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Protocol for Study 2042-201-008

Glabellar Lines: OnabotulinumtoxinA X in the Treatment of Moderate to Severe Glabellar Lines

VERSION:	3.0	DATE:	07 February 2022
SPONSOR:	AbbVie Inc.*	PLANNED NUMBER OF SITES:	Approximately 18
ABBVIE INVESTIGATIONAL PRODUCT:	OnabotulinumtoxinA X	EudraCT:	not applicable

FULL TITLE: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Parallel-Group Phase 2 Study Evaluating the Safety and Efficacy of OnabotulinumtoxinA X for the Treatment of Moderate to Severe Glabellar Lines

Incorporating Versions 1.0, 2.0, and 3.0

PRINCIPAL INVESTIGATORS: Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Parallel-Group Phase 2 Study Evaluating the Safety and Efficacy of OnabotulinumtoxinA X for the Treatment of Moderate to Severe Glabellar Lines	
Background and Rationale:	The purpose of this Phase 2 clinical study is to evaluate the safety and efficacy of onabotulinumtoxinA X formulation (hereafter called "OnabotA X"). [redacted]
Objective(s) and Endpoint(s):	The objectives of this study are: Efficacy: To compare the efficacy of OnabotA X with placebo for the treatment of glabellar lines (GL) in subjects with moderate to severe GL Safety: To evaluate the safety of OnabotA X for the treatment of GL in subjects with moderate to severe GL Primary efficacy endpoint: • Achievement of ≥ 1-grade improvement from baseline on the Allergan Glabellar Line Severity Scale (AGLSS) according to investigator assessments at maximum contraction at Day 30 Secondary efficacy endpoints: • Achievement of None or Mild on the investigator-rated AGLSS assessments at maximum contraction at Day 30 • Responses of Very satisfied or Mostly satisfied on satisfaction with treatment per the Facial Line Satisfaction Questionnaire (FLSQ©) follow-up version Item 5 at Day 60 • Achievement of ≥ 14-point psychosocial impact improvement from baseline at Day 30 per the FLSQ Impact domain, among subjects with baseline scores ≥ 14 points Safety will be assessed based upon: • Incidence of adverse events (AEs); [redacted]
Investigators:	Multicenter
Study Sites:	Up to 18 sites in the United States
Study Population and Number of Subjects to be Enrolled:	Approximately 280 subjects with moderate to severe GL; enrollment will be monitored to achieve an approximately balanced [redacted] distribution of subjects with investigator-assessed moderate or severe GL at maximum contraction at baseline.
Investigational Plan:	This is a 270-day, double-blind, randomized, placebo-controlled, Phase 2 study to assess the safety and efficacy of OnabotA X in adult subjects (≥ 18 years old) with moderate to severe GL. Eligible subjects will be randomized in a 2:2:2:1 ratio to receive OnabotA X [redacted] or [redacted] placebo. Randomization will be stratified at each investigator site by the investigator-assessed baseline severity of GL at maximum contraction using the AGLSS.

Key Eligibility Criteria:	To be eligible for enrollment, at baseline subjects must have AGLSS scores of moderate or severe GL at maximum contraction (also called frown or furrow) by investigator and subject assessments. The investigator and subject scores must be the same.
Study Drug and Duration of Treatment:	On Day 1, eligible subjects will receive a single, double-blind treatment of OnabotA X [redacted] or [redacted] placebo. Study drug will be administered as [redacted] intramuscular (IM) injections into the corrugator and procerus muscles.
Date of Protocol Synopsis:	07 February 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

OnabotA X is an onabotulinumtoxinA investigational product being developed for the treatment of moderate to severe glabellar lines (GL). Hyperfunctional facial lines that develop from repeated facial expression, such as GL, are typically treated by selectively weakening specific muscles with small quantities of botulinum toxin.[1-5] Botulinum toxins act selectively at the neuromuscular or neuroglandular junction to reversibly block presynaptic acetylcholine release. BOTOX® (onabotulinumtoxinA) was first approved for aesthetic treatment of GL in 2001 and is one of the most common nonsurgical procedures in aesthetic medicine.[6]

[redacted]

2.2 Benefits and Risks to Subjects

OnabotulinumtoxinA is the active drug substance in BOTOX/BOTOX Cosmetic and in OnabotA X; therefore, safety data from prior studies of BOTOX are relevant to the benefit/risk assessment for this first-in-human study of OnabotA X.

The clinical efficacy and safety profile of BOTOX has also been demonstrated in multiple Allergan- and non-Allergan-sponsored clinical trials across several indications, with favorable benefit/risk profiles. In general, adverse reactions occur within the first few days following injection of BOTOX, and while generally transient, may have a duration of several months or, in rare cases, longer.

In a meta-analysis conducted by Brin et al, the most frequently reported adverse events (AEs) among subjects treated for GL with BOTOX [redacted] were headache, nasopharyngitis, eyelid sensory disorder, eyelid ptosis, injection site pain, and nausea.[9] All of these events were mild or moderate in severity, and the incidence decreased with increasing number of treatment cycles.

[redacted]

[redacted]

More detailed information about the known and expected benefits and risks and reasonably expected AEs of OnabotA X may be found in the Investigator's Brochure and the subject's informed consent form (ICF).

For further details, please see findings from completed studies, including safety data in the current OnabotA X Investigator's Brochure.

Considering the coronavirus disease – 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Based on the limited information to date, no additional risk to study subjects is anticipated with the use of OnabotA X.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objectives of this study are:

Efficacy: To compare the efficacy of OnabotA X and placebo for the treatment of GL in subjects with moderate to severe GL.

Safety: To evaluate the safety of OnabotA X for the treatment of GL in subjects with moderate to severe GL.

3.2 Primary Endpoint

The primary efficacy endpoint is achievement of ≥ 1-grade improvement from baseline on the Allergan Glabellar Line Severity Scale (AGLSS) according to investigator assessments at maximum contraction at Day 30.

Estimand attributes of the primary efficacy endpoint are detailed in Table 1.

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for primary endpoint	OnabotA X or placebo	Achievement of ≥ 1-grade improvement from baseline on the AGLSS according to investigator assessments at maximum contraction at Day 30	ITT (All randomized)	Missing data will be imputed using multiple imputation.	Difference in response proportions between each active treatment group and placebo, after MI using CMH test stratified by baseline investigator-rated AGLSS at maximum contraction

AGLSS = Allergan Glabellar Line Severity Scale; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat; MI = multiple imputation; OnabotA X = onabotulinumtoxinA X

3.3 Secondary Endpoints

Secondary Endpoints

- Achievement of None or Mild on the investigator-rated AGLSS assessments at maximum contraction at Day 30
- Responses of Very satisfied or Mostly satisfied on satisfaction with treatment per the FLSQ follow-up version Item 5 at Day 60
- Achievement of ≥ 14-point psychosocial impact improvement from baseline at Day 30 per the FLSQ Impact domain, among subjects with baseline scores ≥ 14 points

3.4 Additional Efficacy Endpoints

[redacted]

[redacted]

3.5 Safety Endpoints

Safety evaluations include AEs; [redacted]

3.6 Immunogenicity and Hypersensitivity Sampling

Immunogenicity

Blood samples for immunogenicity testing will be collected from all subjects according to the Study Activities Table (Appendix D). Collected samples will be processed to yield serum for detection of binding and neutralizing antibodies to OnabotulinumtoxinA.

Hypersensitivity

In suspected cases of anaphylaxis, blood samples should be collected within 2 hours after dosing or as soon as possible. See Appendix F Operations Manual, Section 3.5 and Section 7.2.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a double-blind, randomized, placebo-controlled, Phase 2 study to assess the safety and efficacy of OnabotA X for the treatment of moderate to severe GL. To be eligible for enrollment, at baseline subjects must have AGLSS scores of moderate or severe GL at maximum contraction (also called frown or furrow) by investigator and subject assessments.

Approximately 280 subjects will be enrolled at approximately 18 sites. Eligible subjects will be randomized in a 2:2:2:1 ratio to receive OnabotA X [redacted] or [redacted] placebo. Randomization will be stratified at each investigator site by the investigator-assessed baseline severity of GL (AGLSS score) at maximum contraction. Overall study enrollment will be monitored to achieve an approximately balanced [redacted] distribution of subjects with investigator-assessed moderate or severe GL at maximum contraction at baseline.

[redacted]

Safety parameters [redacted] will be monitored (see Operations Manual [Appendix F] Section 3). At [redacted] females of childbearing potential will undergo pregnancy testing. For all subjects, AEs will be collected, whether solicited or spontaneously reported by the subject. Blood samples for immunogenicity testing will be collected [redacted]

Efficacy will be evaluated based on AGLSS assessed by the investigator and subject, and based on subject responses to FLSQ, [redacted] Standardized facial photography will be collected at all study visits from Day 1 through study exit.

[redacted]

The schematic of the study is shown in Figure 1. Further details regarding study procedures are in the Operations Manual.

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schematic

4.2 Discussion of Study Design

Choice of Control Group

A placebo control group is the gold standard for comparative evaluations of safety and efficacy in clinical trials.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are appropriate for assessing a novel formulation of a neuromodulator. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

The study population will include male and female adults with moderate to severe GL at maximum contraction (also called frown or furrow). To avoid confounding the study results, use of any botulinum neurotoxin for any indication within the 6 months prior to Day 1 is excluded, and washout from prior facial aesthetic treatments is required as described in the eligibility criteria.

Selection of Doses in the Study

There is growing evidence from clinical practice and within published literature that the use of higher doses of onabotulinumtoxinA for facial aesthetic indications, namely treatment of the GL area, provides longer durability of therapy benefit with no deleterious change to the overall product safety profile.[10-12] A sustained clinical benefit [redacted] was observed for up to 4 months when the GL area was treated with the approved dose [redacted]. Thus, the evaluation of OnabotA X at doses equal to and greater than the approved label dose for GL [redacted] is justifiable to evaluate whether this formulation at equal or higher doses might meaningfully extend the time to loss of patient benefit of the aesthetic effect.

[redacted]

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation. Screen failures can occur during the screening period up to the point prior to randomization on Day 1. Rescreening is not allowed for individuals who do not meet key safety or efficacy Eligibility [redacted] Any attempt to rescreen a subject must only occur after agreement with the sponsor.

Consent

- 1. Subject must voluntarily sign and date an informed consent approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult male or female, at least 18 years old at the time of ICF signature.
- 3. No clinically significant abnormal values for hematology, chemistry, or urinalysis at screening.

- [redacted]
- [redacted]
- [redacted]
- 7. Subject is willing and able to comply with procedures required in this protocol.

Disease/Condition Activity

- 8. Subject has moderate or severe GL at maximum frown [redacted]

Subject History

- 9. No history of known immunization to any botulinum toxin serotype.
- 10. No history of known hypersensitivity to any botulinum toxin serotype, [redacted] or any other constituents of the study drug or its excipients, and/or other products in the same class.
- [redacted]
- [redacted]
- 13. No presence or history of any medical condition that may place the subject at increased risk following exposure to OnabotA X or interfere with the study evaluation, including:
  - Diagnosed myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other significant disease that might interfere with neuromuscular function
  - Facial nerve palsy
  - Infection or dermatological condition at the site of study drug injection
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

[redacted]

Contraception

[redacted]

- [redacted]
- [redacted]

Concomitant Medications

- [redacted]
- [redacted]

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow [redacted] contraceptive guidelines [redacted]:

- Females, Non-Childbearing Potential

  [redacted]

[redacted]

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

5.3 Prohibited Medications and Therapy

In addition to the medications listed in the eligibility criteria, no other facial cosmetic procedures or treatments are to be performed throughout the duration of the study. [redacted]

[redacted]

[redacted]

During the study, all other investigational drugs are prohibited.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from 30 days prior to study drug administration through study exit. See below for details on special handling for the COVID-19 vaccine.

The use of any medication during the study (including prescription or over-the-counter medication, vitamins, and/or herbal supplements) is to be recorded on the subject's eCRF at each visit along with the reason the medication is taken, dates of use, and dosing regimen. Concurrent procedures will also be collected at each visit. Study site personnel must notify the sponsor immediately if a subject uses a concomitant medication or has a concurrent procedure that is prohibited per protocol (see Section 5.3). Subjects who use prohibited concomitant medications or have a prohibited concurrent procedure may be discontinued at the discretion of the investigator or sponsor. Concomitant medications and concurrent procedures will be tabulated and listed.

Non-live vaccines may be used during screening or treatment periods, if not contraindicated or medically inappropriate. When possible, study drug should be given at least ± 7 days from vaccine administration.

[redacted]

Systemic and topical hormones and their derivatives (i.e., sex steroids - androgens, estrogens, progesterone) should be maintained throughout study period to avoid changes in skin, including but not limited to:

- Oral birth control
- IUDs/implants/injections
- Oral supplements including testosterone & estrogens and their derivatives, dehydroepiandrosterone (DHEA), etc.
- Topicals (anywhere on the body) including testosterone & estrogens and their derivatives, DHEA, etc.

[redacted]

[redacted]

Subjects must maintain their standardized skin care regimen throughout the study period.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie non-emergency contact. Information regarding potential drug interactions with OnabotA X can be located in the OnabotA X Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications as described in the eligibility criteria. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

COVID-19 Pandemic-Related Vaccination Guidance

[redacted]

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons [redacted]

[redacted]

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F, in Section 2 and Section 3.

The investigator should contact the sponsor's non-emergency medical contact before discontinuing a subject from the study for a reason other than described in the protocol, to ensure all acceptable mitigation steps have been explored.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment on Day 1 should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse events (SAE) have been resolved.

5.7 Study Drug

All subjects will receive OnabotA X or Placebo prepared at the investigational site [redacted] administered on Day 1 (Baseline).

[redacted]

[redacted]

[redacted]

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

Randomization will be stratified by baseline investigator-rated AGLSS at maximum contraction, using central by block stratified randomization. The same block will not be shared across investigative sites or by baseline GL severity assessment.

[redacted]

[redacted]

Study drug will be labeled with kit numbers in an open-label fashion. The IRT will provide the IDR with the specific kit number for each randomized subject at the time of randomization (Day 1). The IDR will dispense study drug according to the IRT. The IDR will receive the IRT confirmation notifications for each transaction and will maintain these with the other unblinded study source documents with restricted access to the blinded site staff. [redacted] The IDR will then provide the filled syringes to the blinded investigator, who will inject the subject according to the study treatment administration instructions in the Operations Manual (Appendix F), Section 3.15.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring Committee

[redacted] Study sites and subjects will remain blinded for the duration of the study.

The details of the interim analyses are included in Section 7.6.

[redacted]

[redacted]

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

[redacted]

Medical Complaints/Adverse Events and Serious Adverse Events: OnabotA X

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

[redacted]

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has

been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or Clinical Research Organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual [Appendix F] for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration will be collected for at least 30 days or until the last follow-up visit, whichever is longer, whether solicited or spontaneously reported by the subject.

In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

[redacted]

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

[redacted]

Possible Distant Spread of Toxin

Possible distant spread of toxin (PDSOT) is defined as a possible pharmacologic effect of botulinum toxin at sites noncontiguous and distant from the site of injection. Utilizing a standardized methodology to assess for PDSOT, Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) that may be associated with botulinum toxin effects have been prospectively identified (see the statistical analysis plan [SAP] for a complete list of these PTs). AEs reporting any of these terms will be medically reviewed on a regular basis throughout the study and will be summarized in the clinical study report.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe.

The investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

[redacted]

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study will be encouraged to remain in the study for safety follow-up. If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

[redacted]

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP.

[redacted]

7.2 Definition for Analysis Populations

The Intent to Treat (ITT) Population includes all randomized subjects. The ITT Population will be used for all efficacy analyses. [redacted]

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. The safety analyses will be based on the safety population. [redacted]

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Missing data will be imputed using multiple imputation (MI) method for the primary and secondary endpoints (see Section 3.2).

[redacted]

After imputation, the changes from baseline values will be calculated. The responder status based on raw values or change from baseline values will then be derived for each post baseline visit.

Each of the 5 imputation data sets will be analyzed individually.

To obtain pooled CMH p-value, the Wilson-Hilferty transformation will be used. [redacted]

[redacted]

A sensitivity analysis will also be performed for the primary efficacy variable using observed data.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

Analysis of the primary endpoint will be conducted on the ITT population based on treatment as randomized. Missing data will be imputed using MI method described in Section 7.3. The evaluation of the equality of the proportions of responders will be based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline investigator-rated AGLSS at maximum contraction. Wald confidence intervals for proportions of responders and difference in the proportion of responders will be presented.

The Breslow-Day homogeneity of the odds-ratio test will be performed to test the treatment-by-investigator-rated baseline GL severity at maximum contraction interaction.

Summary and Analysis of Secondary Endpoints

The proportion of responders will be analyzed using CMH test, stratified by baseline investigator-rated AGLSS at maximum contraction. Missing data will be imputed using MI method.

Statistical testing will only be done between each OnabotA X group and the placebo group.

[redacted]

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population. The safety parameters will include incidence of AEs, change from baseline in vital signs and laboratory (hematology/chemistry) assessments, and ECG. Safety endpoints will be summarized using descriptive statistics and/or shift tables, as applicable. [redacted]

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent.

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of [redacted] AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study treatment according to the investigator
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- Any PDSOT AEs
- All deaths

[redacted]

SAEs (including deaths) will be summarized by SOC and PT and in listing format.

PDSOT AEs will be identified in the SAP and summarized by PT.

[redacted]

[redacted]

Statistical Analyses for Immunogenicity and Hypersensitivity

Immunogenicity results, manifested as the binding antibodies and neutralizing antibodies, will be summarized in a table for each sampling timepoint. [redacted]

[redacted]

7.6 Interim Analyses

An interim analysis is planned to occur [redacted] If a dose recommendation cannot be made at this point, then a second interim analysis will be performed, [redacted]

The primary and secondary efficacy analyses will be performed for each interim analysis, as well as summaries of all safety variables.

The SAP will describe the planned interim analyses in detail. No separate SAP will be prepared for the interim analyses.

7.7 Overall Type I Error Control

Analyses will be conducted using a gated hierarchical testing procedure to preserve a familywise Type I error rate of α=0.05 for each OnabotA X group. [redacted]

7.8 Sample Size Determination

The sample size was chosen empirically. The primary efficacy parameter is the proportion of subjects with a ≥ 1-grade improvement from baseline according to investigator-rated AGLSS at maximum contraction at Day 30. Based on previous BOTOX studies, the responder rate of ≥ 1-grade improvement from baseline on the GL severity scale [redacted] Assuming [redacted] responder rate for OnabotA X and placebo, respectively, at least 28 OnabotA X and 14 placebo subjects will be required to detect the above intervention difference with a power of 90% or greater at the 2 sided 5% significance level for the primary endpoint.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab) and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH GCP, and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AGLSS	Allergan Glabellar Line Severity Scale
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease – 2019
CRF	case report form
CS	clinically significant
DHEA	dehydroepiandrosterone
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ePRO	electronic patient-reported outcome device
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good clinical practice
GL	glabellar lines
[redacted]	[redacted]
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDR	Independent Drug Reconstitutor
IEC	Independent ethics committee
IM	intramuscular
IMP	Investigational medicinal product
IRB	Institutional review board
IRT	Interactive response technology
[redacted]	[redacted]

Abbreviation	Definition
ITT	intent-to-treat
IUD	intrauterine device
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
N/A	not applicable
NCS	not clinically significant
[redacted]	[redacted]
OnabotA X	onabotulinumtoxinA X
PCR	polymerase chain reaction
PDSOT	possible distant spread of toxin
PRO	patient-reported outcomes
PT	preferred term
QT	time from the start of the Q wave to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reactions
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	system organ class
SUSAR	Suspected unexpected serious adverse reactions
TCA	trichloroacetic acid
U	units
VDS	verbal descriptor scale
WOCBP	woman of child-bearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 2042-201-008: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Parallel-Group Phase 2 Study Evaluating the Safety and Efficacy of OnabotulinumtoxinA X for the Treatment of Moderate to Severe Glabellar Lines

Protocol Date: 07 February 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

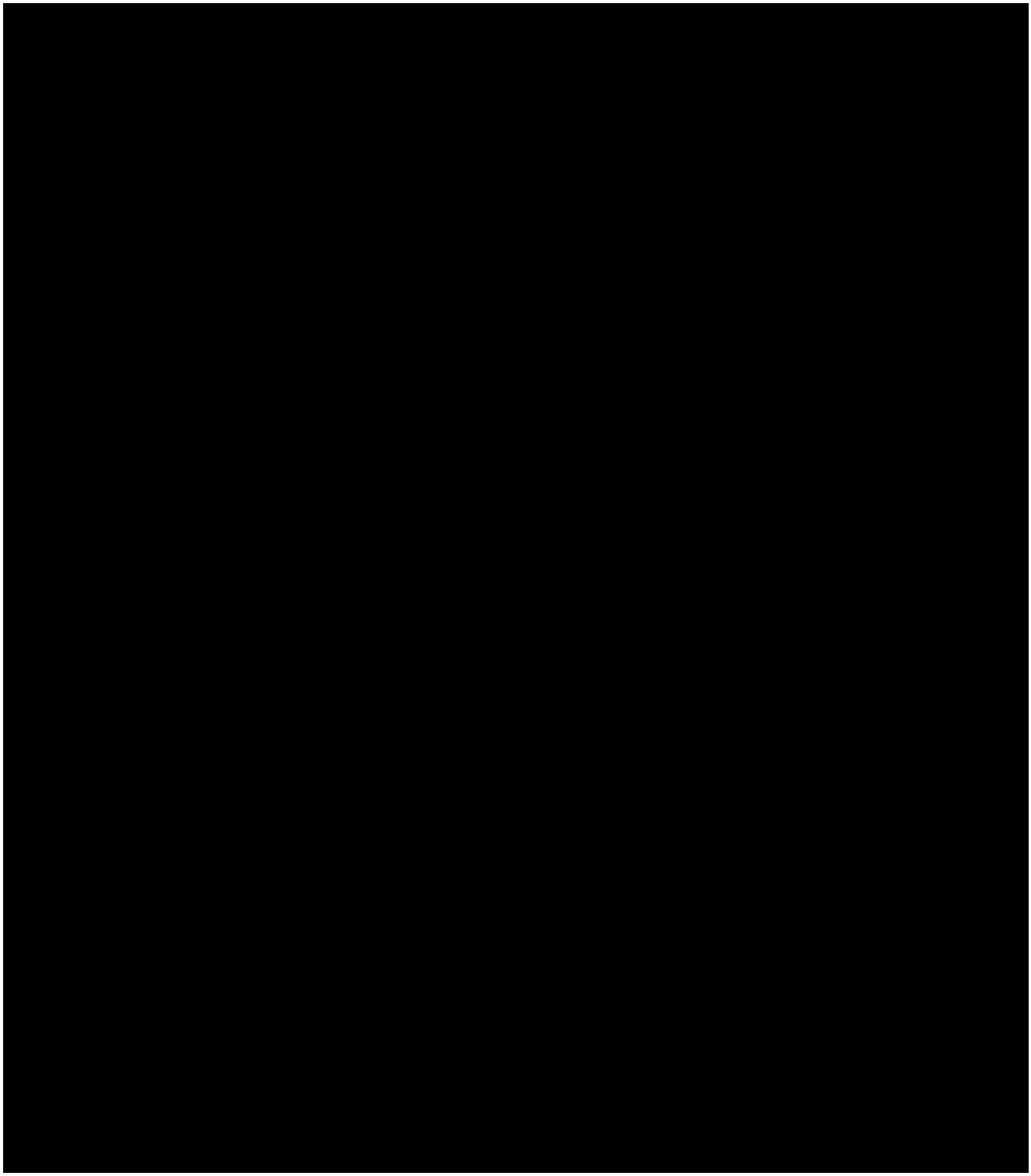
Name of Principal Investigator (printed or typed)	

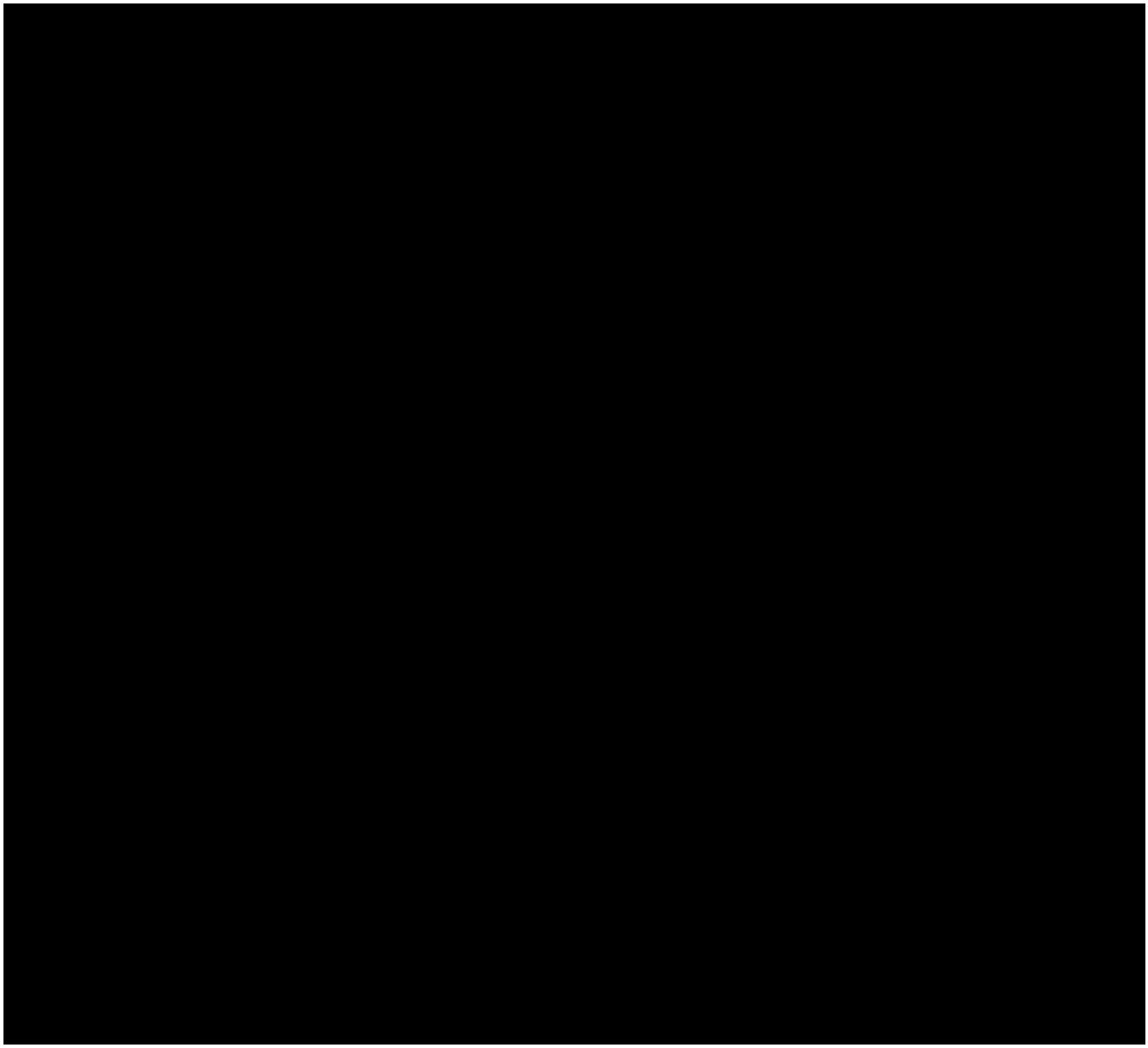
APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted] Clinical Program Development	Clinical Study Leadership
[redacted]	[redacted]	Medical Writing
[redacted]	[redacted] Head of Clinical Development, Aesthetic Medicine	Therapeutic Area
[redacted]	[redacted] Biostatistics	Statistics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the study. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual (Appendix F) in Section 2 and Section 3.





APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 2.0	07 September 2021
Version 1.0	14 June 2021

Version 3.0

The purpose of the version update to 3.0 is to change the number of estimated sites from approximately 15 to 18.

Version 2.0

[redacted]

Additional edits were made, as follows:

[redacted]

Added the following eligibility criterion to Section 5.1 Eligibility Criteria: "If the subject has received a [redacted]

[redacted]

[redacted]

[redacted]