1.0 TITLE PAGE

1789-301-008

BOTOX® (onabotulinumtoxinA) Treatment of Masseter Muscle Prominence: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

STATISTICAL ANALYSIS PLAN - Clinical Study Report

Version 1.0: 20 Dec 2022

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
BOTOX	Botulinum toxin type A purified neurotoxin
bpm	beats per minute
CMH	Cochran-Mantel-Haenszel
eCRF	electronic case report form
FWER	familywise error rate
[redacted]	[redacted]
MCMC	Markov chain Monte Carlo
MI	multiple imputation
MCP	multiple comparisons procedure
mITT	modified Intent-to-Treat
MMP	masseter muscle prominence
MMPS	Masseter Muscle Prominence Scale
MMPS-P	Masseter Muscle Prominence Scale – Participant
OL	Open-Label
PCS	potentially clinically significant
[redacted]	[redacted]
PDSOT	possible distant spread of toxin
PSAC	Participant Self-Assessment of Change
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	Schedule of Activities
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
U	unit
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 final protocol of Study 1789-301-008 (version dated 17 Dec 2018). Specifications of tables, figures, and data listings are contained in a separate document.

This is an 18-month, multicenter study consisting of 2 periods, a double-blind placebo-controlled single-treatment period and an open-label period in which a maximum of 2 further study treatments can be received. Up to 20 scheduled visits are planned: screening (Day -14 to Day -1), baseline (Day 1), follow-up monthly thereafter (Days 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510), and study exit (Day 540).

Period 1 (Days 1 through 180) will be a double-blind, randomized, placebo-controlled, single-treatment design, which will assess the safety and efficacy of botulinum toxin type A purified neurotoxin (BOTOX) treatment of masseter muscle prominence (MMP). On Day 1, participants will be randomized in a 3:1 ratio to receive BOTOX 72 unit (U) or placebo. Randomization will be stratified at each investigator site by the participant's baseline Masseter Muscle Prominence Scale (MMPS) Grade (4 or 5). On Day 180, final Period 1 assessments will be collected, after which all participants will continue into Period 2, the open-label treatment portion of the study.

Period 2 (Days 180 through 540) will be open-label. All BOTOX and placebo-treated participants from Period 1 are eligible to receive up to 2 open-label treatments of BOTOX 72 U in Period 2 if they meet protocol-specified retreatment criteria on or after the Day 180 visit. If the participant does not meet the retreatment criteria at the Day 180 visit, he or she will be reassessed at the next visit. For Treatment 2, participants who qualify can be retreated from the Day 180 visit through the Day 420 visit. [redacted]

Retreatment Criteria:

- Participant has presence of MMP of at least marked (Grade 4) on each side, as assessed by the investigator using the MMPS, AND
- Females of childbearing potential must have a negative pregnancy test prior to treatment, AND

- [redacted]

If a participant qualifies for retreatment in Period 2 and declines it, retreatment will not be administered at that visit and the participant's reason for declining retreatment will be captured on the electronic case report form (eCRF). If the participant still meets retreatment criteria at the next visit [redacted] he or she may receive retreatment at that time.

[redacted]

Table 1. Schedule of Activities (SoA)

	Period 1: Double-blind treatment (BOTOX or placebo)				Period 2: Open-label treatment (BOTOX)		
	Visit 1	Visit 2	Visits 3-7	Visit 8	Visits 9-16	Visits 17-19	Visit 20
Study Procedures	Screening	Baseline[a] Day 1	Follow-Up Days 30, 60, 90, 120, 150	Follow-up/ Retreatment[b] Day 180	Follow-Up/ Retreatment[b] Days 210, 240, 270, 300, 330, 360, 390, 420	Follow-Up Days 450, 480, 510	Study Exit[c] Day 540
Visit Windows	Day -14 to Day -1	-	± 7 Days	± 7 days	± 7 Days	± 7 Days	± 7 Days
Informed Consent, Privacy Authorization	X						
Training for MMPS-P and PSAC[d]	X						
Inclusion/Exclusion Criteria	X[e]	X					
Demographics	X						
Medical/Surgical History	X						
Concomitant Medications/Procedures	X	X	X	X	X	X	X
Height	X[f]						
Body Weight	X[f]	X	X	X	X	X	X
Vital Signs (blood pressure, respiratory rate, pulse rate)		X	X	X	X	X	X
Pregnancy Test[g]	X	X		X (if retreatment visit)	X (if retreatment visit)		X
Standardized Imaging	X[h]	X	X	X	X	X	X

Study Procedures	Period 1: Double-blind treatment (BOTOX or placebo)				Period 2: Open-label treatment (BOTOX)		
	Visit 1	Visit 2	Visits 3-7	Visit 8	Visits 9-16	Visits 17-19	Visit 20
	Screening	Baseline[a] Day 1	Follow-Up Days 30, 60, 90, 120, 150	Follow-up/ Retreatment[b] Day 180	Follow-Up/ Retreatment[b] Days 210, 240, 270, 300, 330, 360, 390, 420	Follow-Up Days 450, 480, 510	Study Exit[c] Day 540
Clinical Outcome Assessments:							
Masseter Muscle Prominence Scale – Participant (MMPS-P)[i]	X	X	X	X	X	X	X
Masseter Prominence Participant Self-Assessment of Change[j] (PSAC)			X	X	X	X	X
Participant Lower Facial Shape Questionnaire (LFSQ)- Sign Assessment	X	X	X	X	X	X	X
Participant Global Impression of Bother (PGIB)[i]	X	X	X	X	X	X	X
LFSQ- Impact Assessment	X	X	X	X	X	X	X
LFSQ- Satisfaction Assessment	X	X	X	X	X	X	X
LFSQ- Treatment Satisfaction Assessment (Baseline Version)	X	X					
LFSQ- Treatment Satisfaction Assessment (Follow-up Version)			X	X	X	X	X
Masseter Muscle Prominence Scale (MMPS) – Investigator Assessment	X[k]	X[k]	X	X	X	X	X
Randomization		X					
Study Intervention[l]		X		X[b] (if retreatment visit)	X[b] (if retreatment visit)		
Adverse Events[m]	X	X	X	X	X	X	X

a. All baseline (Day 1) study procedures, from confirmation of all study inclusion/exclusion criteria through imaging, must be completed before randomization and study treatment (BOTOX or placebo). Randomization will be stratified at each investigator site by the participant's baseline MMPS Grade (4 or 5).

b. Participants must meet retreatment criteria to receive up to 2 open-label study treatments with BOTOX. For Treatment 2, participants who qualify can be retreated from the Day 180 visit through the Day 420 visit. For Treatment 3, the earliest visit that participants may qualify and receive the third treatment is the Day 270 visit (3 months after the earliest visit for Treatment 2).

c. Or early discontinuation from the study. All exit assessments should be completed as soon as possible after a decision to discontinue a participant from the study.

d. Training on the MMPS-P and PSAC may be repeated at other visits, as needed.

e. During the evaluation of inclusion criteria at the Screening Visit, MMPS, standardized imaging, and MMPS-P evaluations will be completed (in that order) prior to other COAs. All other procedures at Screening are suggested to be performed in the order listed in the table.

f. At the Screening Visit, height and weight will be used to calculate BMI to determine eligibility for enrollment. BMI = weight (kg)/[height (m)]^2.

g. Females of childbearing potential must have a negative test result before receiving study treatment/retreatment. This test may also be performed at any other visit, at the investigator's discretion. At each visit, the investigator should discuss contraceptive use compliance with females of childbearing potential. Urine tests will be used unless the study site requires the use of serum testing, in which case serum tests will be used.

h. Prior to Day 1, Canfield Scientific, Inc. must review and accept each participant's screening images; 1 retake will be allowed before Day 1 if the screening images are not acceptable.

i. The MMPS-P and PGIB will be conducted using the images collected at the current visit. If retakes are required for the screening images, the MMPS-P and PGIB will be collected again at the image retake visit, using the new images.

j. The PSAC will be conducted using images from the current visit and the Baseline Visit (unless the Baseline images did not pass validation by Canfield, in which case the Screening images will be used instead).

k. Investigator MMPS should be conducted prior to other COAs at the Screening and Baseline visits (only). At all other visits, it should occur after the other COAs.

l. Prepared by an IDR in Period 1 and injected by the investigator in both Periods 1 and 2. After completing injections on one side of the lower face, direct pressure should be applied to the injection sites for approximately 30 seconds before injecting the other side. Participant should be observed at least 30 minutes after the injections for AEs.

m. At each treatment visit, AEs must be collected both before and after study treatment.

5.0 STUDY OBJECTIVES AND CLINICAL HYPOTHESES

5.1 STUDY OBJECTIVES

The primary and secondary objectives of this study are to compare the efficacy and safety of BOTOX versus placebo in participants with MMP.

Objectives	Endpoints
Primary	
• To compare the efficacy of BOTOX with placebo in participants with bilateral MMP	• Achievement of ≥ 2-grade improvement from baseline at Day 90, per investigator assessments of MMP using the MMPS (5 severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked)
• To compare the safety of BOTOX with placebo in participants with MMP	• Incidence of adverse events (AEs) and change from baseline in vital signs
Secondary	
• To compare the efficacy of BOTOX with placebo in participants with MMP	• Achievement of MMPS Grade ≤ 3 at Day 90, according to investigator • Achievement of MMPS-P Grade ≤ 3 at Day 90, according to participant • Achievement of ≥ 2-grade improvement from baseline at Day 90 using the Masseter Muscle Prominence Scale - participant (MMPS-P) • Achievement of Participant Self-assessment of Change (PSAC) Grade ≥ 1 (at least minimally improved from baseline) at Day 90 • Change from baseline in lower facial width (mm) at Day 90, calculated from standardized images • Duration of effect for BOTOX-treated MMPS responders

Objectives	Endpoints
Other (COA)	
[redacted]	[redacted]

5.2 CLINICAL HYPOTHESES

BOTOX treatment of MMP is more effective than placebo as measured by investigator assessment of MMP severity using the MMPS.

BOTOX has an acceptable safety profile after single and repeat MMP treatment.

6.0 PARTICIPANT POPULATIONS

6.1 MODIFIED INTENT-TO-TREAT POPULATION

The Modified Intent-to-Treat (mITT) Population will consist of all randomized participants with at least one postbaseline MMPS assessment. For efficacy analyses, data will be analyzed according to participants' randomization assignments, regardless of actual treatment received.

6.2 SAFETY POPULATION

The Safety Population will consist of all participants who received at least one dose of study treatment. All safety analyses will be performed using the Safety Population. For safety analyses, the participants will be analyzed according to actual treatment received (rather than as randomized).

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants in the study populations (Safety, and mITT) will be summarized by treatment group which will include both the cycle 1 and Open-Label (OL) treatments (e.g., cycle 1 treatment/OL treatment). The number of participants screened will be summarized overall only.

The number and percentage of participants who receive injection, complete, and prematurely discontinue within each treatment cycle will be presented for each treatment group and pooled across treatment groups for all randomized participants. The reasons for premature discontinuation from each treatment cycle as recorded on the termination pages of the eCRF will be summarized (number and percentage) by treatment group for all randomized participants. All participants who prematurely discontinue during each treatment cycle will be listed by discontinuation reason for all randomized participants.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic parameters (age; age group; race; race group [Asian with Asian subgroups, non-Asian]; ethnicity; sex; country/region [Canada, China, Taiwan]), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2, baseline MMPS Grade, and baseline MMPS-P Grade) will be summarized descriptively by treatment group for the mITT Population. Continuous variables will be summarized by number of participants and mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), 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 25.1 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 treatment group.

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 treatment group. Prior and concomitant medications will be summarized separately.

9.0 EFFICACY ANALYSES

The efficacy analyses will be based on the mITT population. Baseline for efficacy is defined as the last approved (imaging data) non-missing efficacy assessment before the first dose of study treatment. Pairwise comparisons will be conducted between BOTOX 72 U group and the placebo group. All statistical tests will be 2-sided hypothesis tests performed at 5% level of significance for main effects, with Type I error controlled as described further in Section 14.0.

For the primary and secondary efficacy variables, subjects with missing values at a given visit will be imputed using multiple imputation (MI) up to Day 180 in Period 1. The other efficacy variables will not be imputed.

For subjects who continue in Period 2, efficacy visits beyond Day 180 but prior to retreatment (if any) will be displayed by assigned treatment group in double-blind treatment cycle 1.

9.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy assessment is masseter muscle prominence assessed by the investigator using the MMPS (1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked). [redacted]

The primary efficacy endpoint is the achievement of ≥ 2-grade improvement from baseline at Day 90 using the MMPS.

The following set of hypotheses will be used to compare the BOTOX 72 U group with placebo:

- Null hypothesis: BOTOX and placebo are equally effective in reducing MMP as measured by the proportion of participants achieving ≥ 2-grade improvement from baseline at Day 90 using the MMPS.
- Alternative hypothesis: BOTOX and placebo are not equally effective in reducing MMP as measured by the proportion of participants achieving ≥ 2-grade improvement from baseline at Day 90 using the MMPS.

The proportion of participants who achieve ≥ 2-grade improvement from baseline, per investigator assessments of MMP using the MMPS, will be analyzed using Cochran-Mantel-Haenszel (CMH) model stratified by baseline MMPS Grade (4 or 5) at each visit. A 2-sided p-value ≤ 0.05 will be claimed as statistically significant. The Breslow-Day homogeneity of the odds-ratio test will be performed to test the interaction of treatment by baseline MMPS Grade. A

two-sided p-value ≤ 0.1 will be claimed as statistically significant. Responder rate 2-sided 95% CIs within each treatment group will be based on normal approximation to the binomial. [redacted]

Sensitivity analyses will be performed for the primary efficacy variable based on observed data.

The attributes of the estimands corresponding to the primary efficacy endpoint are summarized in Table 2.

Table 2. Summary of the Estimand Attributes of the Primary Efficacy Endpoint

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for primary endpoint	BOTOX 72 U vs placebo	Achievement of ≥ 2-grade improvement from baseline based on MMPS at Day 90	mITT (all randomized participants with at least one postbaseline MMPS assessment)	Participants who discontinue prior to Day 90 assessments or who do not have Day 90 MMPS assessments will be included in the analysis as a hypothetical scenario in which they had not missed the MMPS assessments	Difference in response proportions between treatments after MI using CMH test stratified by baseline MMPS

9.2 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints are:

- Achievement of MMPS Grade ≤ 3 at Day 90, according to investigator
- Achievement of MMPS-P Grade ≤ 3 at Day 90, according to participant
- Achievement of ≥ 2-grade improvement from baseline at Day 90 using the MMPS-P
- Achievement of PSAC Grade ≥ 1 (at least minimally improved from baseline) at Day 90
- Change from baseline in lower facial width (mm) at Day 90

- Duration of effect for BOTOX-treated MMPS responders [redacted]

The proportion of participants who achieve MMPS Grade ≤ 3, the proportion of participants who achieve MMPS-P Grade ≤ 3, the proportion of participants who achieve ≥ 2-grade improvement from baseline using the MMPS-P, and the proportion of participants who achieve PSAC Grade ≥ 1 will be analyzed in the same manner as that used to analyze the primary endpoint. Missing MMPS, MMPS-P, and PSAC values in Period 1 will be imputed using the same MI method as for primary endpoint. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 3. Summary of the Estimand Attributes of the Secondary Efficacy Endpoints

Estimand Label	Attributes of the Estimand				
	Treat-ment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Hypothetical estimand for binary secondary endpoints	BOTOX 72 U vs placebo	Achievement of the following at Day 90: • MMPS Grade ≤ 3 • MMPS-P Grade ≤ 3 • MMPS-P ≥ 2-grade improvement from baseline • PSAC Grade ≥ 1	mITT (all randomized participants with at least one postbaseline MMPS assessment)	Participants who discontinue prior to Day 90 assessments or who do not have specified Day 90 secondary efficacy assessments will be included in the analysis as a hypothetical scenario in which they had not missed the assessments	Difference in response proportions between treatments after MI using CMH test stratified by baseline MMPS
Hypothetical estimand for continuous secondary endpoints	BOTOX 72 U vs placebo	Change from baseline in lower facial width (mm) at Day 90	mITT (all randomized participants with at least one postbaseline MMPS assessment)	Participants who discontinue prior to Day 90 assessments or who do not have Day 90 lower facial width will be included in the analysis as a hypothetical scenario in which they had not missed the lower facial width assessments	Difference between treatments in LS Mean and SE after MI using ANCOVA

9.3 ADDITIONAL EFFICACY ENDPOINTS

[redacted]

[redacted]

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 vital signs, the last non-missing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety 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.

For subjects who continue in Period 2, safety data beyond Day 180 but prior to retreatment (if any) will be ascribed to the double-blind treatment received in treatment cycle 1.

10.1 EXTENT OF EXPOSURE

The number of treatments received will be summarized by treatment group for the Safety Population.

10.2 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 25.1 or newer.

An AE will be considered as 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 double-blind study treatment.

A TEAE for treatment cycle 1 is an adverse event with onset after the initiation of study treatment or became serious after the initiation of study treatment for cycle 1.

In each of the analysis periods (treatment cycle 1 in the double-blind period, open-label period, BOTOX cycle, or BOTOX overall), a specific TEAE will only count once per participant, associated with its worst severity during the time period of interest. Unless stated otherwise, the methods of analyses described in this section will be applied to each of the study period.

TEAEs will be summarized for each treatment group by treatment cycle 1 in the double-blind period, open-label period, by BOTOX cycle, and BOTOX exposure overall. Participants will be counted according to the treatment received at baseline (Placebo or BOTOX 72 U) for treatment cycle 1. For open-label period and Any BOTOX exposure tables, participants will be summarized according to the treatment received at cycle 1 baseline and treatment received during open-label (Placebo/BOTOX 72 U or BOTOX 72 U/BOTOX 72 U and Total). The only

exception is BOTOX cycle 3, where participants will be summarized by BOTOX 72 U/BOTOX 72 U.

Overall summary of AEs will be provided on a per-participant basis for categories of TEAEs, treatment-related TEAEs, deaths, serious adverse events (SAEs), AEs leading to discontinuation, and possible distant spread of toxin (PDSOT).

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term, and further categorized by severity and causal relationship to the study treatment separately. If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The incidence of TEAEs will be summarized by preferred term and treatment.

An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any SAE criterion.

The number and percentage of participants in the Safety Population who have TESAEs or TEAEs leading to premature discontinuation of the study treatment will be summarized by SOC, preferred term, and treatment.

10.3 POTENTIAL DISTANT SPREAD OF TOXIN ADVERSE EVENTS

[redacted] All TEAEs associated with PDSOT will be tabulated by preferred term, and treatment group; in addition, all PDSOT TEAEs will be listed by subject.

10.4 ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI) is a TEAE which may warrant ongoing monitoring. The following MedDRA preferred terms are considered AESI in this study:

- facial paralysis
- Bell's palsy

These AESIs will be summarized by preferred term and treatment group.

10.5 VITAL SIGNS

Descriptive statistics for vital signs (systolic and diastolic blood pressures, respiratory rate, pulse rate, and weight) values at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group.

[redacted]

11.0 HEALTH OUTCOMES ANALYSES

All data collected from questionnaires are discussed in the efficacy analyses (see Section 9.0).

12.0 SUBGROUP ANALYSES

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 OVERALL TYPE-I ERROR CONTROL

The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ for the set of primary and secondary endpoint comparisons between BOTOX 72 U vs placebo.

The overall serial gatekeeping multiple comparisons procedure (MCP) is defined in Table 5.

15.0 DETERMINATION OF SAMPLE SIZE

[redacted] approximately 360 participants (270 BOTOX and 90 placebo) will provide > 90% power [redacted].

16.0 STATISTICAL SOFTWARE

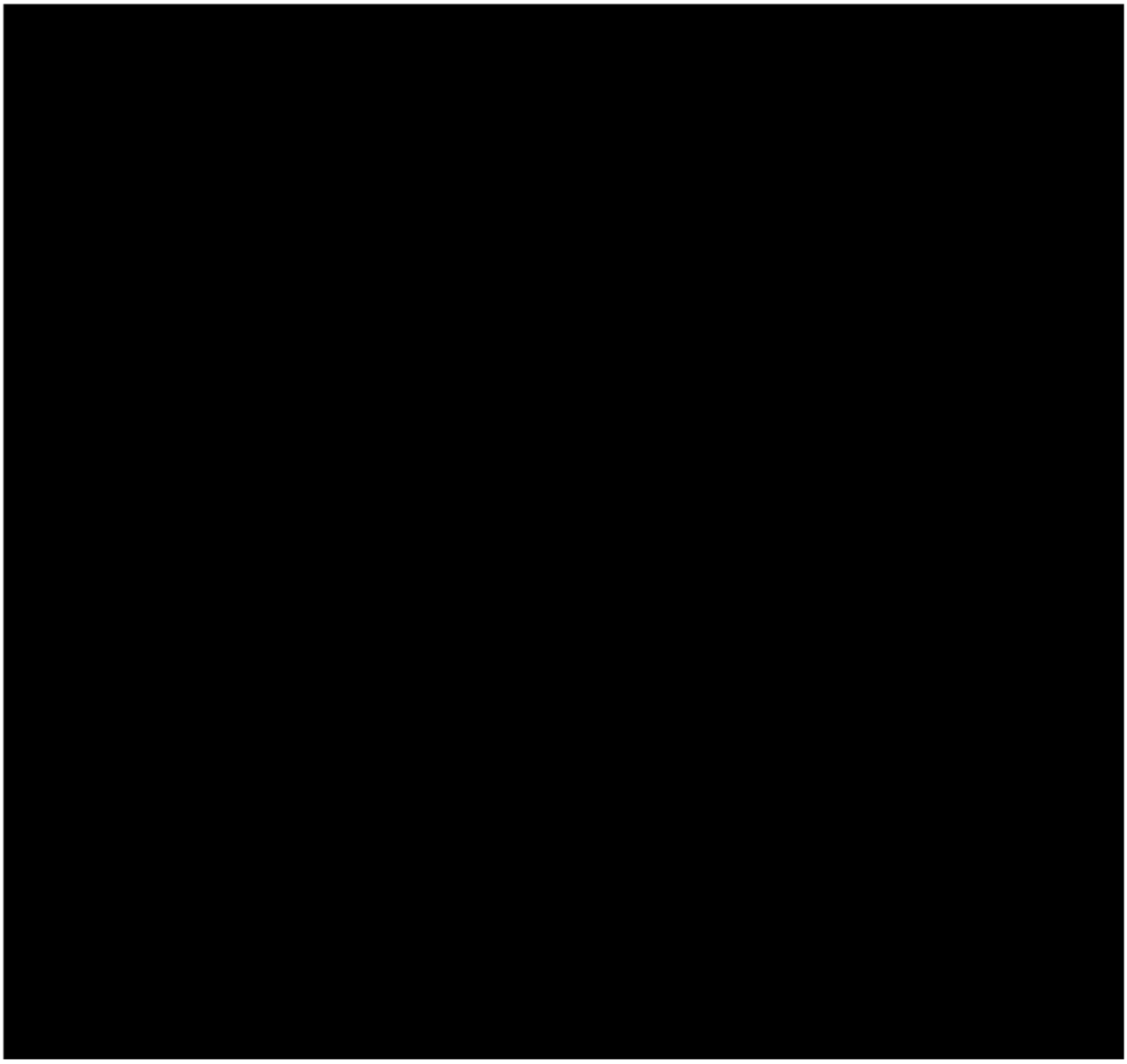
Statistical analyses will be performed using version 9.4 (or newer) of SAS.

17.0 DATA HANDLING CONVENTIONS

17.1 VISIT TIME WINDOWS

For efficacy and safety analyses, the following visit windows will be used to determine the visit day assignment, based on the observed number of days relative to the start of each treatment cycle (the day of treatment).

[redacted]



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

If there are values from multiple visits in a given window, the value collected from the visit closest to the target day will be used to represent the window. If 2 visits are equidistant from the

target day, the value from the first scheduled visit of the 2 visits chronologically will be used to represent the window.

17.2 TREATMENT CYCLES

A treatment cycle is considered to start on the day of treatment with study medication and end on the day prior to the next study treatment or on the study exit day if there are no subsequent treatments.

17.3 BASELINE, CHANGE FROM BASELINE, AND DIRECTION OF DIFFERENCES

The latest measurement taken on or before day 1 prior to the first injection will be the baseline measurement. Changes from baseline will be based on the day 1 baseline (rather than cycle baseline) unless otherwise stated.

Change from baseline will be calculated as postbaseline minus baseline. The interpretation of a positive or negative change from baseline is specific to the outcome measure and will be discussed as needed. Treatment differences will be reported as BOTOX minus placebo.

17.4 STRATIFICATION

Randomization is stratified by baseline MMPS (4 or 5) at baseline (day 1). In case of mis-stratification, the subjects' actual baseline MMPS will be used for analyses.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

17.6 COLLECTION AND DERIVATION OF SECONDARY AND OTHER EFFICAY ASSESSMENTS

17.6.1 Secondary Efficacy Assessments

Masseter Muscle Prominence Scale – Participant (MMPS-P)

[redacted]

[redacted]

Participant Self-Assessment of Change (PSAC)

[redacted]

The participant will answer the questions on the accompanying assessments via electronic tablet that will be provided to the study participant at the study site.

Lower Facial Width

The lower facial width (mm) will be calculated from 2D projections of 3D images.

17.6.2 Other Efficacy Assessments

[redacted]

[redacted]

[redacted]

17.7 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the start of the study treatment 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. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

17.8 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a participant in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

17.9 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.

17.10 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG 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.

17.11 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of study treatment, December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of study treatment, January 1 will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day
- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

17.12 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including incomplete (i.e., partly missing) start dates and/or stop dates will not be imputed.

If start or stop dates for medications are only partially reported but can be classified as prior to Day 1, then the medications will be included as prior medications.

If start or stop dates for medications are only partially reported and cannot be definitively classified as having stopped prior to Day 1, then the medications will be included as concomitant medications.

18.0 REFERENCES

1. Agresti A. Categorical Data Analysis. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2013.
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APPENDIX A POSSIBLE DISTANT SPREAD OF TOXIN