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Protocol for Study M21-606

Forehead Lines: OnabotA X for the Treatment of Moderate to Severe Forehead Lines

VERSION:	2.0	DATE:	18 July 2022
SPONSOR:	AbbVie Inc.*	PLANNED NUMBER OF SITES:	Approximately 10
ABBVIE INVESTIGATIONAL PRODUCT:	OnabotulinumtoxinA X	EudraCT:	not applicable

FULL TITLE: A Phase 2, Multicenter, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of OnabotulinumtoxinA X for Forehead Lines

Incorporating Versions 1.0 and 2.0

PRINCIPAL INVESTIGATORS: Investigator information on file at AbbVie.

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*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix F).

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1 SYNOPSIS

Title: A Phase 2, Multicenter, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of OnabotulinumtoxinA X for Forehead Lines	
Background and Rationale:	The purpose of this study is to evaluate the safety and efficacy of 3 different onabotulinumtoxinA X doses (hereafter called "OnabotA X") compared with placebo for the treatment of moderate to severe forehead lines (FHL). The results from this study will support dose selection for future Phase 3 studies.
Objective and Endpoints:	The objective of this study is to evaluate the safety and efficacy of 3 doses of OnabotA X for the treatment of moderate to severe FHL. Primary Efficacy Endpoint: The primary efficacy endpoint is the achievement of ≥ 1-grade improvement from baseline on the investigator-rated Facial Wrinkle Scale (FWS) FHL at maximum contraction (also known as eyebrow elevation or surprise) at Day 30. Primary Safety Endpoints: • Incidence of adverse events (AEs) [redacted] • Change from baseline in vital signs (body temperature, pulse rate, respiratory rate, and blood pressure [systolic and diastolic]).
Investigators:	Multicenter
Study Site:	Approximately 10 sites in the United States.
Study Population and Number of Subjects to be Enrolled:	Approximately 120 subjects in general good health with moderate to severe FHL and glabellar lines (GL); [redacted]
Investigational Plan:	This is a 180-day, multicenter, randomized, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of 3 doses of OnabotA X in adult subjects (≥ 18 years old) with moderate to severe FHL and GL. On Day 1, eligible subjects will be randomly assigned in a 1:1:1:1 ratio to receive OnabotA X [redacted] or [redacted] placebo in the frontalis. All treatment groups will also receive [redacted] of OnabotA X in the glabellar complex. Randomization will be stratified by the investigator-assessed baseline severity of FHL (FWS-FHL) at maximum contraction and investigator site.
Key Eligibility Criteria:	To be eligible for enrollment, subjects must have symmetrical moderate to severe FHL at maximum contraction as assessed by both investigator and subject using the FWS-FHL at Screening and on Day 1 prior to study treatment. Both investigator and subject assessments must match. Additionally, subjects must have GL of moderate or severe rating at maximum contraction (also known as frown or furrow)

	as assessed by investigator using the FWS-GL at Screening and on Day 1 prior to study treatment.
Study Drug and Duration of Treatment:	On Day 1, eligible subjects will receive a single double-blind treatment of OnabotA X [redacted] or [redacted] in the frontalis muscle. All subjects will also concurrently receive [redacted] OnabotA X in the glabellar complex. Study drug will be administered as [redacted] intramuscular (IM) injections into the frontalis muscle and [redacted] IM injections into the glabellar complex (procerus and corrugator muscles). Subjects will be followed for up to 180 days after treatment.
Date of Protocol Synopsis:	18 July 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Botulinum toxins act selectively at the neuromuscular or neuroglandular junction to reversibly block presynaptic acetylcholine release. OnabotulinumtoxinA is the active drug substance in BOTOX/BOTOX Cosmetic and in OnabotA X. BOTOX® (onabotulinumtoxinA) was first approved for aesthetic treatment in the United States for glabellar lines (GL) in 2002 and for forehead lines (FHL) in 2017, and is one of the most common nonsurgical procedures in aesthetic medicine.[1]

OnabotA X is an onabotulinumtoxinA investigational product being developed for the treatment of moderate to severe upper facial lines. Hyperfunctional facial lines that develop from repeated facial expression, such as GL and FHL, are typically treated by selectively weakening specific muscles with small quantities of botulinum toxin.[2-6]

Resting eyebrow position results from a balance between eyebrow elevator muscles, primarily the frontalis, and eyebrow depressor muscles, including the procerus, corrugators, and orbicularis oculi. Thus, isolated weakening of the frontalis muscle with cosmetic botulinum toxins treatment may result in eyebrow ptosis due to an imbalance between eyebrow elevators and depressors. Most clinicians agree that concurrent treatment of the glabellar area is recommended to reduce the risk of undesirable aesthetic outcomes (e.g., eyebrow malposition and eyebrow or eyelid ptosis).[7,8] As a result, the treatment regimen proposed for this FHL study is the treatment of the frontalis muscle in conjunction with the glabellar complex.

[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 Study M21-606.

The clinical safety and efficacy 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. Below is a brief summary of safety for BOTOX utilized in the treatment of FHL, multiple facial areas (including FHL, GL, and lateral canthal lines [LCL]), and GL. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of OnabotA X may be found in the Investigator's Brochure (IB) and the subject's informed consent form (ICF).

Safety data for BOTOX treatment of FHL come from 3 double-blind, placebo-controlled trials conducted in North America and Europe ( ). A total of 1260 subjects were exposed to at least 1 BOTOX treatment), the majority of whom received either 40 U (N = 749) or 64 U (N = 746), the doses approved for treatment of FHL and of FHL and LCL, respectively.

The most frequently reported treatment-emergent adverse events (TEAEs) were commonly occurring conditions in the general population (e.g., headache [11.1% of all BOTOX-treated subjects,] and nasopharyngitis [7.9%,]) or events commonly occurring following injections to vascularized areas (e.g., injection site bruising [6.9%,]). Most of these events were mild or moderate in severity.

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, and based on the information to date, no additional risk to study participants is anticipated with the use of OnabotA X. While AbbVie does not consider COVID-19 to be a safety concern for OnabotA X due to its mechanism of action and route of administration, the Marketing Authorization Holder is monitoring COVID-19 events during the pandemic closely. A recent review of COVID-19 events for the period of 01 January 2019 through 31 December 2021 did not identify any new or significant safety findings for the patients receiving BOTOX (onabotulinumtoxinA) treatment. Overall, the clinical course and presentation of patients with

COVID-19 infection coincident with BOTOX (onabotulinumtoxinA) is consistent with what has been described for the general population.

3 OBJECTIVE AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The objective of this study is to evaluate the safety and efficacy of 3 doses of OnabotA X for the treatment of moderate to severe FHL.

3.2 Primary Endpoint

The primary efficacy endpoint is the achievement of ≥ 1-grade improvement from baseline on the investigator-rated Facial Wrinkle Scale (FWS-FHL) at maximum contraction (also known as eyebrow elevation or surprise) 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 investigator-rated FWS-FHL 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 FWS-FHL at maximum contraction

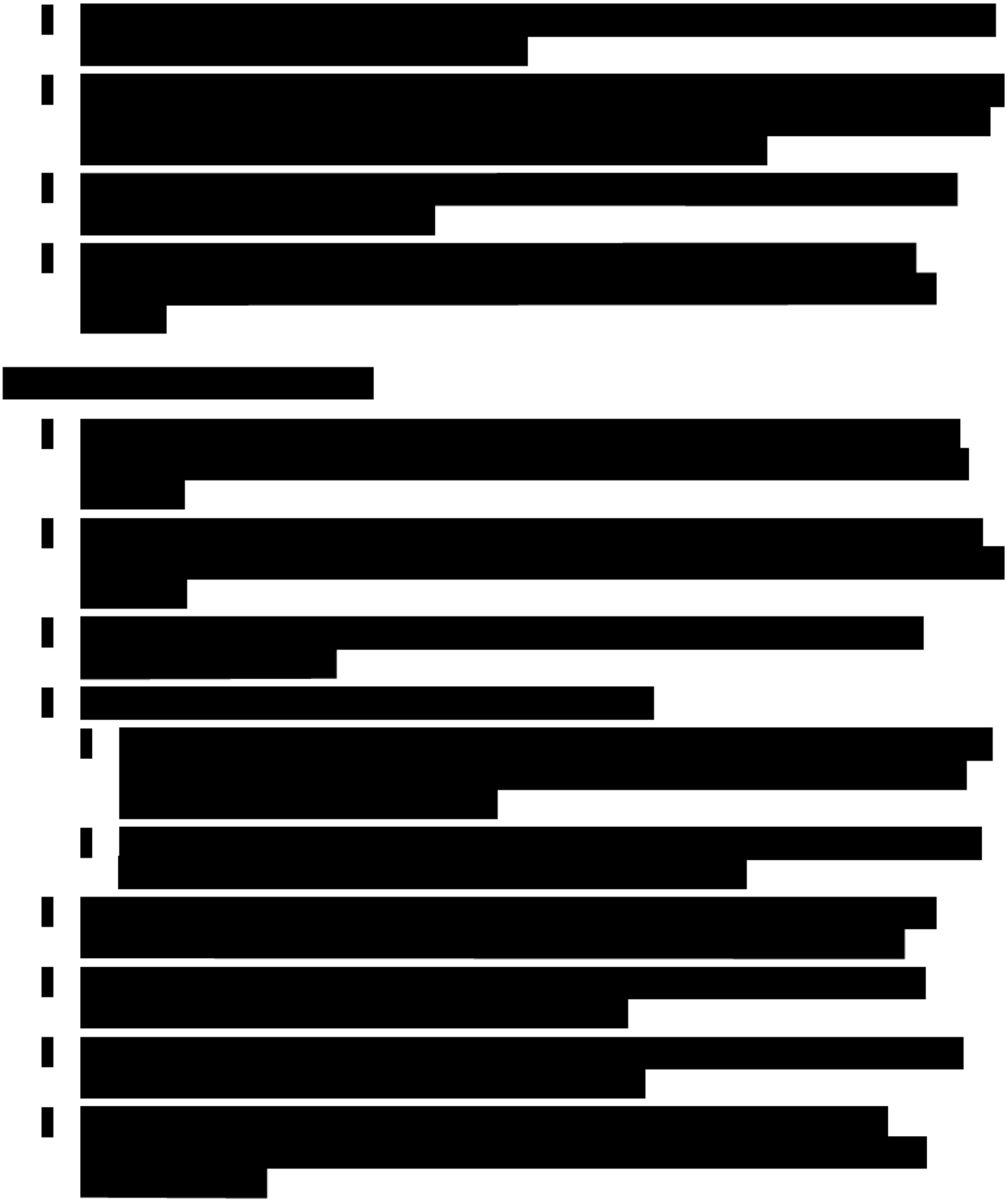
CMH = Cochran-Mantel-Haenszel; FWS-FHL = Facial Wrinkle Scale; Forehead Lines; ITT = intent-to-treat; MI = multiple imputation; OnabotA X = onabotulinumtoxinA X

3.3 Secondary Endpoints

Secondary Endpoints

No secondary endpoints are identified in this study.

[redacted]



3.5 Safety Endpoints

Primary Safety Endpoints include:

- Incidence of adverse events (AEs) [redacted]
- Change from baseline in vital signs (body temperature, pulse rate, respiratory rate, and blood pressure [systolic and diastolic]).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a 180-day, multicenter, randomized, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of 3 doses of OnabotA X for the treatment of moderate to severe FHL. To be eligible for enrollment, subjects must have symmetrical moderate to severe FHL at maximum contraction as assessed by both investigator and subject using the FWS-FHL at screening and on Day 1 prior to study treatment. Both investigator and subject assessments must match. Additionally, subjects must have GL of moderate or severe rating at maximum contraction as assessed by investigator using the FWS-GL at screening and on Day 1 prior to study treatment.

[redacted] Approximately 120 subjects will be randomized to 4 treatment groups in a 1:1:1:1 ratio. At Day 1, all randomized subjects will receive a fixed dose of [redacted] of OnabotA X in the glabellar complex, followed by injections in the frontalis. The dose injected in the frontalis will vary depending on the treatment group the subject is assigned to, as follows:

[redacted]

[redacted]

[redacted] For all subjects, AEs will be collected, whether solicited or spontaneously reported by the subject.

Efficacy will be evaluated based on FWS-FHL as assessed by the investigator at maximum contraction. Additional efficacy evaluation for FHL will include investigator-rated FWS-FHL at rest, and subject-rated FWS-FHL at maximum contraction and at rest. [redacted] Standardized facial photography will be collected at all study visits from Day 1 through study exit.

[redacted] A data snapshot and interim analysis will occur after the majority of subjects have completed the Day 90 visit or have prematurely discontinued. Study sites, study team, and subjects will remain blinded for the duration of the study.

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. Further details regarding study procedures are located in the Operations Manual (Appendix F).

Figure 1. Study Schema

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. The control group will be used in this study in order to optimally evaluate the safety and efficacy of 3 different OnabotA X doses for treatment of moderate to severe FHL, defined as treatment of the frontalis muscle with simultaneous treatment of the glabellar complex.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All safety and efficacy-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 adults with moderate to severe FHL at maximum contraction and GL at maximum contraction, assessed by using FWS.

There is an important interplay between the frontalis and other main muscular components of the upper face, including glabellar complex muscles. As a result, the treatment regimen proposed for use in this study is a single treatment of FHL, composed of injections in the frontalis muscle, with simultaneous treatment of GL, composed of injections in the procerus and corrugator muscles. Hence, subjects must meet the criteria for moderate to severe for both FHL and GL to be suitable to participate in this study.

In addition, the selection of subjects in general good health is standard for safety studies.

Selection of Doses in the Study

OnabotulinumtoxinA is approved as a safe and effective treatment for GL and FHL at doses of [redacted] each and FHL treated simultaneously with GL ([redacted]). However, facial lines and wrinkles are strongly influenced by individual differences in anatomy and muscle activity, with some individuals requiring a higher dose to meet desired results.[21] In the literature, higher cosmetic neurotoxin doses were reported to show greater efficacy and longer duration of effect in treating facial aesthetic indications including FHL.[18-20,22]

[redacted]

Considering the importance of the aesthetic evaluation, musculature variables among patients within same or different gender, a patient's desired outcome, and potential retreatment intervals, high and low doses will be tested to assess an optimal safe dose.

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 Criteria: [redacted] Any attempt to rescreen a subject must only occur after agreement with the sponsor.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent** approved by an institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.
- 2. Subject is willing and able to comply with procedures required in this protocol.

Demographic and Other Assessments

- 3. Adult male or female, ≥ 18 years of age, at the time of signing the informed consent.
- 4. Subject must have sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial lines.

- 5. Subject must be able to follow study instructions and complete study assessment tools without any assistance or alterations to the assessment tools, and complete all required study procedures.
- 6. Subject is in good health as determined by medical history, vital signs, and investigator's judgment, including no known active pandemic infection.

Condition Activity

- 7. Subject must have symmetrical moderate to severe FHL at maximum contraction [redacted]
- 8. [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]

Prior and Concomitant Medications/Therapy

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

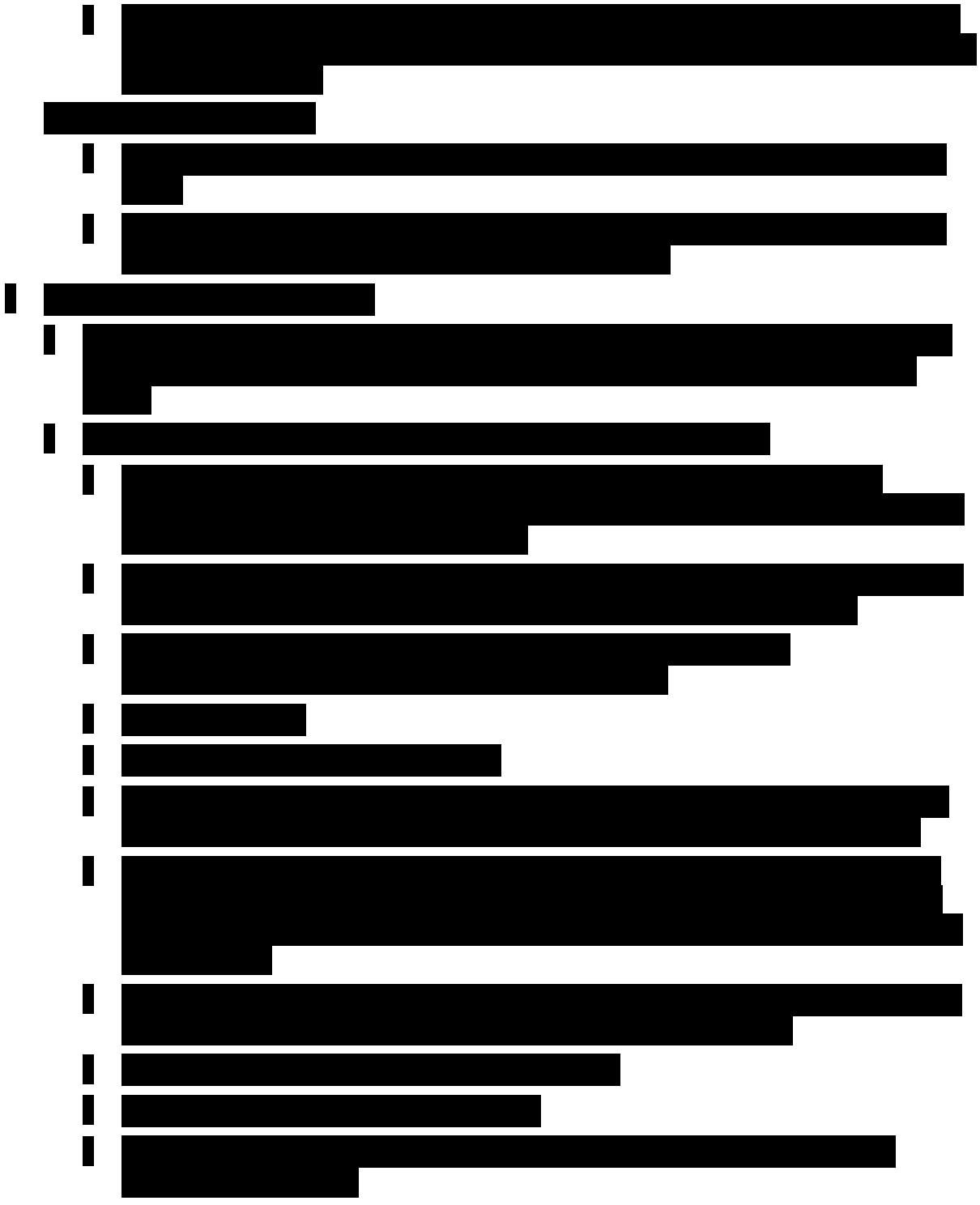
5.2 Contraception Recommendations

Contraception Requirements for Females

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

- Females, Non-Childbearing Potential

  [redacted]



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

5.3 Prohibited Medications/Therapy and Procedures

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] Additionally, the medication/treatment listed below are prohibitive due to the potential confounding impact to efficacy assessment and not due to any potential safety risk to the subject. When possible, the sponsor is to be notified before the prohibited medication/treatment is administered.

Prohibited treatments and procedures include, but are not limited to:

- Concurrent treatment with botulinum neurotoxin of any serotype for any indication (other than the study intervention)
- Medium depth to deep facial chemical peels [redacted] to the face
- Energy-based treatments [redacted] to the face
- Microneedling to the face
- Facial lift or cosmetic/surgical suspension threads (upper facial area or full face)
- Rhinoplasty
- Blepharoplasty
- [redacted]

During the study, all other investigational drugs are prohibited.

5.4 Prior and Concomitant Medications/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 medications/therapy and concomitant procedures 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.

[redacted]

[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 including, but not limited to, the following:

- [redacted]
- [redacted]
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- [redacted]
- Subject is significantly noncompliant with study procedures.

This is a single dose study and treatment will be administered on Day 1 only. In case of pregnancy or AE during the study, after study treatment is provided, the subject should continue in the study for safety follow-up.

In case the subject has a desire to end his/her participation, or is discontinued for any reason, the Premature Discontinuation Visit procedures should be completed.

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.

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 safety and efficacy 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/SAEs have been resolved.

5.7 Study Drug

OnabotA X is an intramuscular injectable [redacted] and will be prepared and administered on Day 1 only, as a single treatment. All components of the investigational product admixture will be supplied unblinded and labeled as required per US FDA requirement. Components will be packaged as three kits, as per Table 2. [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 the investigator-assessed baseline severity of FHL (FWS-FHL) at maximum contraction and investigator site. [redacted]

[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 3.12.

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

An independent DMC will be instituted to review interim safety and efficacy data to provide a dose [redacted] The interim analysis will occur after the majority of subjects have completed the Day 90 visit or prematurely discontinued. A snapshot will include all data collected up to the data cutoff date. Study sites, study team and subjects will remain blinded for the duration of the study.

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

The DMC will review the results of the interim analyses and make a recommendation to the sponsor in accordance with the DMC Charter.

A separate DMC charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications.

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 serious adverse event (SAE) within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual [Appendix FAppendix E] 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 after the last dose of study drug 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, 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. Partner pregnancy information will not 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 the primary analysis. Complete and specific details of the statistical analysis will be described in the SAP.

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 Efficacy Endpoint

Missing data will be imputed using multiple imputation (MI) method for the primary efficacy endpoint (see Section 7.4).

[redacted]

run;

[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.[25,26] [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 FWS-FHL 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 FWS-FHL severity at maximum contraction interaction.

[redacted]

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population. Safety evaluations include AEs, abbreviated physical examination, neurological assessment, and change from baseline in vital signs (body temperature, pulse rate, respiratory rate, and blood pressure [systolic and diastolic]). Safety endpoints will be summarized using descriptive statistics and/or shift tables, as applicable. For each safety endpoint evaluating change from baseline, the last nonmissing safety assessment before study intervention administration will be used as the baseline for all analyses of that endpoint.

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 the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study treatment according to the investigator
  - Any treatment-emergent AE related to study procedure according to the investigator
  - Any treatment-emergent AE related to study drug according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to death
- Any PDSOT AEs
- All deaths

Treatment-emergent AEs will be summarized by system organ class (SOC) and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific treatment-emergent AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and closest relationship to investigational product will be reported.

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.

Vital sign will be summarized for changes from baseline at each assessment timepoint.

7.6 Interim Analysis

An interim analysis is planned to occur after the majority of subjects have completed the Day 90 visit or prematurely discontinued. The interim analyses will be unblinded to a group of AbbVie personnel who

are not directly involved in ongoing day-to-day study conduct. Further details are provided in DMC Charter.

Key efficacy analyses will be performed for the interim analysis, as well as summaries of key 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 Type I error rate of α=0.05 for each OnabotA X group. The p-values will be presented as unadjusted p-values that are deemed statistically significant if $p \leq 0.05$.

7.8 Sample Size Determination

Approximately 120 subjects will be randomized into the study in a 1:1:1:1 ratio (30 in each group) yielding approximately 90 subjects receiving OnabotA X in the frontalis muscle for treatment of FHL. The sample size of 120 is chosen empirically to allow for an adequate safety data of subjects treated with OnabotA X for this indication.

The primary efficacy endpoint is the achievement of ≥ 1-grade improvement from baseline on the investigator-rated FWS-FHL at maximum contraction at Day 30. [redacted] Assuming [redacted] the sample size of N = 30 per group will provide 97% power.

All calculations are based on a 2-sided type I error rate of 0.05. [redacted]

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 of Technical Requirements for Pharmaceuticals for Human Use (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. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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 Good Clinical Practice (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
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease – 2019
CRF	case report form
DHEA	dehydroepiandrosterone
DMC	data monitoring committee
eCRF	electronic case report form
EDC	electronic data capture
ePRO	electronic patient-reported outcome device
FDA	Food and Drug Administration
FHL	forehead lines
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FWS	Facial Wrinkle Scale
FWS-FHL	Facial Wrinkle Scale – Forehead Lines
FWS-GL	Facial Wrinkle Scale – Glabellar Lines
[redacted]	[redacted]
GCP	Good clinical practice
GL	glabellar lines
[redacted]	[redacted]
IB	Investigator's Brochure
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

Abbreviation	Definition
[redacted]	[redacted]
ITT	intent-to-treat
IU	International units
IUD	intrauterine device
LCL	lateral canthal lines
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
N/A	not applicable
[redacted]	[redacted]
[redacted]	[redacted]
OnabotA X	onabotulinumtoxinA X
PCR	polymerase chain reaction
PDSOT	possible distant spread of toxin
PRO	patient-reported outcomes
PT	preferred term
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
TEAE	treatment-emergent adverse event
U	units
US	United States
VDS	verbal descriptor scale
WOCBP	woman of child-bearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-606: A Phase 2, Multicenter, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of OnabotulinumtoxinA X for Forehead Lines

Protocol Date: 18 July 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 to AbbVie, the ethics committee/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated.
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]	Study Project Manager II	Clinical Study Leadership
[redacted]	Vice President, Head of Clinical Development, Aesthetic Medicine	Therapeutic Area
[redacted]	Executive Director, Biostatistics	Statistics