Effective date: 2019-02-04 17:25

Statistical Analysis Plan

Clinical Trial Number: **43USD1802**

Table of Contents

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 43USD1802 (v2.0), dated 03 AUG 2018.

The SAP was written in accordance with the recommendations outlined in the International Conference 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 multicenter, open-label, interventional, phase 4 study to assess subject satisfaction with a twice-yearly abobotulinumtoxinA treatment regimen in moderate to severe glabellar lines.

Following the screening process, eligible subjects will be treated at the baseline visit with [redacted] abobotulinumtoxinA in the glabellar region. [redacted]

The planned clinical study duration (from first subject first visit to last subject last visit) is approximately 15 months. Clinical study participation for each subject is up to 13 months.

1.1.2 Number of Subjects

The study is planned to enroll approximately [redacted] at approximately 6 centers in the United States. [redacted]

1.2 Study Objectives

1.2.1 Primary Efficacy Objective

The primary objective of the study is to evaluate subject satisfaction after abobotulinumtoxinA treatment every six months (twice yearly) using the proportion of subjects satisfied ("highly satisfied" or "satisfied") with the treatment results assessed by the satisfaction question at the Month 12/early termination visit.

[redacted]

[redacted]

1.2.3 Safety Objectives

The safety objective is to evaluate the effect on safety endpoints of abobotulinumtoxinA in the treatment of 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. Likewise, change from baseline will be calculated as the value at a given time point minus the baseline value.

1.3.1 Overall Subject Satisfaction by Direct Questioning

[redacted]

[redacted]The subject will document their response of Highly Satisfied, Satisfied, Dissatisfied, or Highly Dissatisfied.[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Efficacy Endpoints

1.4.1 Primary Efficacy Endpoint

The primary endpoint will evaluate the proportion of subjects satisfied ("highly satisfied" or "satisfied") with the treatment results assessed by the satisfaction question at the Month 12/early termination visit.

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:

(i) Treatment Emergent Adverse Events (TEAEs)

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 (eCRFs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 first study treatment.

Adverse events endpoints include:

- Incidence,
- Causality (related/not related to investigational product),
- Intensity (mild/moderate/severe),
- Leading to study withdrawal,
- Seriousness.

(ii) Focused Physical Examination

At all study visits (prior to treatment as applicable), 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

Any change made to the finalized SAP will be documented in the Clinical Study Report (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

[redacted]

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.

Analysis datasets will be mapped from eCRF data for use in table and figure production. Clinical Data Interchange Standards Consortium (CDISC) standards are not required for this Phase 4 study.

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. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the CSR.

All study data from the eCRFs as well as derived variables will be provided in subject data listings. An indication of specific listings for each data type will not be indicated in the text of subsequent SAP sections. Data listings supplied as part of the CSR will be sorted by study center number concatenated with subject number, assessment dates, and/or time point.

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, 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 standard deviation 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).
- Date variables will be formatted as DDMMMYYYY for presentation.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2.4 Safety Population

The safety population includes all subjects who were administered the investigational product. 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.

[redacted]

The disposition of subjects will be presented, including numbers of subjects who were:

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

These numbers will also be presented by study center. The number of completed and withdrawn subjects will also be presented by visit.

2.3.2 Protocol Deviations

Subjects with any protocol deviations will be summarized by study center 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. The focus will be on major deviations which are considered to have a substantial impact on the primary efficacy outcome. Reasons for exclusion from the PP population will be presented.

[redacted]

2.4 Efficacy Analysis

[redacted]

statistical analyses will account for missing data as appropriate (SAP Section 2.4.2 below).

2.4.2 Handling of Missing Data

All analyses will be carried out based on the observed cases (OC). [redacted]

[redacted]

2.4.3 Primary Efficacy Analysis

The primary objective of the study will be evaluated by calculating the proportion of subjects that respond "Highly satisfied" or "Satisfied" to the question [redacted] osed at the Month 12/earl termination visit. [redacted] The aim is to show that the confidence interval is above 50%, i.e. the majority of subjects are satisfied.

[redacted]

2.5 Safety Analysis

All safety data will be summarized descri ptively based on the safety population using the Observed Cases (OC). [redacted]

[redacted]

2.5.2 Adverse Events

An overall summary of all AEs will be provided, which will include:

- number and percentage of subjects with at least one AE and number of events,
- number and percentage of subjects with at least one TEAE and number of events,
- number and percentage of subjects with at least one treatment-related TEAE and number of events,

- number and percentage of subjects with at least one mild, moderate, and severe TEAE and number of events,
- number and percentage of subjects with at least one TEAE leading to discontinuation and number of events,
- number and percentage of subjects with at least one serious TEAE and number of events.

[redacted]

All TEAEs by maximum intensity, serious TEAEs by maximum causality, TEAEs related to treatment by maximum intensity, TEAEs unrelated to treatment by maximum intensity, and TEAEs leading to discontinuation by maximum causality will be summarized by SOC and PT including number of subjects with at least one event, percentages, and number of events. In addition, action taken due to treatment-related TEAEs will be summarized by SOC and PT including the number of events.

For treatment-related TEAEs, the number of days to onset and 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 most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment.

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. Missing stop date will not be imputed and therefore no duration will be calculated in these cases.

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.

[redacted]

2.5.3 Other Safety Assessments

The numbers and percentages of subjects with abnormalities in focused physical examination will be summarized. The results of the urine pregnancy tests will only be listed.

[redacted]

[redacted]

[redacted]

2.8 Changes in the Analysis Planned in the Protocol

There are no significant changes to the analysis planned in the protocol.

3 Reference List

There are no other references beyond those that are included in the protocol.

[redacted]