A Multicenter, Randomized, Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of AbobotulinumtoxinA for the Treatment of Moderate to Severe Platysmal Bands

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Statistical Analysis Plan

Clinical Trial Number: **43USD1804**

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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 43USD1804 (v6.0), dated 09 AUG 2019. No subjects were enrolled prior to Protocol v6.0.

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 phase 2, multicenter, randomized, dose-ranging, double-blind, placebo-controlled, United States (US) study to assess the efficacy, safety, and duration of response of abobotulinumtoxinA for the treatment of moderate to severe platysmal bands.

After undergoing a screening visit, enrolled subjects will receive a single treatment of abobotulinumtoxinA or placebo at baseline. The planned clinical study duration (from first subject first visit to last subject last visit) is approximately 21.5 months. [redacted]

1.1.2 Number of Subjects and Randomization

The study is planned to enroll approximately 240 subjects who will be treated with [redacted] abobotulinumtoxinA (approximately 60 subjects/dose) or placebo (up to 60 subjects depending on the number of dose groups that will run in the study).

Initially, eligible subjects will be randomly assigned at baseline to the following treatment [redacted]

1.2 Study Objectives

The objectives of the study are to evaluate the safety and efficacy of a single dose of [redacted] of abobotulinumtoxinA compared to placebo in the treatment of moderate to severe platysmal bands. [redacted]

1.2.1 Primary Efficacy Objective

The primary objective is to evaluate the efficacy of a single dose of [redacted] abobotulinumtoxinA, respectively, compared to placebo in the treatment of moderate to severe platysmal bands using the Investigator Live Assessment (ILA) [redacted] Photographic Scale at maximum contraction at Month 1.

1.2.2 Secondary Efficacy Objectives

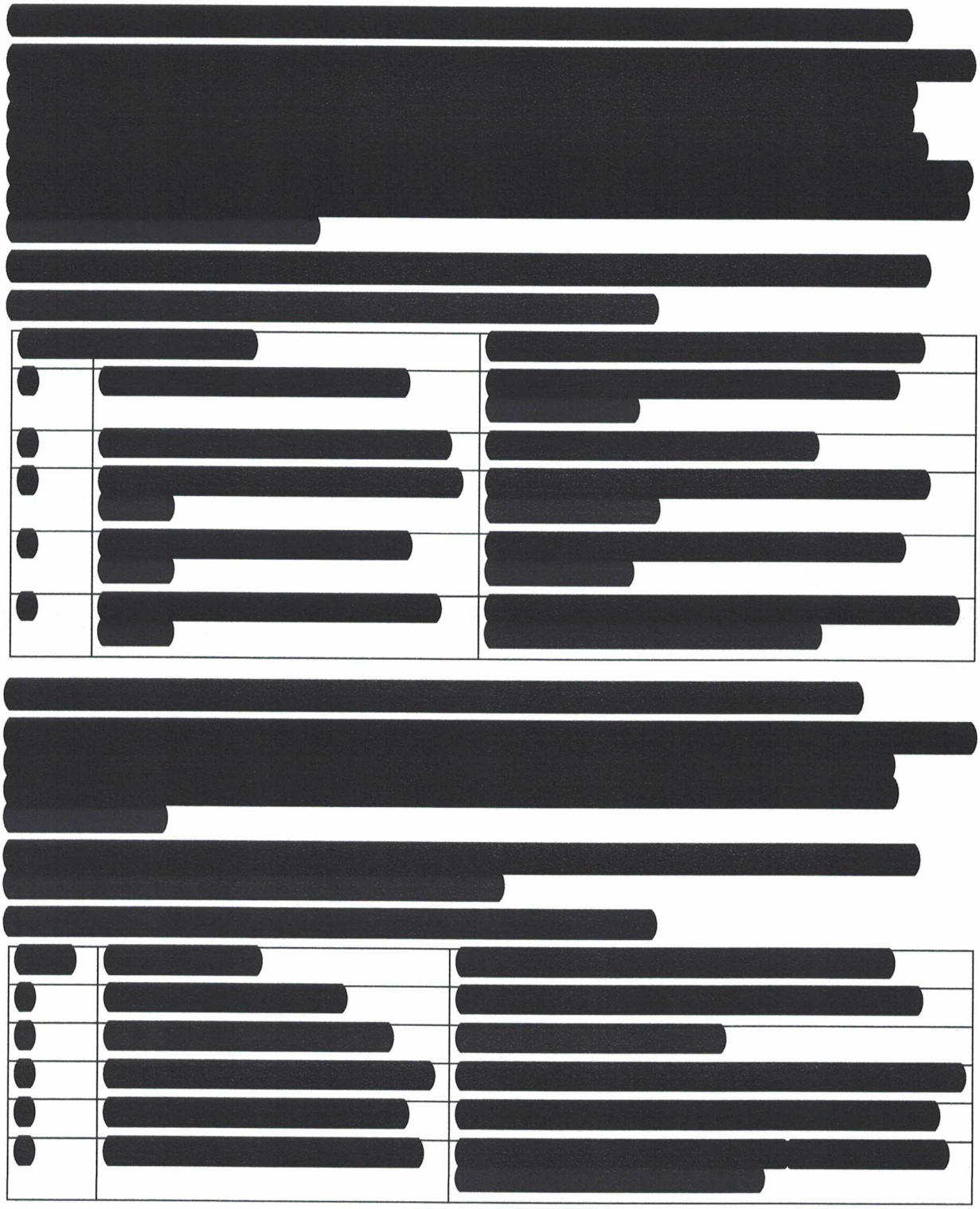
[redacted]

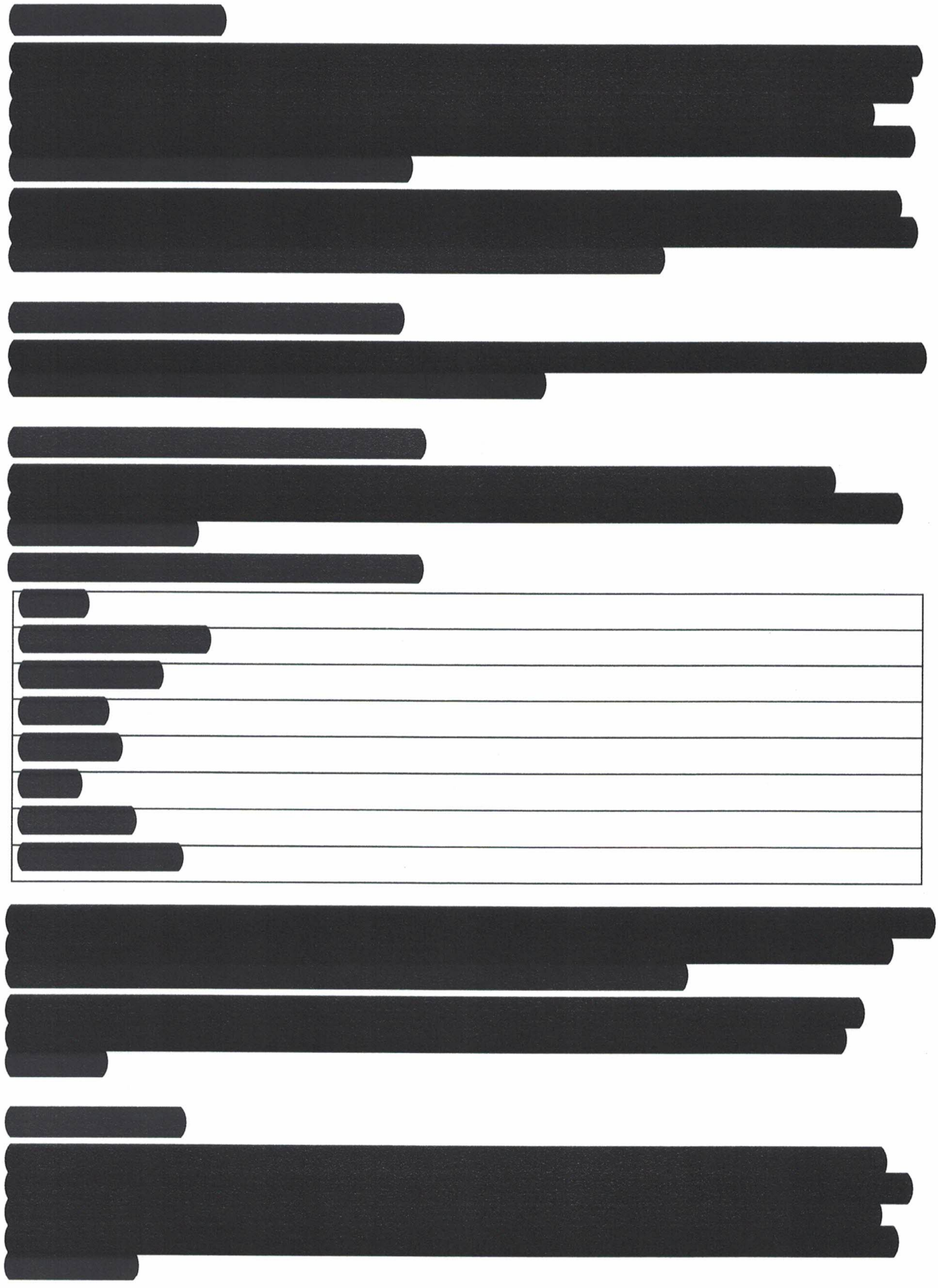
1.2.4 Safety Objectives

The safety objective is to evaluate the effect on safety endpoints of a single dose of [redacted] abobotulinumtoxinA and placebo in the treatment of platysmal bands.

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.





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1.4 Efficacy Endpoints

1.4.1 Primary Efficacy Endpoint

The responder rate will be evaluated using the ILA [redacted] Photographic Scale of Platysmal Band Severity at maximum contraction at Month 1. [redacted]

1.4.2 Secondary Efficacy Endpoints

[redacted]

[redacted]

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 study treatment.

Adverse events endpoints include:

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

(ii) Focused Physical Examination

At all visits the Investigator or designee will perform a physical examination of the subject that includes the face, head, 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.

[redacted]

(iii) Vital Signs

Vital signs (including blood pressure, heart rate, and respiratory rate) will be evaluated at the baseline visit (pre and post-treatment), and at each study visit thereafter through the [redacted] termination visit.

Vital signs endpoints include:

- Values,
- Changes from baseline.

All abnormal values at the screening visit identified as clinically significant by the Investigator will be recorded in the medical history.

For any clinically significant changes from the screening visit, an AE is to be recorded.

Normal ranges checks, as programmed in the eCRF to alert the investigator to assess clinical significance for values outside of these ranges, are shown in Table 4 below.

Table 4. Vital Sign Normal Ranges

Measure	Normal Range
Sitting Systolic blood pressure	90-150 mmHg
Sitting Diastolic blood pressure	60-90 mmHg
Sitting Heart rate	50-100 beats/min
Sitting Respiratory rate	12-24 breaths/min

(iv) Jawline and Oral Commissure Safety Assessment

To determine if treatment with abobotulinumtoxinA or placebo of the platysmal bands adversely affects the subject's jawline or oral commissures, the Investigator will assess these areas relative to the subject's pre-treatment appearance[redacted]

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 respects 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

EMB Statistical Solutions will have responsibility for performing analyses. All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. 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 eCRF 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. 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 treatment group, 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:

- Placebo-treated subjects will be pooled together in summary tables and for analyses.
- Treatment groups to be summarized include [redacted] abobotulinumtoxinA and pooled placebo.
- 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) in each treatment group.
- Date variables will be formatted as DDMMMYYYY for presentation.

2.1.3 Data Transformations

[redacted]

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 (i.e., administered) the investigational product, and will be analyzed according to the randomization scheme. All efficacy 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 treatment group, and in total, including numbers of subjects who were:

- Randomized,
- 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 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). Medical history, allergen history (food and drug), and prior and concomitant procedures/non-pharmacological treatments will be coded according to MedDRA.

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

The number and percent of subjects reporting medical history, allergen history, cosmetic treatments/procedures, and prior and concomitant procedures/non-pharmacological 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.

2.4 Efficacy Analysis

2.4.1 Datasets Analyzed

All efficacy variables will be analyzed based on the ITT population. A sensitivity analysis of the primary efficacy endpoint will be performed based on the PP population, if the PP population contains less than 90% of the subjects in the ITT. Summary statistics will be computed for each

efficacy endpoint using the Observed Cases (OC) with no imputation for missing data. Inferential statistical analyses will account for missing data as appropriate (SAP Section 2.4.2 below).

2.4.2 Handling of Missing Data

The OC will be used for all secondary efficacy analyses, safety analyses, as well as the exploratory analyses. The primary ITT analysis will be performed using the baseline observation carried forward (BOCF). A sensitivity analysis of the primary endpoint will be performed using multiple imputation (MI) for missing values. If deemed necessary, any analyses may be repeated using OC, BOCF, or MI as appropriate.

Multiple Imputation

The imputation using MI will assume Missing Completely at Random (MAR). The MI procedure of the SAS® system will be used to generate five sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Linear regression will be employed to model the missing ILA scores, with the following covariates included in the imputation model: treatment and non-missing data from earlier visits than Month 1 [redacted] The imputed datasets will be analyzed using the methodology described for the primary analysis. The results from the analysis of the multiple imputed datasets will be combined by the MIANALYZE procedure of the SAS® system. [redacted]

2.4.3 Primary Efficacy Analysis

The Month 1 ILA[redacted] Photographic Scale at maximum contraction responder rates [redacted] of abobotulinumtoxinA will be compared with placebo [redacted]

[redacted]

2.4.4 Secondary and Exploratory Efficacy Analysis

[redacted]

2.5 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

An overall summary of all AEs will be provided by treatment group, 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 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.

All TEAEs, serious TEAEs, TEAEs by maximum intensity, TEAEs by causality, TEAEs by maximum intensity and causality, related TEAEs, and TEAEs leading to discontinuation will be summarized by treatment group, SOC, and PT including number of subjects with at least one event, percentages, and number of events.

For related AEs, the number of days to onset and duration of event will be summarized by treatment group, SOC, and PT.

Time to onset of an AE will be derived as the start date minus the date of treatment. If the start date is missing, it will be assumed that the AE started on the day of 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 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.

2.5.3 Other Safety Assessments

Data for vital signs will be summarized by treatment group using descriptive statistics with the value at each visit as well as the change from baseline. The numbers and percentages of subjects with abnormalities in focused physical examination and for the safety assessment of jawline and oral commissures will also be summarized by treatment group. The results of the urine pregnancy tests will only be listed.

AEs 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 BoNT-A and based on the recommendations from the Committee for Medicinal Products for Human Use (CHMP) and the FDA. TEAEs potentially representing hypersensitivity reactions will be identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions. A list of adverse events potentially suggestive of remote spread of toxin is in Section 5 Appendix A. A list of MedDRA PTs in the hypersensitivity SMQ is in Section 6 Appendix B.

All TEAEs identified using the search strategy described above will be medically evaluated during the study, before the database lock and unblinding, 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 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 the tables and listings, only the final list of AESIs confirmed by the sponsor as "a possible remote spread event" or "hypersensitivity reactions" will be taken into account.

2.6 Data Safety Monitoring Committee Reviews

There will be two reviews by an unblinded independent DSMC during the study. [redacted]

2.6.1 Pre-Specified Stopping Criteria

The DSMC reviews will be based on tables of summary statistics and listings. No statistical inference will be performed.

Evaluation of safety data will include application of the following stopping criteria:

- [redacted]
- [redacted]

Further, the DSMC will review the list of AEs (including confirmed AEs of local or remote spread of toxin) and advise the Sponsor of safety findings that may result in discontinuation of study enrollment. If study enrollment is discontinued, all previously enrolled subjects will continue in the study[redacted]

2.7 Interim Analyses

An interim analysis is not planned for this study.

2.8 Determination of Sample Size

[redacted]

[redacted]

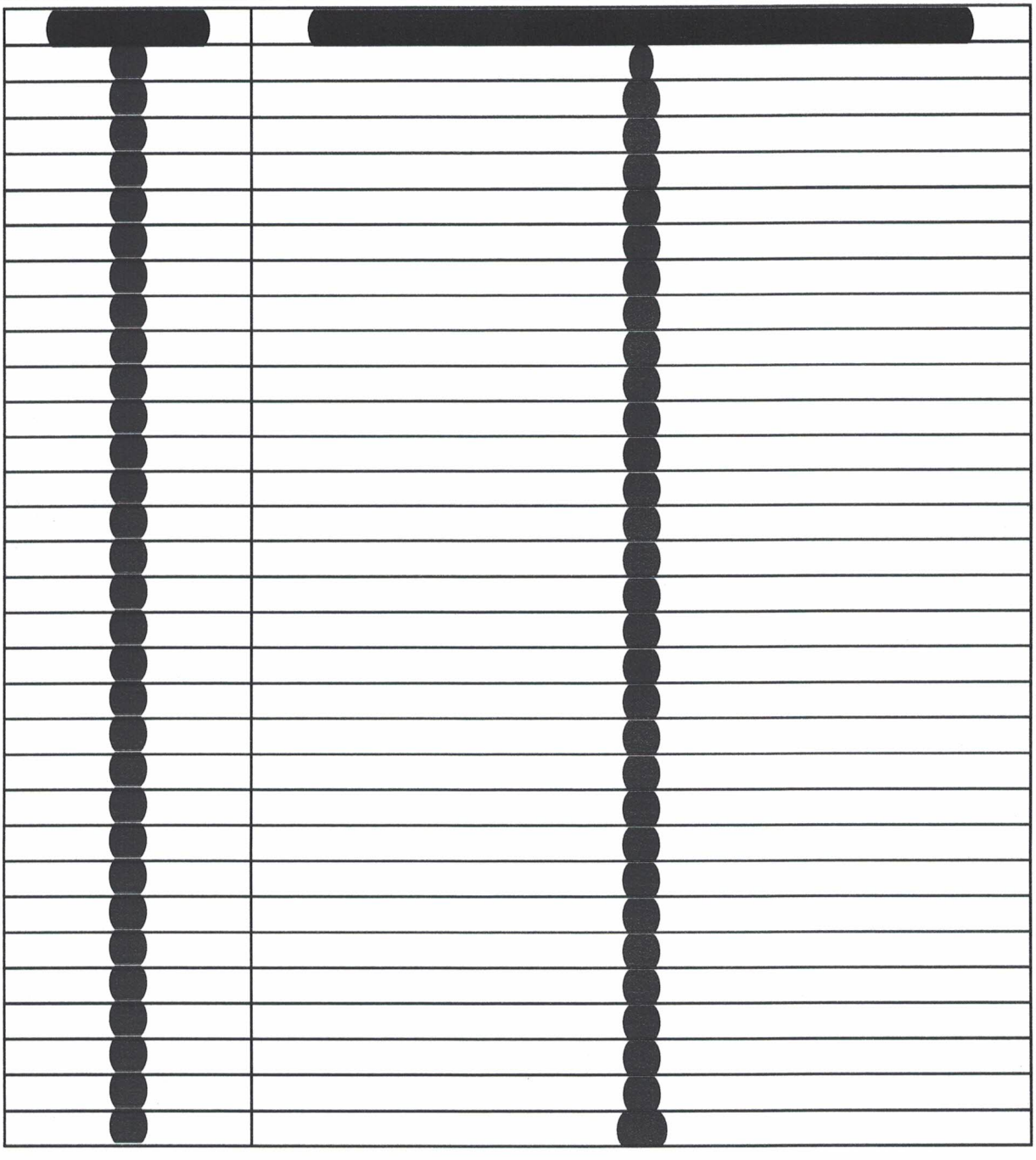
Thus, a sample size of 60 in each group is planned to be sufficient to explore the safety and responder rates.

[redacted]

3 Reference List

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

[redacted]



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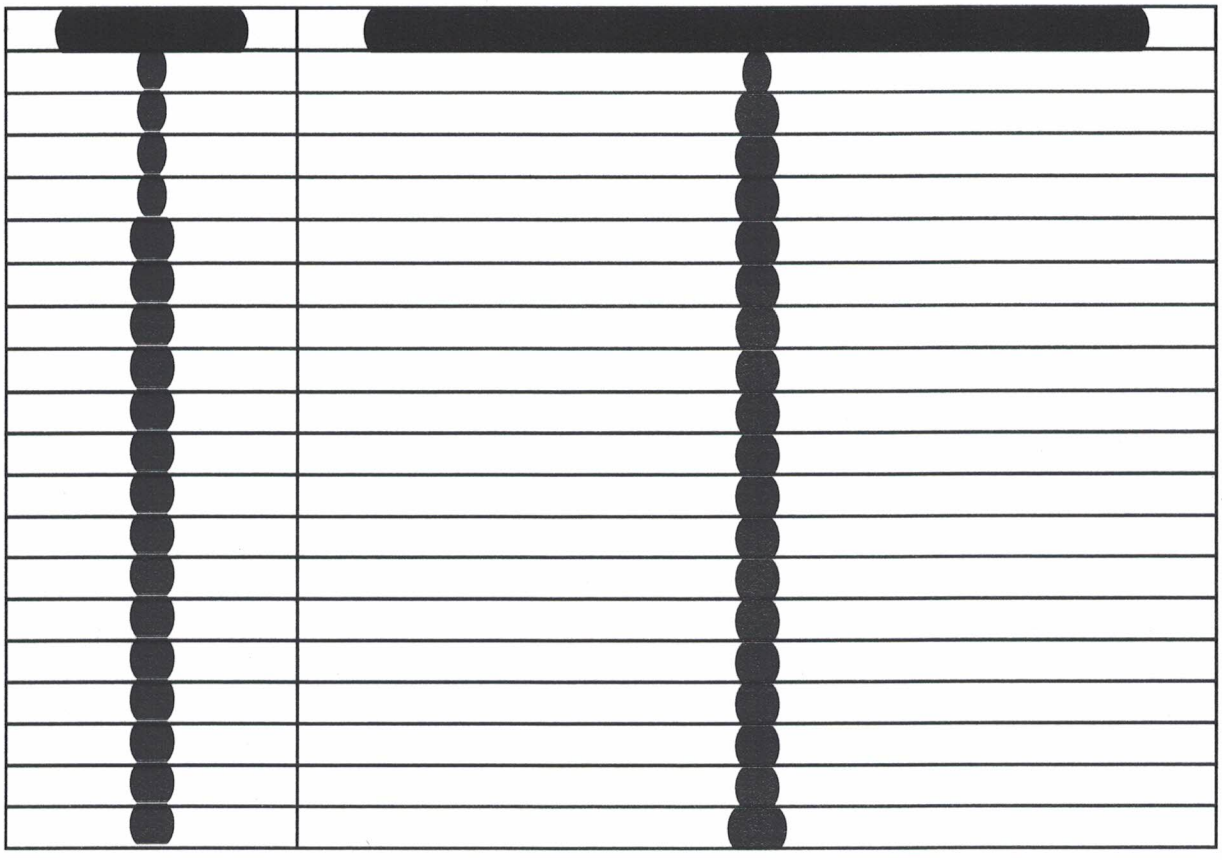

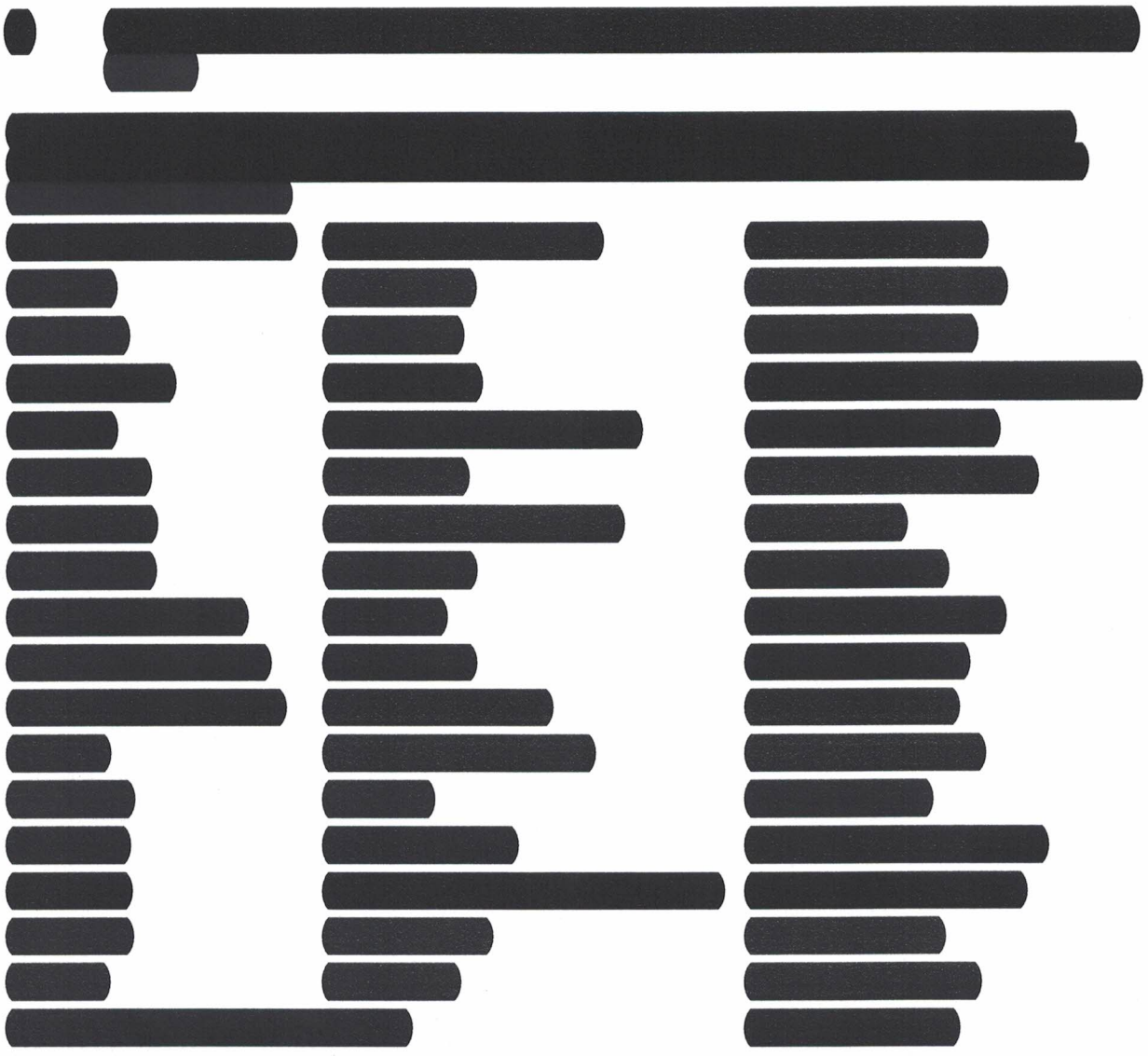

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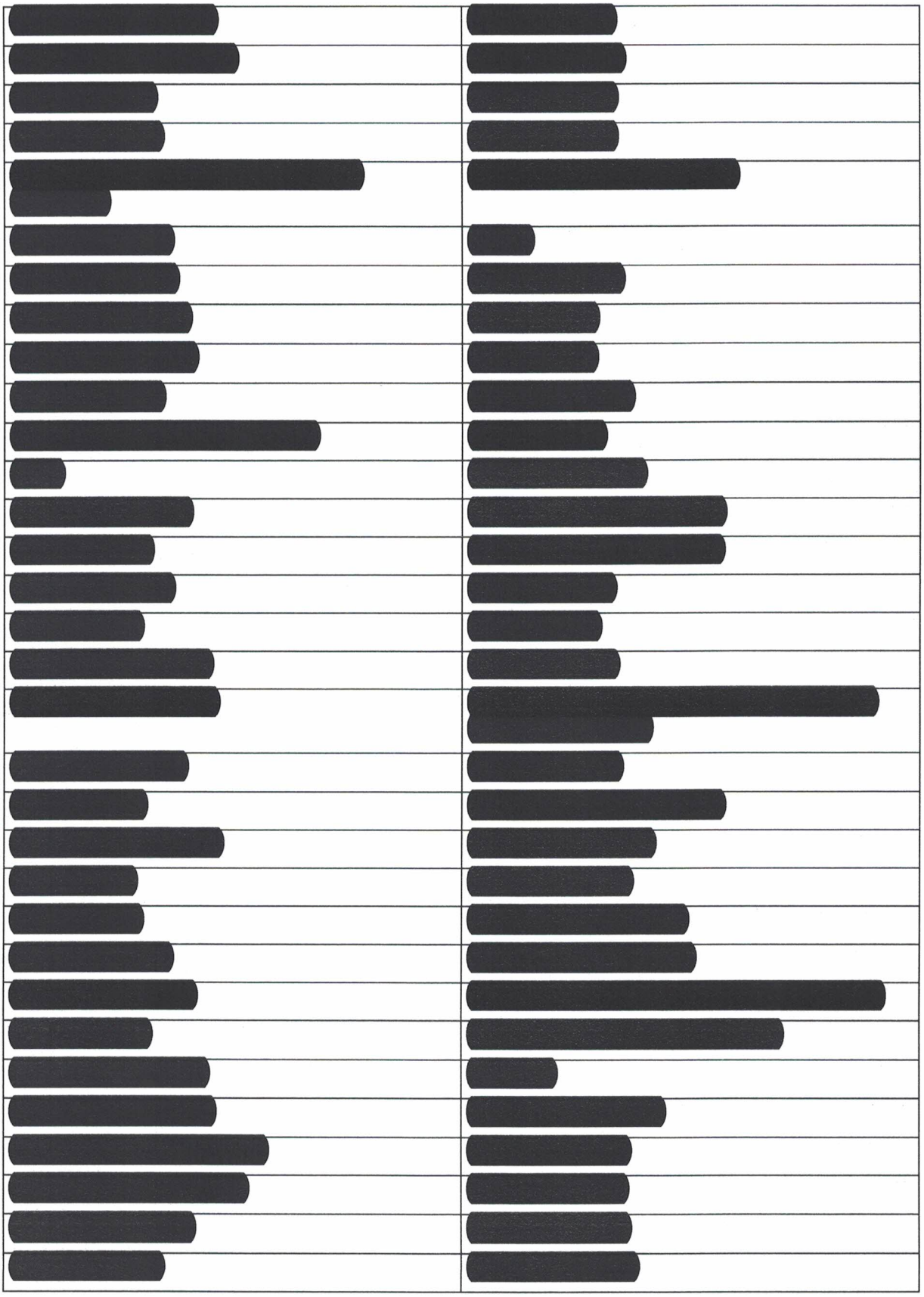

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