A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a New Dilution and Injection Volume of AbobotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines

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Statistical Analysis Plan

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List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Class
BOCF	Baseline Observation Carried Forward
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSR	Clinical Study Report
DBL	Database Lock
EDC	Electronic Data Capture
ET	Early Termination
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
ICH	International Council on Harmonisation
ILA	Investigator Live Assessment
IND	Investigational New Drug
ITT	Intent-to-Treat
KM	Kaplan-Meier
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
OC	Observed Case
PP	Per-Protocol
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Tabulation Model
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SSA	Subject Self-Assessment
TEAE	Treatment Emergent Adverse Event
U	Units
US	United States
VAS	Visual Analog Scale
WHODD	World Health Organization Drug Dictionary

1 Study Information

1.1 Background

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from Protocol 43USD1805 (v1.0), dated 24JAN2019.

The SAP was written in accordance with the recommendations outlined in the International Council on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

1.1.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, United States (US) study to evaluate the efficacy and safety of a new dilution and injection volume of abobotulinumtoxinA for the treatment of moderate to severe glabellar lines.

[redacted]

1.1.2 Number of Subjects and Randomization

[redacted]

1.2 Study Objectives

The objective of this study is to evaluate the efficacy and safety of a single dose of a new dilution and injection volume of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.

1.2.1 Primary Efficacy Objective

The primary objective of this study is to evaluate the efficacy of a single dose of 50 U of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines, based on the primary efficacy endpoint.

1.2.2 Secondary Efficacy Objectives

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

1.2.3 Exploratory Efficacy Objectives

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

1.2.4 Safety Objectives

The safety objective is to evaluate the safety of a single dose of 50 U of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe glabellar lines.

1.3 Efficacy Assessments

For all assessments, baseline will be defined as the observation that is closest to but prior to study treatment on Day 0. Change from baseline will be calculated as the value at a given time point minus the baseline value.

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1.3.4 Subject Satisfaction Questionnaire

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1.3.5 [redacted]

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[redacted]

[redacted]

1.3.6 Diary Card

Subjects will be asked to record their assessment of study treatment response in a diary card on Days 1 through 7. They will be asked to respond "Yes" or "No" to the following question: "Since being injected have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows)?"

1.4 Efficacy Endpoints

1.4.1 Primary Efficacy Endpoint

The composite responder rate will be evaluated using the ILA 4-point Photographic Scale and the SSA Static 4-Point Categorical Scale of Glabellar Line Severity at maximum frown at Month 1. A composite responder is defined as a subject who achieves a score of 0 or 1 in glabellar line severity and at least 2 grades improvement from baseline on both scales concurrently.

1.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- [redacted]
- [redacted]

- [redacted]

1.4.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

1) [redacted]

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4) [redacted]

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1.5 Safety Assessments

The methods for collecting safety data are described in Section 7.2 of the Clinical Study Protocol.

1.6 Safety Endpoints

Safety endpoints include:

1) Treatment Emergent Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the study. The study period for the purpose of AE collection is defined as the period from the signing of a study specific informed consent to study exit for a subject. AEs recorded on the electronic case report forms (CRFs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. AEs will be classified as treatment emergent adverse events (TEAEs) if the AE had an onset time greater than or equal to the time of the dose of study treatment.

AE endpoints include:

- Incidence,
- Causality (related/not related to investigational product),
- Intensity (mild/moderate/severe),
- Time to onset,
- Duration,
- Leading to study withdrawal,

- Seriousness.

2) Focused Physical Examination

At screening, baseline, Days 2 and 14, and Months 1 and 6, the Investigator or designee will perform a physical examination of the subject that includes the face and neck. The Investigator may choose to investigate any other sign that he/she observes during the physical examination and should assess all abnormal findings for clinical significance.

2 Statistical Methods

2.1 General Methods

If any SAP changes are needed before database lock (DBL), the SAP will be amended. Changes after DBL will be documented in the Clinical Study Report (CSR). If additional supportive or exploratory analyses are requested after SAP approval, this will not require amendment of the SAP, but these additional analyses will be described in the CSR.

Some of the analyses detailed here may be more explicit or in some aspects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

2.1.1 Programming Conventions

Prosoft Clinical will have responsibility for performing analyses. All computations for statistical analyses will be performed using SAS® software, Version 9.4. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

The CRF data for all subjects will be provided in Standard Data Tabulation Model (SDTM) datasets. Analysis Data Model (ADaM) datasets will be developed from the SDTM datasets for use in table and figure production.

2.1.2 Reporting Conventions

The formats for the tables, listings, and figures described in this SAP will be provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment.

All study data from the CRFs as well as derived variables will be provided in subject data listings. Data listings supplied as part of the CSR will be sorted by treatment group, study center number concatenated with subject number, assessment dates, and/or time point. In listings, subjects will be identified by the treatment group in which they were randomized.

The following conventions will be applied to all data presentations and analyses:

- Quantitative variables will generally be summarized by the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Unless otherwise specified, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the SD will be displayed to two extra decimal places compared to the raw data.

- Categorical variables will be summarized by the number and percentage of subjects within each category. Unless otherwise specified, the percentage will be presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as '0' rather than '0 (0)'.
- All summary tables will include the analysis population sample size (i.e. number of subjects) in each treatment group.
- Date variables will be formatted as ISO8601 dates (YYYY-MM-DD) for presentation.
- For analysis of duration of effect and time to onset of treatment response, Kaplan-Meier plots and estimates of the median event times will be used. Responder rates over time will be presented in graphs.

2.1.3 Data Transformations

The Rasch transformation scoring of the [redacted] appears in SAP Section 4 below.

2.1.4 Early Termination Visit

For Early Termination (ET) subjects, the Month 6/ET visit will be assigned to the appropriate scheduled timepoint based on the following relative day windowing (where Day 0 is the day of treatment). If a result already exists for the calculated visit or the calculated visit was not a scheduled visit, the next scheduled visit will be assigned.

Study Day Range	Calculated Visit
1 ≤ Study Day ≤ 8	Day 2
9 ≤ Study Day ≤ 21	Day 14
22 ≤ Study Day ≤ 42	Month 1 (Week 4)
43 ≤ Study Day ≤ 70	Month 2 (Week 8)
71 ≤ Study Day ≤ 98	Month 3 (Week 12)
99 ≤ Study Day ≤ 126	Month 4 (Week 16)
127 ≤ Study Day ≤ 154	Month 5 (Week 20)
Study Day ≥ 155	Month 6 (Week 24)

2.2 Analysis Populations

The statistical analyses will be performed based on the following subject populations.

2.2.1 Intent-to-Treat Efficacy Population

The Intent-to-Treat (ITT) population includes all subjects who are randomized and dispensed the investigational product, and will be analyzed according to the randomization scheme. All primary efficacy, secondary efficacy, and exploratory variables will be analyzed based on the ITT population.

2.2.2 Per-Protocol Efficacy Population

The Per-Protocol (PP) population includes all ITT subjects who have no protocol deviations considered to have a substantial impact on the primary efficacy outcome, and will be analyzed

according to the randomization scheme. If the PP population contains less than 90% of the subjects in the ITT, a sensitivity analysis of the primary efficacy endpoint will be performed based on the PP population.

2.2.3 Safety Population

The safety population includes all subjects who were administered the investigational product, and will be analyzed according to as-treated principle. All safety data will be summarized descriptively based on the safety population.

2.3 Study Subjects

2.3.1 Subject Disposition

The number of subjects screened will be shown in total and by study center.

The number of subjects in each study population (i.e. ITT, PP, and Safety) will be summarized by study center and in total (by treatment group and overall).

The disposition of subjects will be presented by study center and in total (by treatment group), including numbers of subjects who were:

- Randomized,
- Completed,
- Withdrawn (including primary reason for withdrawal).

Subject accountability will be summarized by visit with the following:

- Number of subjects expected at each visit (all subjects *minus* number of withdrawn subjects up until that visit)
- Number of subjects completed each visit (all subjects completed that visit)
- Number of subjects missed at each visit (number of expected subjects *minus* the number of subjects completed that visit)
- Number of subjects withdrawn at each visit (all subjects who have withdrawn up until that visit).

2.3.2 Protocol Deviations

Subjects with any protocol deviations will be summarized by study center and in total (by treatment group and overall).

Depending on the seriousness of the deviation, a subject might be excluded from the PP population, which shall be documented prior to database lock. Since the PP population will be used for the primary analysis at Month 1 only, the focus will be on major deviations occurring before and on the Month 1 visit which are considered to have a substantial impact on the primary efficacy outcome. Reasons for exclusion from the PP population will be presented by treatment group and overall.

2.3.3 Demographic Characteristics

Subject demographic data will be summarized for the ITT population by treatment group and overall. Age and body mass index will be analyzed as continuous variables. Gender, race, ethnicity, Fitzpatrick skin type, childbearing potential, and toxin naïve status will be analyzed as categorical variables.

2.3.4 Medical History, Medications, and Procedures

All summaries will be done for the ITT population by treatment group and overall.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD) March 2019. Medical history, allergies and procedures (excluding facial treatments/procedures), and prior and concomitant facial treatments/procedures will be coded according to MedDRA Version 22.0.

Prior medications/procedures are the medications/procedures with stop dates prior to study treatment. Medications/procedures after the study treatment will be considered concomitant.

The number and percent of subjects reporting medical history, allergies and procedures, and prior and concomitant facial procedures/treatments will be summarized by System Organ Class (SOC) and Preferred Term (PT).

The number and percent of subjects reporting prior and concomitant medications will be summarized separately, by WHODD Anatomical Therapeutic Chemical (ATC) Class Level 3 (if Level 3 is not available, will use the highest class available) and WHODD generic name.

[redacted]

[redacted]

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[redacted]

[redacted] Safety Analysis

All safety data will be summarized descriptively by treatment group based on the safety population using the OC. There are no planned inferential statistical analyses of safety endpoints.

2.5.1 Extent of Exposure

Because subjects will receive a single dose of investigational product, no summary of extent of exposure will be performed. Extent of exposure will be provided in a subject data listing.

2.5.2 Adverse Events

A summary of all AEs (number and percentage of subjects with at least one event and number of events) by treatment group will be provided, which will include:

- Subjects with at least one AE (in total as well as serious AEs).
- Subjects with at least one treatment-related AE (in total as well as serious AEs).
- Subjects with at least one mild, moderate or severe treatment-related AE (in total as well as serious AEs).
- Subjects with at least one unrelated AE (in total as well as serious AEs).
- Subjects with at least one mild, moderate or severe unrelated AE (in total as well as serious AEs).
- Subjects with at least one AE that led to discontinuation (in total as well as serious AEs).
- Number of subjects who did not have an AE.

All other adverse event tables will also be summarized by treatment. Treatment-related AEs, as well as AEs unrelated to study treatment will be summarized by System Organ Class (SOC), PT and maximum intensity.

In addition, for treatment-related AEs, the number of days to onset and the duration of event will be summarized by SOC and PT.

- Time to onset of an AE will be derived as the start date minus the date of the most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of the most recent treatment. If the start month is available but not the day, it will be assumed that the AE started on the first day of the month.
- Duration of an AE will be derived as the stop date minus the start date + 1. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment. If the start month is available but not the day, it will be assumed that the AE started on the first day of the month. If the stop month is available but not the day, it will be assumed that the AE stopped on the last day of the month. Completely missing stop dates will not be imputed and therefore no duration will be calculated in these cases.

AEs that led to discontinuation from the study will also be summarized.

Serious AEs and treatment-related AEs with late onset (i.e. AEs with onset > 21 days after treatment) will be listed.

For subject counts, a subject will only be counted once per SOC and once per PT in cases where multiple events are reported for a subject within SOC or PT. For event counts, subjects with multiple events in a category will be counted for each event.

2.5.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) for abobotulinumtoxinA are TEAEs that suggest a possible remote spread of effect of the toxin or events suggestive of hypersensitivity like reactions. TEAEs due to possible remote spread of the effects of abobotulinumtoxinA will be identified using the list of MedDRA PTs compatible with the mechanism of action of abobotulinumtoxinA and based on the recommendations from the Committee for Medicinal Products for Human Use (CHMP) and the Food and Drug Administration (FDA). TEAEs potentially representing hypersensitivity reactions will be identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions. A list of MedDRA preferred terms, used to identify any potential AESI, is provided in Section 5.

All TEAEs identified using the search strategy described above will be medically evaluated during the study, before the database lock and unblinding (if applicable), by the sponsor to identify events which could possibly represent ‘remote spread of effect of toxin’, or which are suggestive of ‘hypersensitivity reactions’ due to study treatment administration. Cases will be excluded if they are confounded by presence of alternative clinical etiologies (medical history, concomitant medication or diagnosis which could account for the symptoms); if they are considered to be local effects instead of distant spread as judged by the site of injection; the time period between the last study treatment administration and event onset is not in accordance with the expected mechanism of action; or due to insufficient information/evidence to make an assessment. In order to perform the analysis, variables including alternative etiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to Dysport administration will be considered.

In the TFLs, only the final list of AESIs confirmed by the sponsor as “a possible remote spread event” or “hypersensitivity reactions” will be taken into account.

2.5.4 Focused Physical Examination

The numbers and percentages of subjects with abnormalities in focused physical examination will also be summarized by treatment group.

2.6 Interim Analyses

An interim analysis is not planned for this study.

2.7 Determination of Sample Size

[redacted]

2.8 Changes in the Analysis Planned in the Protocol

[redacted]

3 Reference List

Yan X, Lee S, Li N Missing data handling methods in medical device clinical trials J. Biopharm. Stat. 2009: 19; 1085-1098

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5 Remote Spread or Hypersensitivity Preferred Terms

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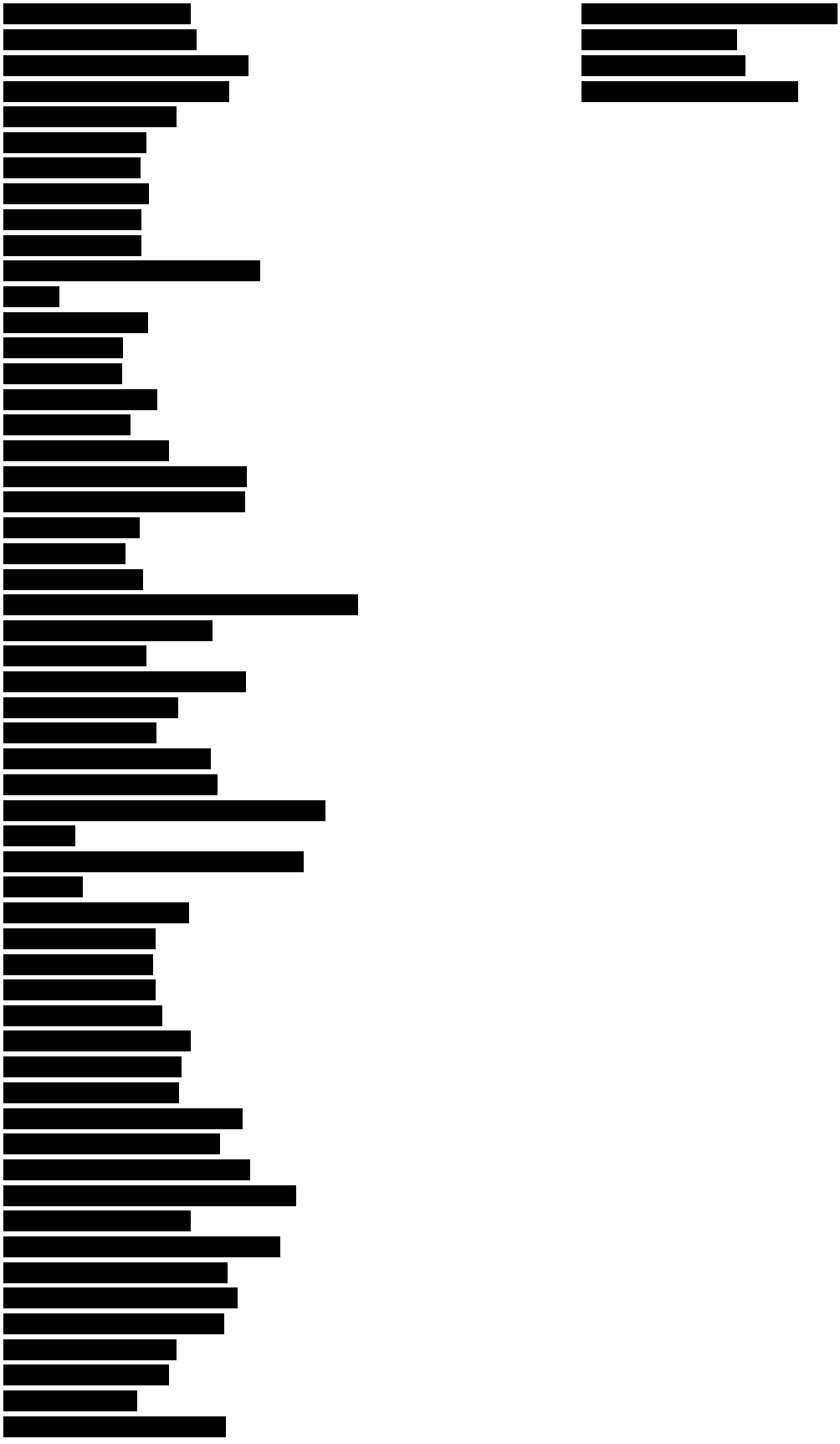

SIGNATURES PAGE

Date	Signed by
2019-08-22 07:44	[redacted]
Justification	Approved by Technical Expert

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Justification	Approved by Owner

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Justification	Approved by Project Manager