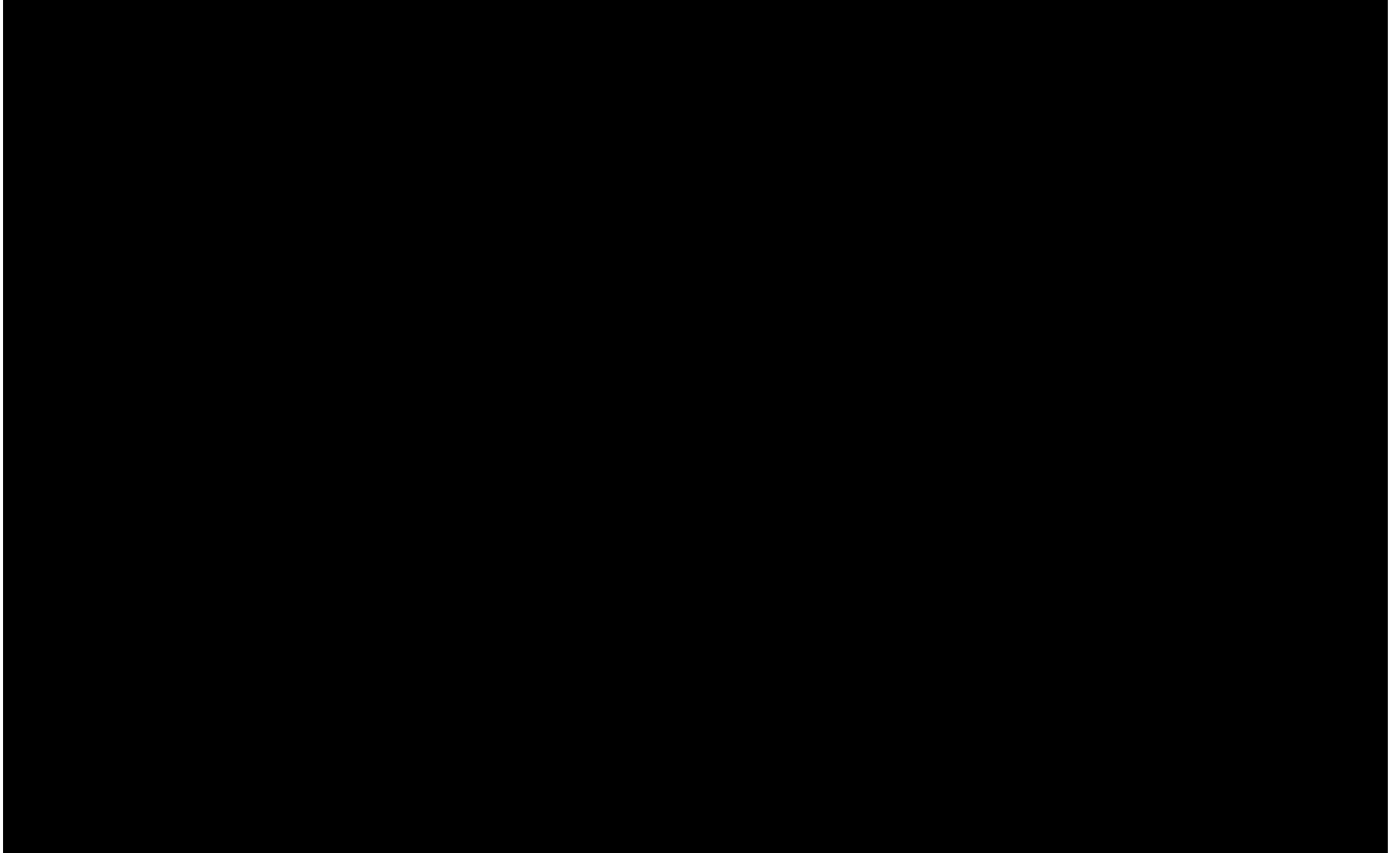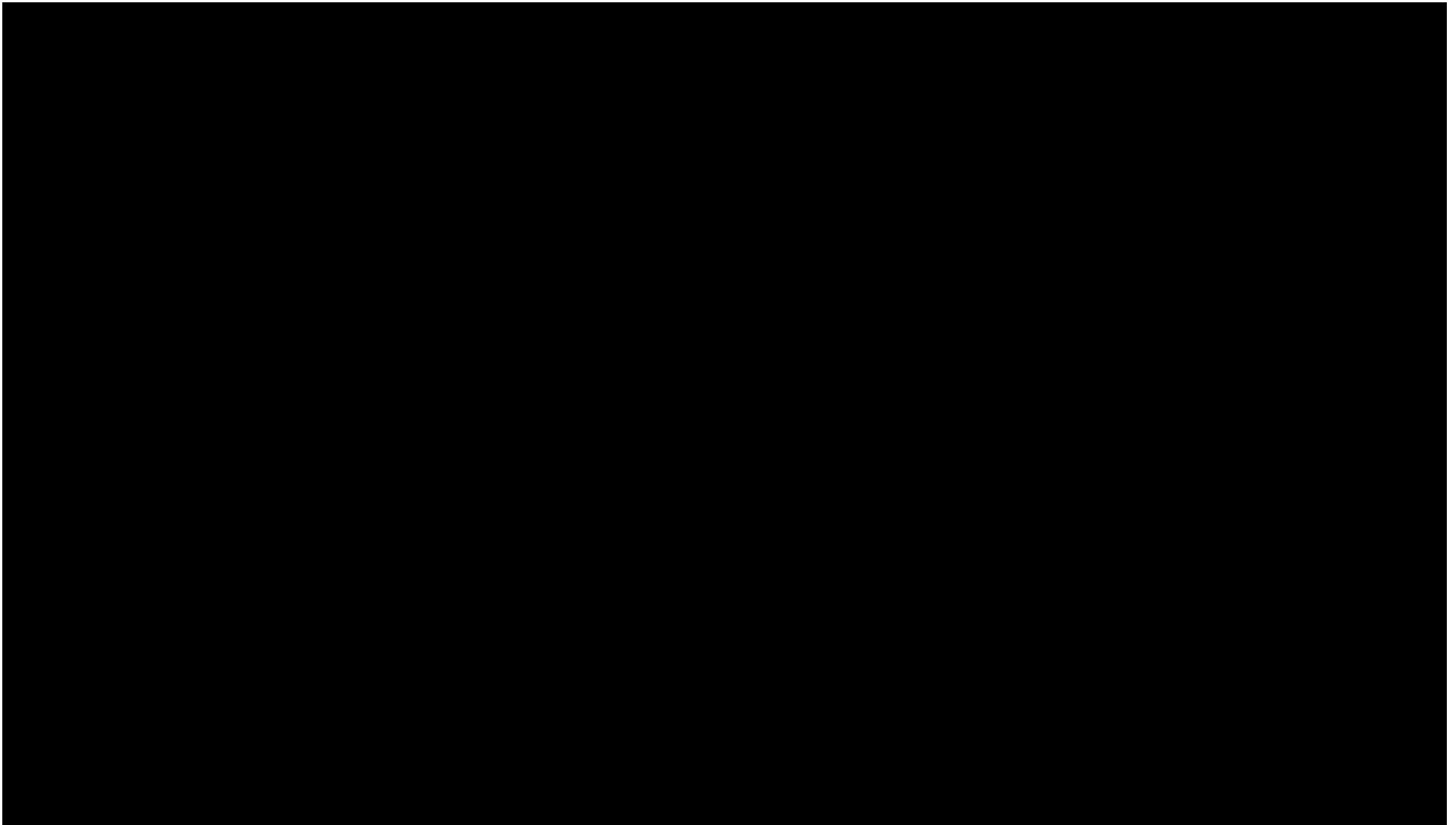
5.0   OBJECTIVES

The objectives of this study are:

- To compare the efficacy and safety of BOTOX with placebo in participants with bilateral masseter muscle prominence (MMP)

- To compare the efficacy of BOTOX with placebo in participants with MMP based on multiple clinical efficacy assessments

6.0   PATIENT POPULATIONS

The patient populations will be summarized in total and by study intervention group for all randomized or treated participants.

6.1   MODIFIED INTENT-TO-TREAT POPULATION

The modified Intent-to-Treat (mITT) Population will consist of all randomized participants with at least 1 postbaseline MMPS assessment. Participants will be summarized according to the randomized study intervention.

6.2   SAFETY POPULATION

The Safety Population will consist of all participants who received at least 1 administration of study intervention. Participants will be summarized according to the study intervention received.

7.0   PATIENT DISPOSITION

Participant disposition encompasses the distribution of participants screened, randomized, treated, and who completed or discontinued the study (along with reasons for withdrawal/discontinuation). Participant disposition will be summarized for all screened participants in total and by study intervention group.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic parameters (age; age group; sex; race; ethnicity), baseline characteristics (weight; height; body mass index, calculated as weight [kg]/(height [m])^2; baseline MMPS and MMPS-P) will be summarized descriptively for the mITT Population by study intervention group and in total. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

8.2 MEDICAL HISTORY

Medical history, encompassing abnormalities and surgeries reported as occurring before Day 1, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or newer. Unique participants who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the mITT Population by study intervention group. Medical history will be summarized separately for those ongoing at Day 1 and those not ongoing at Day 1.

8.3 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications are medications taken ≥ 1 time before the study intervention start date, regardless of medication end date. Concomitant medications are medications taken ≥ 1 time on or after the study intervention start date, regardless of medication start date. Unique participants who reported medications will be summarized by WHO Drug class and preferred drug name for the mITT Population by study intervention group. Prior and concomitant medications will be summarized separately.

9.0 EFFICACY ANALYSES

The efficacy analyses will be based on the mITT Population, defined as randomized participants with at least 1 postbaseline MMPS assessment. The last-observation-carried-forward approach will be used to impute missing postbaseline values. *Baseline* for efficacy is defined as the last approved non-missing efficacy assessment before the first dose of study intervention. Pairwise comparisons will be conducted between each BOTOX group and the placebo group. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

9.1 PRIMARY EFFICACY PARAMETER

The primary efficacy variable is the investigator's assessment of MMP using the MMPS (1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked). Each participant's MMPS score will be based on the worst score of the left and right side of the face. If a score is missing for 1 side of the face, then the participant's MMPS score will be based on the score for the other side of the face. The primary efficacy endpoint will be the proportion of responders who achieve MMPS Grade ≤ 3 at Day 90.

The following set of hypotheses will be used to compare the BOTOX groups with placebo:
- Null hypothesis: BOTOX and placebo are equally effective in reducing MMP as measured by the proportion of responders achieving MMPS Grade ≤ 3 at Day 90.
- Alternative hypothesis: BOTOX and placebo are not equally effective in reducing MMP as measured by the proportion of responders achieving MMPS Grade ≤ 3 at Day 90.

Frequency counts of participants achieving a MMPS Grade ≤ 3 will be tabulated by study intervention group at each postbaseline visit. The difference between each BOTOX dose and placebo in the proportion of participants with MMPS ≤ 3 will be analyzed using Cochran-Matel-Haenszel (CMH) model stratified by baseline MMPS Grade (4 or 5).

A sensitivity analysis will be performed based on all observed data for the mITT Population.

9.2 SECONDARY EFFICACY PARAMETERS

The following are considered secondary endpoints at Day 90:

- Proportion of responders who achieve MMPS-P Grade ≤ 3
- Proportion of responders who achieve ≥ 2-grade MMPS improvement from baseline

- Proportion of responders who achieve ≥ 2-grade MMPS-P improvement from baseline
- Proportion of responders who achieve PSAC Grade ≥ 2 (at least moderately improved from baseline)
- Change from baseline in lower facial volume by VECTRA M3 measured using landmark area of interest (AOI) and statistical MMP AOI

For all the responder analyses, frequency counts of responders for each of the responder definitions above will be tabulated by study intervention group at each postbaseline visit. The difference between each BOTOX dose and placebo in the proportion of responders will be analyzed using CMH model stratified by baseline MMPS Grade (4 or 5).

The change from baseline in lower facial volume using both landmark AOI and statistical MMP AOI will be analyzed using analysis of covariance (ANCOVA) with study intervention and investigator site as factors and baseline MMPS Grade (4 or 5) as a covariate. Missing values for change from baseline in lower facial volume at Day 30 will be imputed using the average of participants with non-missing values.

Summary statistics for each endpoint will be tabulated by study intervention group at each postbaseline visit.

Each of the responder analyses will be analyzed using CMH model stratified by baseline MMPS grade.

The change from baseline analyses will be analyzed using ANCOVA with study intervention and investigator site as factors and baseline MMPS grade and baseline score as covariates.

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10.0   SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and vital signs. For each safety parameter of the vital signs, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that parameter. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

10.1   ADVERSE EVENTS

Adverse events will be coded by SOC and PT using the MedDRA, version 22.0 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of study intervention.

An overall summary of AEs by study intervention group will be provided.

The number and percentage of participants reporting TEAEs will be summarized by study intervention group using MedDRA PT nested within SOC. Events will be in alphabetic order of SOC and by descending frequency of PTs within each SOC.

The total number of TEAEs by severity will be summarized by study intervention group.

Treatment-related TEAEs will be tabulated by descending frequency of PTs within the SOC. If more than 1 AE is coded to the same PT for the same patient, the patient will be counted only once for that PT using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The number and percentage of participants who have treatment emergent serious adverse events (TESAEs) will be summarized by SOC, PT, and study intervention group if 5 or more participants reported such events.

The number and percentage of participants in the Safety Population who have TEAEs leading to premature discontinuation of the study intervention will be summarized by SOC, PT, and study intervention group if 5 or more participants reported such events.

To assess possible distant spread of toxin (PDSOT), MedDRA preferred terms that may be associated with botulinum toxin effects have been identified and are shown in Table 10-1. All AEs associated with PDSOT will be tabulated by PT and study intervention group; in addition, all PDSOT AEs will be listed by subject.

Table 10-1   MedDRA System Organ Class and Preferred Terms Evaluated for Possible Distand Spread of Toxin

Cardiac Disorders	**Nervous System Disorders**
Bradycardia	Bulbar palsy
	Cranial nerve palsies multiple
Eye Disorders	Cranial nerve paralysis
Accommodation disorder	Dysarthria
Diplopia	Facial paralysis
Extraocular muscles paresis	Facial paresis
Eyelid function disorder	Hyporeflexia
Eyelid ptosis	Hypotonia
Pupillary reflex impaired	Paralysis
Vision blurred	Paresis cranial nerve
	Peripheral nerve palsy
Gastrointestinal Disorders	Peripheral paralysis
Constipation	Speech disorder
Dry mouth	Vocal cord paralysis
Dysphagia	Vocal cord paresis
Ileus paralytic	
	Renal and Urinary Disorders
Infections and Infestations	Urinary retention
Botulism	
	Respiratory, Thoracic and Mediastinal Disorders
Musculoskeletal and Connective Tissue Disorders	Aspiration
Muscular weakness	Diaphragmatic paralysis
	Dysphonia
	Dyspnoea
	Pneumonia aspiration
	Respiratory arrest
	Respiratory depression
	Respiratory failure
	Reproductive System and Breast Disorders
	Pelvic floor muscle weakness

Note: Table is based on MedDRA 22.0; the actual list used for analysis will be based on the MedDRA version in use at the time of database lock.

10.2 VITAL SIGNS

Descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) for vital signs (systolic and diastolic blood pressures, respiratory rate, and pulse rate) and changes from baseline values at each visit and at the end of study will be presented by study intervention group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 10-2. A listing of patients with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

Table 10-2   Criteria for Potentially Clinically Significant Vital Signs

Parameter	*Flag*	*Criteria^a*	
		Observed Value	*Change From Baseline*
Sitting systolic blood pressure, mm Hg	High	> 140	Increase of ≥ 20
	Low	< 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	> 90	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	> 100	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15

a   A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute.

11.0 INTERIM ANALYSIS

No interim analyses are planned for this study.

12.0 DETERMINATION OF SAMPLE SIZE

The primary efficacy parameter is proportion of responders who achieve MMPS Grade ≤ 3 at Day 90 (last observation carried forward). Based on previous data from study 191622-130 and the assumption of ≥ 34% difference in MMPS response rate between BOTOX 48 U or 72 U and placebo and 10% dropout rate, approximately 50 participants will provide > 90% power using a 2-sided Mantel-Haenszel test at 5% significance level.

13.0   STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS version 9.4 (or newer) on a Linux operating
system.

14.0   DATA HANDLING CONVENTIONS

14.1   VISIT TIME WINDOWS

Table 14-1 presents the visits assigned for efficacy and safety analyses and the corresponding
range of study intervention days (window) during which an actual visit may occur.

Table 14-1   Visit Time Windows

Derived Visit	Scheduled Visit Day[a]	Window
Baseline	Day 1	Days ≤ 1
Day 30	Day 30	Days [2, 45]
Day 60	Day 60	Days [46, 75]
Day 90	Day 90	Days [76, 105]
Day 120	Day 120	Days [106, 135]
Day 150	Day 150	Days [136, 165]
Day 180	Day 180	Days ≥ 166
End of Study[b]	Final or Termination Visit during the double-blind treatment period	

a   Relative to the date of the first dose of study intervention. Day 1 = the date of the first dose of study intervention. There is
      no Day 0.

b   Presented in analysis tables for safety parameters, including but not limited to vital signs.

If the assessment date is on or after the date of the first dose of study intervention, the study day
is calculated by assessment date – date of the first dose of study intervention + 1. If the
assessment date is before the date of the first dose of study intervention, the study day is
calculated by assessment date – date of the first dose of study intervention. Therefore, a negative
day indicates a day before the start of the study intervention. If the assessment date is
unavailable, use the visit date instead.

If a participant has 2 or more visits within the same window, the last visit with a nonmissing
value will be used for analysis.

14.2   DERIVED VARIABLES

Not applicable.

14.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first study intervention, the results from the final nonmissing assessment made prior to the start of the study intervention will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics.

14.4 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study intervention, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study intervention (based on date, and time if known), an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

14.5 MISSING CAUSAL RELATIONSHIP TO STUDY INTERVENTION FOR ADVERSE EVENTS

If the causal relationship to study intervention is missing for an AE that started before first dose of study intervention, a causality of no will be assigned. If the causal relationship to the study intervention (per the investigator) is missing for an AE that started on or after the date of the first dose of study intervention (based on date, and time if known), a causality of yes will be assigned. The imputed values for causal relationship to study intervention will be used for the incidence summary; the values will be shown as missing in the data listings.

14.6 MISSING DATE INFORMATION FOR ADVERSE EVENTS

Missing/incomplete AE start dates will be imputed on a case by case basis.

Imputed partial AE dates will only be used to determine if an AE is a TEAE. All partial dates will be listed "as is" in the data listings.

14.7 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

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