AEON Biopharma, Inc

ABP-19002

An Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of Repeat Intramuscular ABP-450 (prabotulinumtoxinA) Injection for the Treatment of Cervical Dystonia

24 Aug 2023

Final Statistical Analysis Plan

Version 2.0
Protocol Version 2.1

Prepared by:

[redacted]

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List of Abbreviations

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CGI-C	Clinical Global Impression of Change
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRF	case report form
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	Electronic case report form
EOS	End of study
FAS	full analysis set
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HEENT	head, ears, eyes, nose, throat
ICH	International Conference on Harmonisation
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
MITT	modified intent-to-treat
OLE	Open label extension
PGI-C	Patient Global Impression of Change
[redacted]	[redacted]
PPS	per protocol set
PT	preferred term
PVG	Pharmacovigilance
SAF	Safety analysis set
SAFR	Safety analysis set with retreatment
SAP	Statistical analysis plan
SAE	serious adverse event
SE	Standard error
SOC	system organ class
SOP	Standard operating procedures
TEAE	treatment-emergent adverse events
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
WHO	World Health Organization
WHODRUG	World Health Organization drug dictionary

1. Introduction

Cervical dystonia (spasmodic torticollis) is the most common form of focal dystonia, affecting the neck and shoulder muscles (Defazio 2004, Mittal 2019). Cervical dystonia is characterized by abnormal head and neck posture with involuntary head and neck movements. It is often associated with neck and shoulder pain.

Botulinum toxin A is considered first-line therapy for cervical dystonia, helping to improve pain, posture, and disability (Comella 2011, Simpson 2016, Mittal 2019). ABP-450 (prabotulinumtoxinA) is a toxin produced by *Clostridium botulinum*. It blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. Blocking the release of acetylcholine plays a role in relaxing muscles by reducing muscle activity.

[redacted]

ABP-450 was evaluated in multiple non-clinical safety and toxicological tests to determine the pharmacologic and safety profile of the product to in complying with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines/requirements for biologic products. [redacted]

PrabotulinumtoxinA has also been found to be non-inferior to BOTOX® for the treatment of moderate to severe glabellar lines in adult patients and upper limb spasticity in patients with stroke

(Nam 2015, Rzany 2019). The doses of ABP-450 used in the Phase 3 study for upper limb spasticity were similar to the doses of BOTOX® used (no significant differences were seen between the 2 groups) (Nam 2015).

ABP-19000 is an ongoing, Phase 2, randomized, double-blind, multicenter, placebo-controlled study to evaluate the safety and effectiveness of intramuscular ABP-450 injection for the treatment of cervical dystonia. [redacted] ABP-19002 is the open-label extension (OLE) study, wherein eligible patients from [redacted] ABP-19000 [redacted] studies, irrespective of treatment allocation, will have the option to continue treatment with ABP-450. [redacted] The ABP-19002 study will help to evaluate safety and efficacy of repeat dosing of ABP-450 for the long-term treatment of cervical dystonia.

Clostridium botulinum toxins have become the standard of care for the treatment of patients with cervical dystonia, but also have significant risks associated with their use in these patients. The labels of marketed products carry prominent warnings concerning their side effects, such as dysphagia and even death, if they are not carefully administered and the patients are not monitored while under treatment. Even so, the benefit for all these products is greater than the potential risk.

Clinical development of drugs has been impacted by the ongoing COVID-19 pandemic. The current study aims to implement several adjustments or mitigations to allow the study to continue despite pandemic-related disruption. To prioritize patient and site staff safety several planned office visits have been converted to tele visits to allow the required data collection to meet the study objectives.

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used [redacted] in the analysis and presentation of data for Aeon Biopharma, Inc protocol number ABP19002 entitled 'An Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of Repeat Intramuscular ABP-450 (prabotulinumtoxinA) Injection for the Treatment of Cervical Dystonia'. This SAP has been written in accordance with ICH E9 [redacted] standard operating procedures (SOPs) and using the final study protocol version 2.1 dated 13 May 2021 and electronic case report form (eCRF) version 2.0 (28 Jun 2021).

2. Objectives

2.1.1. Primary objective

- To evaluate the safety of repeat intramuscular injections of ABP-450 (150-350 units per dose) in the treatment of cervical dystonia.

2.1.2. Secondary objective

- To evaluate the efficacy of repeat intramuscular injections of ABP-450 (150-350 units per dose) in the treatment of cervical dystonia.

3. Investigational Plan

3.1. Overall Study Design and Plan

Since cervical dystonia is a chronic disease, patients typically receive medications regularly (i.e., repeated therapy), including botulinum toxin injections. For this reason, it is useful to evaluate the safety and efficacy of repeat injections of ABP-450 for the ongoing (long-term) treatment of cervical dystonia.

This is an open-label, Phase 2/3, multicenter, 52-week study of ABP-450 purified neurotoxin complex for the treatment of cervical dystonia. The study population will consist of all patients who had their initial dose of study drug in the ABP-19000 study, irrespective of treatment allocation, and who consented to being treated for cervical dystonia with ABP-450 in the ABP-19002 OLE study [redacted]

At the investigator's discretion and with the patient's consent, patients will enter the OLE study at Week 8 (Week 8 will be Day 1 "rollover" for the OLE study) with the opportunity to either maintain the original Phase 2 dose or modify the dose. If there is no efficacy (or loss of efficacy) between 6 and 20 weeks in the ABP-19000 study, then patients can roll over to the OLE study at a dose determined per the investigator's discretion.

[redacted] During this OLE study, patients will receive any dose between 150 and 350 units of ABP-450, based on the investigator's discretion. There will be no additional retreatments after Week 48.

3.2. Study Estimands

For all estimands, the target population is patients diagnosed with cervical dystonia. Patients are expected to:

- Have not had previous treatment with BOTOX® within the last 8 weeks.
- Have not had previous treatment with ABP-450 within the last 8 weeks.
- Be receiving stable doses of treatment for focal dystonia treatment (e.g., anticholinergics and benzodiazepines)
- Meet other inclusion/exclusion criteria.

3.2.1. Primary Estimand

[redacted]

[redacted]

3.2.2. Secondary Estimands

These are the hypothetical estimands regarding alternative prohibited medications (e.g., BOTOX®), assuming (treatment policy) no change in background treatment and administration of treatment within the 150- to 350-unit dose range:

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

3.3. Treatments

Investigational study drug is a *Clostridium botulinum* toxin type A. Each vial contains 100 units of lyophilized ABP-450. All study patients, will be administered between 150 and 350 units of ABP-450, based on the investigator's discretion and clinical judgment.

[redacted]

[redacted]

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

There will be no additional retreatments after Week 48.

3.4. Dose Adjustment/Modifications

Patients were enrolled in the ABP-19002 OLE study with the opportunity to either maintain the original Phase 2 dose or modify the dose at the investigator's discretion. As the blind will not be broken, the placebo patients (who were entered into one of the dose groups in the ABP-19000

study) can be administered any dose between 150 and 350 units of ABP-450, based on the investigator's discretion and clinical judgment. Retreatments are also based on investigator's discretion and clinical judgement.

4. General Statistical Considerations

4.1. General considerations

The statistical principles applied in the design and planned analyses of this study are consistent with International Council for Harmonisation (ICH) E9 guidelines (ICH 1998). All descriptive summaries will be presented by dose group, treatment cycle and nominal visit/timepoint (where applicable). [redacted] All efficacy analyses will be based upon the modified Full Analysis Set (mFAS, Section 4.5.2), and all safety as well as demographic and baseline characteristic analyses will be based upon the Safety Analysis Set (Section 4.5.3). Summary of safety and efficacy analyses will be displayed by treatment group and treatment cycle. Additional analyses will be performed on selected populations as specified in the sections below.

Unless otherwise stated, the following methods will apply:

- Treatment groups: For a given assessment or event, treatment group will be assigned to a patient based on the last dose received as follows:

Range of total dose	treatment group
a. Non-missing dose ≤ 200 units	ABP-450 150 units
b. > 200 to ≤ 300 units	ABP-450 250 units
c. > 300 units	ABP-450 350 units

  In addition, three dose groups (low, medium, high) based on total dose across the whole study will be assigned to a patient for a given assessment or event as follows:

Range of overall total dose	Overall treatment group
a. Non-missing dose ≤ 800 units	ABP-450 low
b. > 800 to ≤ 1200 units	ABP-450 medium
c. > 1200 units	ABP-450 high

- Continuous variables: will be summarized using summary statistics (i.e., non-missing values (n), mean, standard deviation, median, minimum, and maximum). For the summary statistics of all continuous data, minimum and maximum values will be displayed to the same level of precision as reported, unless otherwise specified. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

- Categorical variables: will be described using the patient count and percentage in each category. When counts are presented, in cases where the count is zero, the percentage will

not be displayed to draw attention to the non-zero counts. A row denoted 'Missing' will be included in count tabulations where specified on the shells to account for missing values. The denominator for all percentages will be the number of populated patients in that treatment within the analysis set of interest, unless otherwise specified. Frequency statistics will be displayed using one decimal place except for the display of 100% frequency which will be displayed as 'XX (100)'.

- Rules for multiple assessments: To summarize data collected over time, summary tables will be presented by scheduled visit. Unscheduled visits may be included in specific summaries (such as worst post-baseline measurement) and will be described in the relevant sections. Both scheduled and unscheduled visits will be included in the data listings.

- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
  Date only: DDMMMYYYY
  Date and time: DDMMMYYYY HH:MM
  Partial dates will be listed as such (i.e., where day or day and month is missing, only MMMYYYY or YYYY will be displayed, respectively).

- Multiple comparisons: There will be no statistical adjustment for multiplicity.

- Treatment terminology and order to be used in TLF outputs:
  - Unless specified, the following labels will be used for summary tables:
    a. ABP-450 150 units
    b. ABP-450 250 units
    c. ABP-450 350 units
  - For summary of disposition, demography, medical history, prior medications, and first secondary estimand, the following will be used:
    a. ABP-450 low
    b. ABP-450 medium
    c. ABP-450 high

4.2. Key Definitions

The following key definitions will be used:

[redacted]

- Study Day: Within each treatment cycle, the study day of an event is defined as the relative day of the event starting with the date the study drug administration (reference date) for that Cycle as Study Day 1 (there will be no Day 0 for analysis purposes). The study day of events occurring before the first study drug administration in the first treatment cycle will be calculated as:

  Study Day = (date of event – date of first study drug administration).

  For events occurring on or after Study Day 1 in the first treatment cycle (including protocol specified Day 0 "rollover" visit), study day will be calculated within cycles as:

  Study Day = (date of event/visit within a cycle – Date of study drug administration of that cycle) + 1.

  Study days will only be calculated for events with complete or imputed dates and will be undefined for events that are "ongoing" at the end of the study.

- Baseline: The last observation on or before date of first dose in the ABP-19000 study will be considered as the baseline measurement unless otherwise specified. Repeat or unscheduled assessments may be included in the derivation of the baseline value.

- Change from baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/timepoint within a cycle and the baseline value. The change from baseline value at each post-baseline visit/timepoint within a Cycle will be calculated for all continuous parameters using the formula:

  Change from baseline Value = Result at Visit or Timepoint within a cycle– Baseline Value

  The change from baseline value will only be calculated if the specific post-baseline visit/timepoint within a treatment cycle results and the baseline value for the parameter are both available and will be treated as missing otherwise.

All analyses will be conducted using [redacted]

4.3. Sample Size

All eligible patients who had their initial dose of study drug in the ABP-19000 study, irrespective of treatment allocation, and consented to being treated with ABP-450 can be enrolled in this OLE (i.e., ABP-19002) study.

Approximately 59 patients could enroll in this OLE study from the ABP-19000 study. As there will be no comparative analyses, study power and sample size justifications are not required.

4.4. Randomization, Stratification, and Blinding

This is an OLE study. All eligible patients from the ABP-19002 study will receive ABP-450 in an unblinded fashion. As the blind will not be broken, the placebo patients (who were entered into

one of the dose groups in the ABP-19000 study) can be administered any dose between 150 and 350 units of ABP-450, based on the investigator's discretion.

4.5. Analysis Set

The following analysis sets will be used for this study. Inclusion in each analysis set will be reviewed and confirmed prior to database lock. The number and percent of patients in each analysis set will be summarized. A listing will also be produced displaying patients excluded from each set.

4.5.1. Enrolled Set

Enrolled Set will include every patient who signed informed consent form and attended Visit. The Enrolled Set will only be used for summaries of patient disposition and protocol deviations.

4.5.2. Modified Full Analysis Set (mFAS)

The mFAS will consist of all patients in the Safety Analysis Set but will exclude patients [redacted] The mFAS will be used for analysis of secondary estimands.

4.5.3. Safety Analysis Set (SAF)

The SAF will consist of all patients who received at least one dose of the investigational study drug. The SAF will be used to tabulate all safety data excluding the primary estimand.

4.5.4. Safety Analysis Set with Retreatment (SAFR)

The SAFR will consist of all patients in the SAF but will exclude patients who do not receive more than one treatment of ABP-450 within the OLE study. The SAFR will be used for analysis of the primary estimand.

5. Patient Disposition

5.1. Disposition

Patient disposition will be summarized by overall treatment group and presented in a listing for patients in the Enrolled Set. The disposition of patients will include the number and percentage of patients for the following categories:

- Patients enrolled.
- Patients included in the mFAS.
- Patients included in the SAF.
- Patients included in the SAFR.
- Patients who discontinued treatment with corresponding reasons for treatment discontinuation.
- Patient included in the SAF with corresponding reasons for treatment discontinuation.
- Patients who withdrew from the study with corresponding reasons for study withdrawal.

The reasons for discontinuation of ABP-450 treatment or withdrawal from the study include:

- Adverse Event

- Death
- Lack of Efficacy
- Lost to Follow-up
- Non-Compliance with Study Drug
- Physician Decision
- Pregnancy
- Study Terminated by Sponsor
- Withdrawal by Subject
- Other

5.2. Protocol Deviations

A listing of patients with protocol deviations will be provided.

6. Demographics and Baseline Characteristics

Demographic and baseline information will be summarized descriptively by overall treatment group (low, medium, high) as described in Section 4.1 using the mFAS and SAF and presented in listings using SAF.

6.1. Demographics

The following demographic parameters will be summarized:

Continuous descriptive analysis

- Age (years, as collected on the eCRF)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2). The BMI will be calculated as (body weight in kilograms) / (height in meters)^2.

Categorical descriptive analysis

- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, and Not Reported)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, and Not Reported)

6.2. General Medical History

Medical history and current medical conditions will be coded using the ICH Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later. Relevant prior medical history and current medical conditions will be summarized by overall treatment group (low, medium, high) system organ class (SOC) and preferred term (PT), using the SAF. Summary tables will include the number and proportion of patients (%) experiencing an event. Patients will be counted once for each SOC and PT level. General medical history data will also be listed using the SAF.

6.3. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria not met by patients will be listed using the Enrolled Set. Inclusion criteria and exclusion criteria may be found in Protocol Sections 4.1.1 and 4.1.2, respectively.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Prior and concomitant medications will be documented and updated during the study. Prior and concomitant medications will be coded according to the latest World Health Organization drug dictionary (WHODRUG Sep 2022 or later).

Medications that started prior to and continued after the first dose of ABP-450 will be included as both prior and concomitant medications. Summaries of prior and concomitant medications will be presented by overall treatment group (low, medium, high), PT and based on the SAF..

7.1.1. Prior Medications

A prior medication is defined as any medication that is taken prior to the first dose of ABP-450 regardless of when they stopped. If start and stop dates are missing and the medication is not identified to be ongoing, the medication will be considered ‘prior medications’ if the data was entered at Visit 1 (Baseline). Prior medications will be tabulated and listed. Medications that were started during and prior to the ABP-19000 study will be flagged in the listings.

7.1.2. Concomitant Medications

A concomitant medication is defined as any medication (other than ABP-450) that was used at least once on or after the date of first dose of ABP-450. Medications that were stopped on the same date as the first dose of ABP-450 will be included as concomitant medications. All medications which are ongoing will be considered concomitant. In addition, if a clear determination cannot be made (e.g., missing or partial medication start and/ or end dates), the medication will be included as concomitant. [redacted]

[redacted]

7.2. Study Treatments

7.2.1. Extent of Exposure to ABP-450

The number and percentage of patients exposed to study treatment at each visit within each treatment cycle will be summarized descriptively for categorical parameters by treatment group, while the cumulative number of doses and cumulative dose at each visit within each treatment cycle and total ABP-450 administered overall will be summarized descriptively for continuous parameters as described in Section 4.1, using the SAF.

[redacted]

7.2.2. Treatment Compliance

ABP-450 will be administered to the patient at the trial site by trained trial staff. Precise dose administered, the time and date of dosing in the source document and the dosage administration will be recorded in the eCRF. No analysis of compliance is planned for ABP-450.

8. Safety Analysis

8.1. Adverse Events

AEs will be collected from the time of signing of the ICF until 52 weeks or end of treatment after Day 1 "rollover" (exit from the study). All AEs will be classified by SOC and PT according to the MedDRA, version 24.0 or later.

Serious AEs that occur more than 56 days (i.e., 8 weeks) after the last dose of investigational study drug and the patient has exited the study may be reported if the investigator considers them related to investigational study drug.

The severity or intensity of an AE refers to the extent to which an AE affects the patient's daily activities. Adverse event severity will be classified as "Mild", "Moderate", and "Severe". TEAEs with missing severity will be imputed as 'Severe'.

The investigator will provide an assessment of the relationship of the event to the trial drug. The possible relationships are "Unrelated", "Possibly Related", "Probably Related" and "Definitely Related". Any TEAE reported as "Definitely Related", "Possibly Related" or "Probably Related" will be considered related to the ABP-450. TEAEs that are missing a relationship will be counted in the summary table as "Definitely Related" but will be presented in the data listing with a missing relationship.

Treatment emergent adverse events (TEAEs) are defined as those AEs that started on or after the day of first dose of ABP-450 up to 5 days after the end of treatment or end of study visits. Only TEAEs will be included in the AE summary tables. However, all adverse events will be listed and TEAEs will be flagged.

The TEAEs will be summarized by SOC and PT and will include the number and percentage of patients experiencing an event and the number of events (based on start date of the event) by treatment cycle and treatment group. Patients will be counted only once for each SOC and PT level (categorical descriptive analyses). In general, TEAE summary tables will be sorted by SOC and PT in descending order of frequency from the SOC and PT with the highest total frequency to the SOC and PT with the lowest total frequency.

[redacted]

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed following date imputation guidelines (see Section 13.2).

8.1.1. Primary Estimand

[redacted]

[redacted]

8.1.2. Overall Summary of Adverse Events

An overall summary of TEAEs will be summarized by treatment group and treatment cycle by providing the number and percent of patients who experience the following:

[redacted]

8.1.3. Incidence of Adverse Events

An overall summary of the number and percentage of patients with at least one TEAE will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported one or more events starting in each treatment group in each treatment cycle, and across all cycles (by overall total doses of low, medium, and high). Percentages will be calculated out of the number of patients in the SAF. The table will be sorted by SOC and PT in descending order of incidence from the SOC and PT with the highest total incidence to the SOC and PT with the lowest total incidence. Summaries and listings will be presented for the SAF.

8.1.4. Relationship of Adverse Events to Study Drug

Summaries of TEAEs related to ABP-450 will be presented by SOC and PT in descending order of frequency by treatment group within each treatment cycle. Summaries for TEAEs related to

ABP-450 will be presented using patients in the SAF who received at least one dose of ABP-450. Data will be listed for the SAF.

8.1.5. Severity of Adverse Event

The severity or intensity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be rated as mild, moderate, or severe. Changes in the severity of an AE will be captured in the CRF. The incidence of TEAEs will be tabulated by SOC and PT and severity by treatment group within each treatment cycle. Incidence will be based on the worst severity within each level of summarization.

Listings will be presented for the SAF.

8.1.6. Serious Adverse Events

Treatment-emergent SAEs will be presented by SOC and PT in a manner similar to that described in Section 8.1. Incidence and frequency summaries and listings of all treatment-emergent SAEs will be presented for the SAF by treatment group in each treatment cycle, and across all cycles (by overall total doses of low, medium, and high).

8.1.7. Adverse Events Leading to Treatment Discontinuation

Incidence of TEAEs with a study drug action taken as "Drug Withdrawn" will be summarized by SOC and PT by treatment group within each treatment cycle as described in Section 8.1. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the SAF.

8.1.8. Adverse Events Leading to Study Withdrawal

Summaries of incidence of TEAEs leading to study withdrawal will be tabulated by SOC and PT for each treatment group within each treatment cycle as described in Section 8.1. Percentages will be calculated out of the number of patients in the SAF.

8.1.9. Suspected Unexpected Serious Adverse Events

A suspected unexpected serious adverse event (SUSAR) is defined as an AE, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved investigational medicinal product). The incidence of SUSARs will be summarized by SOC, PT, and treatment group for each treatment cycle.

8.1.10. Non-Serious Adverse Events of Special Interest

Adverse events potentially suggestive of distant spread of toxin effects are listed in Appendix 13.3. The incidence of non-serious AEs of special interest will be summarized by SOC and PT for each treatment group within each treatment cycle.

8.1.11. Death

A listing of patient deaths will be presented using the SAF.

8.2. Clinical Laboratory Evaluations

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.2.6. Urine Pregnancy Test

A urine pregnancy test will be performed as scheduled (see Appendix 13.1). Pregnancy test data will be provided in a listing.

[redacted]

[redacted]

[redacted]

8.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS was developed by the United States FDA in 2012 for measuring suicidal ideation and behavior in clinical trials (Posner et al. 2011). The C-SSRS was designed to distinguish the domains of suicidal ideation and suicidal behavior. Four constructs are measured. The first is the severity of ideation (hereafter referred to as the "severity subscale"), which is rated on a 5-point ordinal scale in which 1 = wish to be dead, 2 = non-specific active suicidal thoughts, 3 = suicidal

thoughts with methods, 4 = suicidal intent, and 5 = suicidal intent with plan. The second is the intensity of ideation subscale (hereafter referred to as the "intensity subscale"), which comprises 5 items, each rated on a 5-point ordinal scale: frequency, duration, controllability, deterrents, and reason for ideation. The third is the behavior subscale, which is rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. The fourth is the lethality subscale, which assesses actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale (Posner et al. 2011).

The C-SSRS will be performed as per schedule of assessment (see Appendix 13.1) and a detailed description of the C-SSRS scale is provided in study protocol Appendix 13.7. The eCRF for 'Since Last Visit' scale will be used for all visits. The frequency and percentage of C-SSRS responses will be tabulated by treatment cycle and treatment group using the SAF. The C-SSRS responses of patients with any suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent will also be provided in a listing for the SAF.

9. Efficacy Analysis

Unless otherwise indicated, all inferential efficacy analyses will include all patients in the mFAS and will be presented by treatment cycle and treatment group. Missing data imputation will be performed as described in each section. Visit windows for efficacy analyses are described in Appendix 13.1. Efficacy analyses will be tabulated, and figures will be produced for measures over time.

9.1. Secondary Estimand

The secondary estimands for this study are:

[redacted]

[redacted]

[redacted]

9.1.1. TWSTRS Total Score

Most studies leading to the approval of currently available botulinum neurotoxins have used the TWSTRS scale as the primary efficacy measure (Espay 2018, Fernandez 2013). The standard TWSTRS is a comprehensive scale that comprises three subsets to assess motor severity, pain, and disability (Comella 2016). The motor severity subscale consists of 10 items, with variable scaling and weighting. It also includes a disability subscale with 6 items and a pain scale with 3 items. The total score is the sum of each of the subscales. [redacted]

[redacted]

[redacted]

[redacted]

9.1.2. TWSTRS Subscale (Disability, Severity, and Pain) Scores

Summary statistics for TWSTRS subscale scores (actual subscale scores and change from baseline in TWSTRS subscale score to each scheduled post baseline visit) will be calculated [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.4. PGI-C

The PGI-C enables the patient to rate changes in their perception of their general health status over the duration of the assessment via a 7-point scale ranging from "very much improved" to "very much worse" (Fischer 1999). Detailed descriptions of the PGI-C are provided in study protocol Section 13.4. PGI-C scores will be measured as per scheduled of assessment (see Appendix 13.1).

Summary statistics for actual PGI-C scores at each scheduled post baseline visit will be calculated as described for continuous variables in section 4.1. [redacted]

[redacted]

[redacted]

9.1.6. CGI-C

The CGI-C is a 7-point scale ranging from "very much improved" to "very much worse" (Guy 1976) based on the physician's perception of the patient's health status. Detailed descriptions of the CGI-C are provided in study protocol section 13.5 and CGI-C scores will be measured as per scheduled of assessment (see Appendix 13.1).

Summary statistics for actual CGI-C scores at each scheduled post baseline visit will be calculated as described for continuous variables in Section 4.1. [redacted]

9.1.7. Time to loss of 80% peak treatment effect of TWSTRS Total Score.

Summary statistics for time to loss of ≥ 80% of peak treatment effect for patients dosed on ABP-450 will be tabulated by treatment cycle and treatment group. [redacted]

[redacted]

[redacted]

9.1.8. Dysphagia Severity Scale scores

[redacted]

[redacted] Listing of dysphagia severity scores for each patient will also be provided using the SAF.

10. Interim Analysis

There is no planned interim analysis for this OLE study.

11. Changes in the Planned Analysis

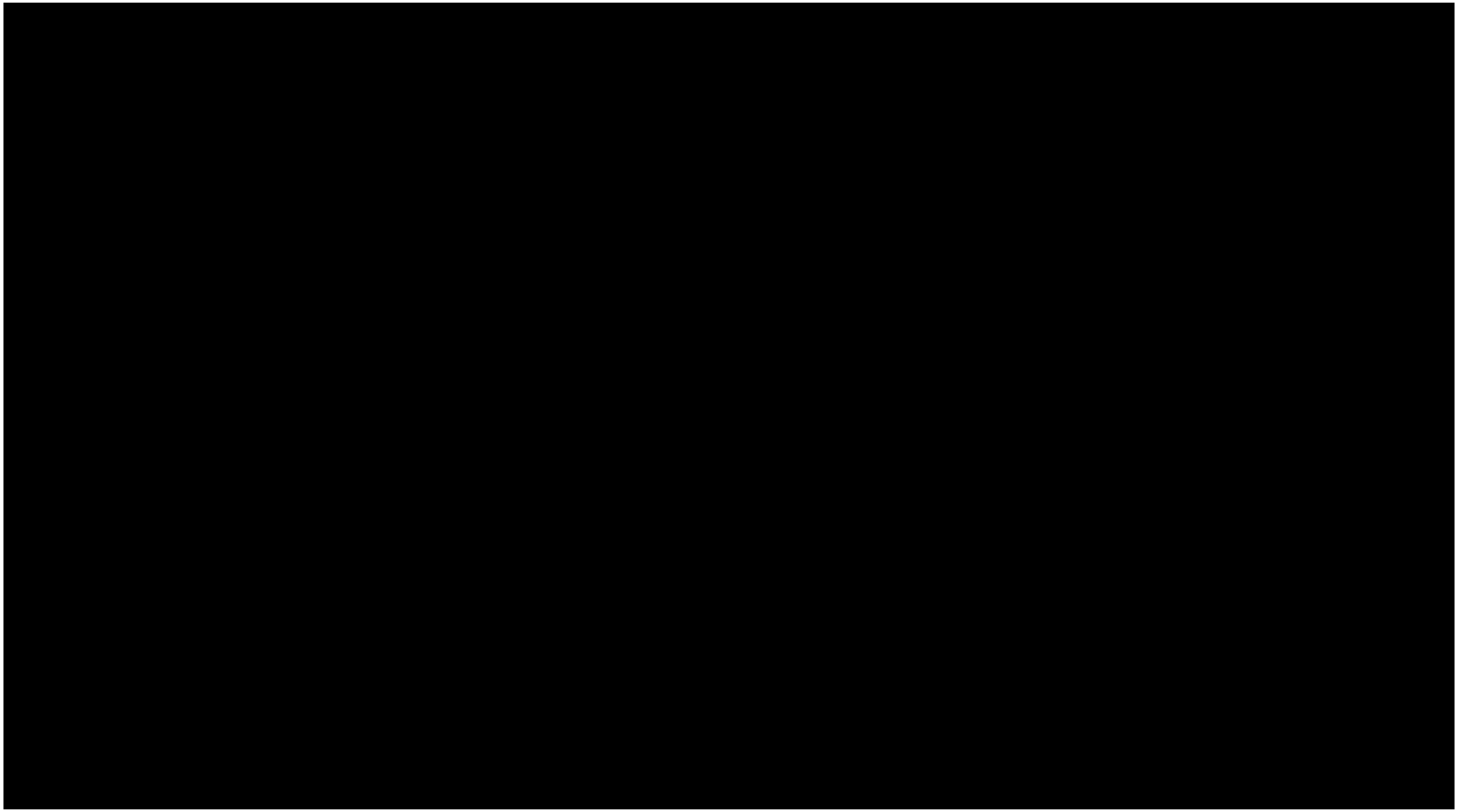
12. References

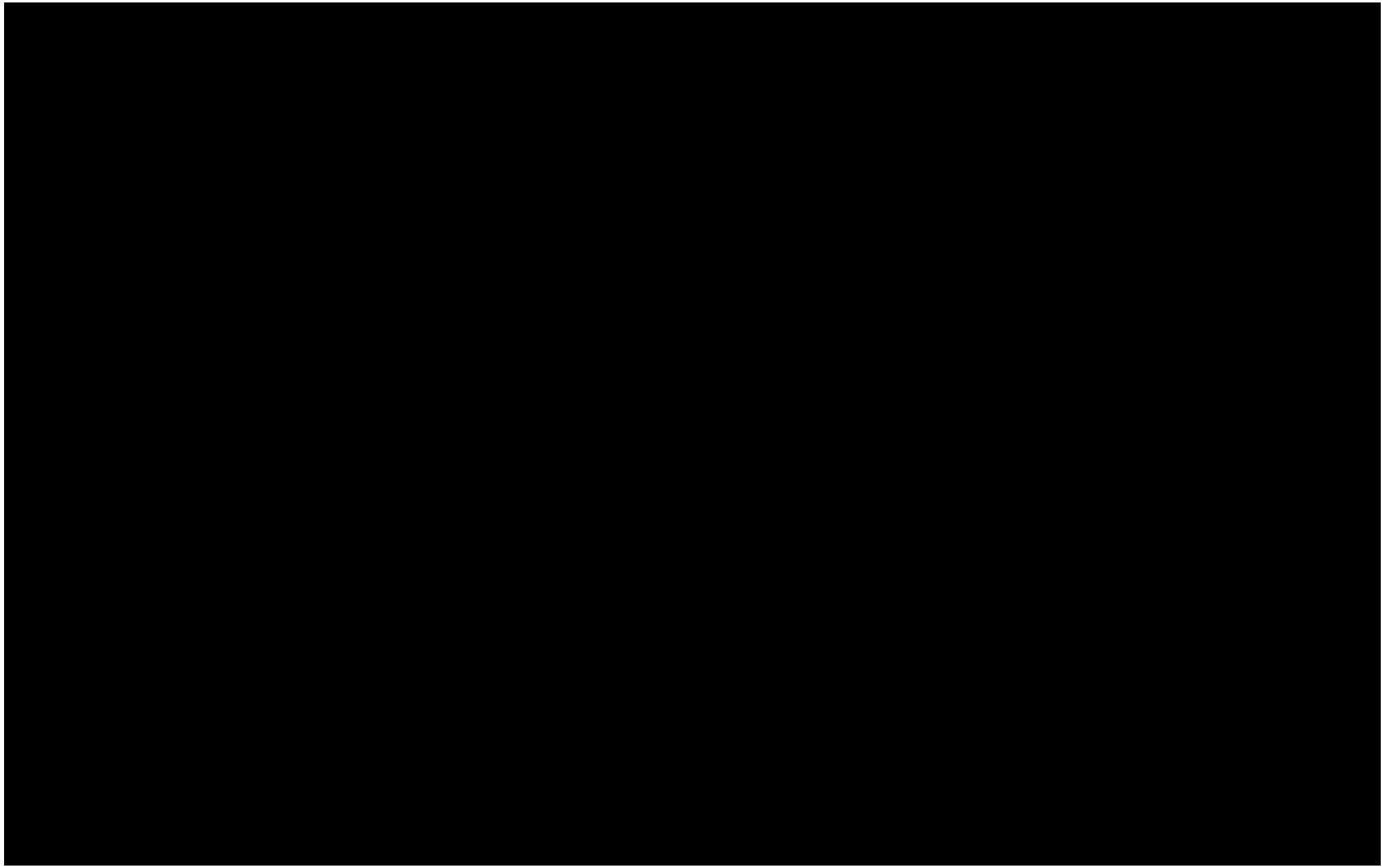
[redacted]

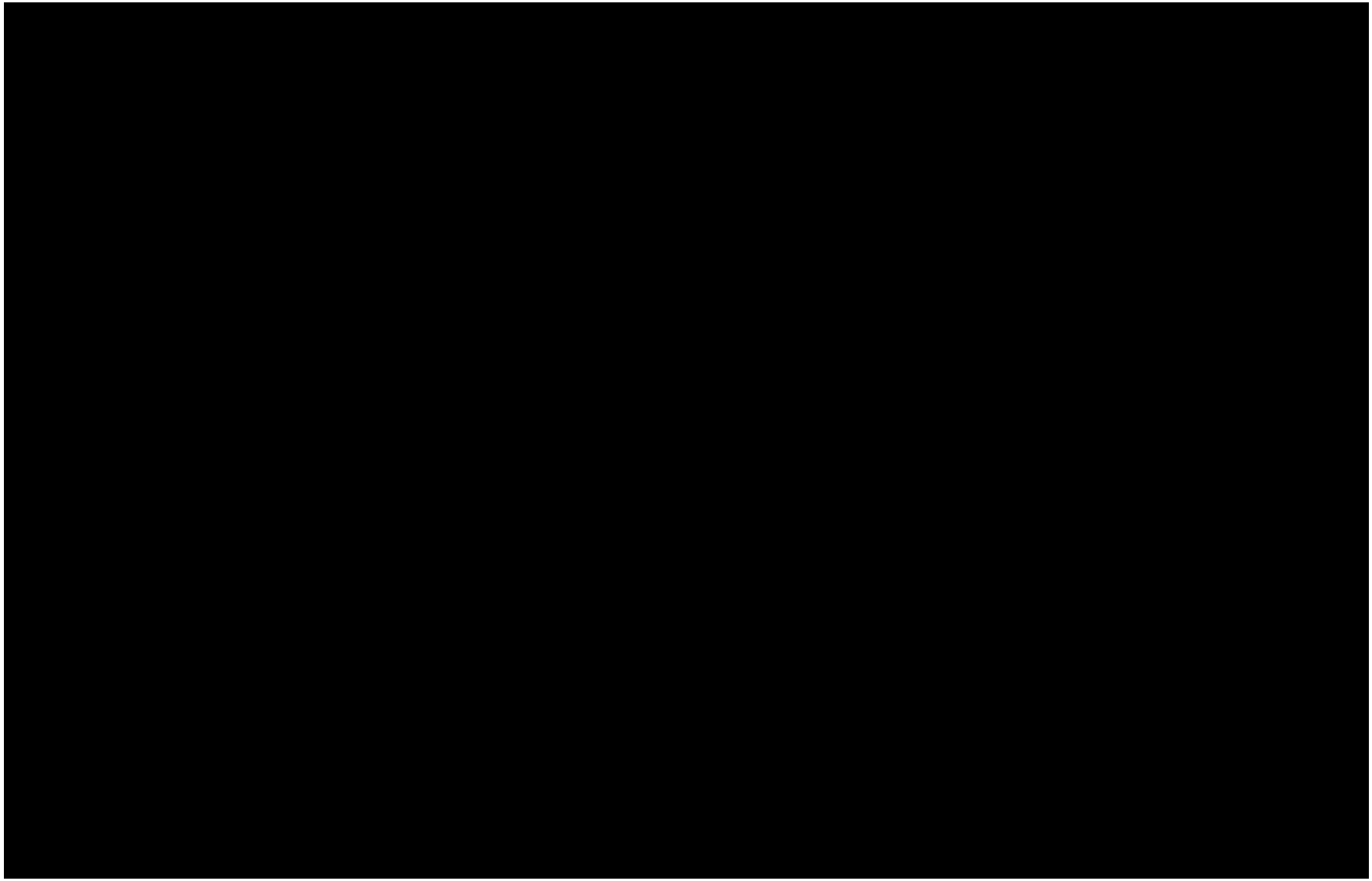
[redacted]

[redacted]

13. Appendices







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