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Protocol for Study M21-324

Glabellar lines: Safety and Efficacy of OnabotulinumtoxinA X in Subjects with Glabellar Lines

VERSION:	3.0	DATE:	07 September 2021
SPONSOR:	AbbVie Inc.	PLANNED NUMBER OF SITES:	Approximately 5
ABBVIE INVESTIGATIONAL PRODUCT:	OnabotA X	EudraCT:	Not applicable

FULL TITLE: A Phase 2a Multicenter Open-label Study to Evaluate the Safety and Efficacy of OnabotulinumtoxinA X in Subjects with Glabellar Lines

Incorporating Versions 1.0, 2.0, and 3.0

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 2a Multicenter Open-label Study to Evaluate the Safety and Efficacy of OnabotulinumtoxinA X in Subjects with Glabellar Lines	
Background and Rationale:	OnabotA X is an onabotulinumtoxinA investigational product being developed for the treatment of glabellar lines (GL). OnabotA X may offer an improved treatment option to patients based on its durability profile, and potential to deliver a prolonged patient benefit. This is a proof-of-concept study to evaluate the safety and exploratory efficacy of OnabotA X.
Objectives and Endpoints:	The primary objective of the study is to evaluate the safety of OnabotA X injection in the glabellar region of female subjects with severe GL. Safety will be assessed based upon adverse events (AEs), abbreviated physical examination (general appearance, head, ears, eyes, nose, throat, and neck), neurologic assessment, vital sign measurements (body temperature, pulse rate, respiration rate, and blood pressure [systolic and diastolic]), clinical laboratory tests (hematology, chemistry, urinalysis), electrocardiogram (ECG), immunogenicity, and hypersensitivity assessment.
Investigators:	Multicenter
Study Sites:	Approximately 5 sites in the United States.
Study Population and Number of Subjects to be Enrolled:	Approximately 90 female subjects with severe GL
Investigational Plan:	This is a 180-day, Phase 2a, open-label, proof-of-concept study to assess the safety and efficacy of a single [redacted] dose of 3 different formulations of OnabotA X (A, B, and C; each with varying amounts of the standard excipients in the formulation) in adult female subjects (≥ 18 years old) with severe GL.
Key Eligibility Criteria:	Adult female subjects aged 18 or older with severe GL based on the Facial Wrinkle Scale – Glabellar Lines (FWS-GL) Investigator and Subject scores.
Study drug and Duration of Treatment:	On Day 1, eligible subjects will receive a single treatment of 1 of 3 different formulations of OnabotA X [redacted] based on randomization, by intramuscular (IM) injections into the corrugator and procerus muscles.
Date of Protocol Synopsis:	07 September 2021

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 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 glabellar lines in 2001 and is one of the most common nonsurgical procedures in aesthetic medicine.[6]

A key factor contributing to patient satisfaction with aesthetic treatments is the durability of therapeutic benefit.[7,8] An enhanced duration could increase patient satisfaction and require fewer clinician visits and injections to maintain the therapeutic benefit. With the intent of developing a formulation of onabotulinumtoxinA that would potentially meet this clinical need, several prototype formulations were screened and lead candidate formulations of OnabotA X were identified. [redacted] OnabotA X formulations may offer an improved treatment option to patients based on their durability profile. This is a proof-of-concept study to evaluate the safety and exploratory efficacy of 3 different formulations of OnabotA X (A, B, and C; [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 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. The safety profile for the [redacted] dose of OnabotA X selected for evaluation in this study is expected to fall within that of BOTOX for the treatment of GL.

[redacted]

[redacted]

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.

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

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective of the study is to evaluate the safety of OnabotulinumtoxinA X injection in the glabellar region of subjects with severe GL.

The clinical hypothesis is that OnabotulinumtoxinA X has an acceptable safety profile when administered to the corrugator and procerus muscles in subjects with severe GL.

No estimands are defined for the safety evaluations.

3.2 Primary Endpoints

No primary efficacy endpoint is defined for this study. The primary objective of the study is an evaluation of safety.

3.3 Secondary Endpoints

No secondary efficacy endpoints are defined for this study.

3.4 Additional Efficacy Endpoints

Additional efficacy endpoints are:

- Number and proportion of subjects who achieve the following at maximum frown, based upon the FWS-GL – Investigator:
  - 1-grade improvement from baseline, by visit
  - 2-grade improvement from baseline, by visit
  - Achievement of None or Mild, by visit

- Number and proportion of subjects who achieve the following at maximum frown, based upon the FWS-GL – Subject:
  - 1-grade improvement from baseline, by visit
  - 2-grade improvement from baseline, by visit
  - Achievement of None or Mild, by visit
- Number and proportion of subjects who achieve a 2-grade improvement from baseline based upon both the FWS-GL Investigator and the FWS-GL – Subject (composite endpoint), at maximum frown, by visit
- Number and proportion of subjects who achieve the following at maximum frown, based upon the Allergan Glabellar Line Severity Scale (AGLSS) (assessed by an independent evaluating investigator):
  - 1-grade improvement from baseline, at Day 30 (among subjects who are rated at least Mild at baseline)
  - 2-grade improvement from baseline, at Day 30 (among subjects who are rated at least Moderate at baseline)
  - Achievement of None or Mild, at Day 30 (among subjects who are rated at least Moderate at baseline)
- Number and proportion of subjects who achieve the following at rest (among subjects who are rated at least Mild at baseline, at rest):
  - 1-grade improvement from baseline, by visit, based upon the FWS-GL Investigator
  - 1-grade improvement from baseline, by visit, based upon the FWS-GL Subject
  - 1-grade improvement from baseline, at Day 30, based upon the AGLSS

3.5 Safety Endpoints

Safety assessments include the following:

- Adverse Events
- Abbreviated Physical Examination (general appearance, head, ears, eyes, nose, throat, and neck)
- Neurologic Assessment
- Vital Sign Measurements (body temperature, pulse rate, respiration rate, and blood pressure [systolic and diastolic])
- Clinical Laboratory Tests (hematology, chemistry, urinalysis)
- ECG

3.6 Immunogenicity and Hypersensitivity Sampling

Immunogenicity

Blood samples for immunogenicity testing will be collected from all subjects treated with OnabotA X according to the Study Activities Table (Appendix D) at Day 1 (Baseline), Day 30, Day 90, and End-of-Study (Day 180 or Premature Discontinuation) visits. Collected samples will be processed to yield serum for detection of binding and neutralizing antibodies to OnabotulinumtoxinA.

Hypersensitivity Assessments

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 180-day, Phase 2a, open-label, proof-of-concept study to assess the safety and efficacy of a single [redacted] dose of 3 different formulations of OnabotA X (A, B, and C; [redacted]). The study will enroll approximately 90 adult female subjects (≥ 18 years old) with severe GL based on FWS-GL ratings. Approximately 5 sites in the United States will enroll subjects.

The study will include up to a 7-day Screening period, occurring from Day -14 to -7. On Day 1, eligible subjects will be randomized (1:1:1) to receive one [redacted] dose of Formulation A, B, or C of OnabotA X. The single treatment of study drug will be administered in an open-label manner as [redacted] to the corrugator and procerus muscles. Following treatment administration for each subject, the investigator will complete the Injector Experience Survey.

Each subject will be in the study for up to 180 days and have 9 visits after screening. Follow-up visits will be on Days 3, 7, 14, 30, 60, 90, 120, and 180 (exit). The visit at Day 3 will be permitted a window of ± 1 day, the visits at Days 7 and 14 will be permitted a window of ± 3 days, and the visits at Days 30, 60, 90, 120, and 180 (exit) will be permitted a window of ± 7 days. Safety parameters such as clinical laboratory test results, neurologic assessment, abbreviated physical examination, ECG, and vital signs will be monitored (see Operations Manual [Appendix F] Section 3). At Screening, Baseline (Day 1) prior to treatment, and study exit, 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 at Days 1, 30, 90, and 180 (exit).

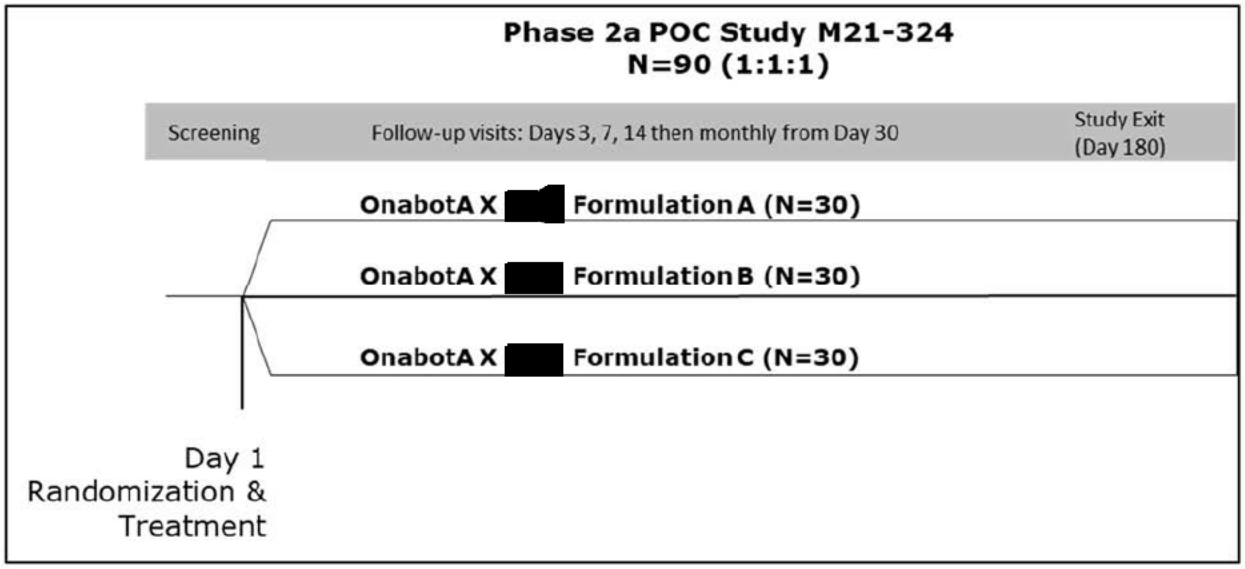
Additional efficacy will be evaluated based on FWS-GL-Investigator (assessed by an independent evaluating investigator), the FWS-GL-Subject, and the AGLSS.

Subjects who discontinue should complete the procedures outlined for the Premature Discontinuation visit as soon as possible, preferably within 2 weeks (see Appendix D Study Activities Table).

Further details regarding study procedures are in the Operations Manual (Appendix F) Section 3.

See Section 5.1 for information regarding eligibility criteria.

Figure 1. Study Schematic



POC = proof of concept; U = units

4.2 Discussion of Study Design

Choice of Control Group

No control group is used for this open-label proof-of-concept study.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All of the 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 female adults with 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

The [redacted] dose is selected for use in this study based on the labeled BOTOX Cosmetic dose for GL. Based on nonclinical DAS assay data, OnabotA X has demonstrated a [redacted] of response when compared to BOTOX. Treatment of moderate or severe GL at maximum contraction with doses higher than the approved dose of [redacted] have been well tolerated with AEs primarily local and

expected, based on the literature[10-12] [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. Rescreening is not allowed for individuals who do not meet key safety and efficacy Eligibility Criteria: numbers 4, 5, 6, 7, or 9. 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 institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult female, at least 18 years old.
- 3. Subject has sufficient visual acuity without the use of eyeglasses (contact lens use is acceptable) to accurately assess their facial lines
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- 8. Subject is willing and able to comply with procedures required in this protocol.

Disease Activity/Condition

- 9. Subject has severe GL at maximum frown as assessed by both the investigator and subject using the FWS-GL at Baseline.

Subject History

- 10. No history of known immunization to any botulinum toxin serotype

- [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
  - History of facial nerve palsy
  - Infection or dermatological condition at the site of study drug injection
  - Marked facial asymmetry, dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, excessively photodamaged skin, or the inability to substantially lessen facial lines even by physically spreading them apart
  - Any eyebrow or eyelid ptosis at baseline or Day 1 as determined by the investigator
- 14. No history of clinically significant medical conditions or any other reason that the investigator determines would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.
- 15. No clinically relevant or significant ECG abnormalities, [redacted]
- [redacted]
- 17. If the subject has received a SARS-CoV-2 vaccination, the subject must have completed their final dose at least 7 days prior to Day 1. Unvaccinated subjects may enroll in the study.
- 18. No reported use of any botulinum neurotoxin of any serotype for any indication within the 6 months prior to Day 1
- 19. No history of the following procedures or treatments in the specified period before enrollment (Day 1):
  - 3 months: any mid-or upper-facial cosmetic procedures with superficial resurfacing/planning (e.g., microdermabrasion, dermaplaning), superficial chemical peels (e.g., glycolic acid), or nonablative energy-based facial treatments (e.g., radiofrequency, ultrasound, electromagnetic, laser, light).

- 6 months: any mid- or upper-facial aesthetic treatments targeting deeper tissue layers including, but not limited to, any ablative or non-ablative laser resurfacing, fractionated laser resurfacing, radiofrequency, ultrasound treatment, medium-depth or deep chemical peels (eg, trichloroacetic acid [TCA] above 35% and phenol), or permanent make-up.
- 18 months: any periorbital, mid-facial, or upper-facial treatment with HA soft tissue/dermal fillers

- 20. No history of prior treatments to the mid- or upper face such as radiation, surgical treatment (including but not limited to cosmetic procedures such as brow lift, eyelid surgery, facelift, rhinoplasty, or other reconstructive surgery), cosmetic/surgical suspension threads, non-HA soft tissue/dermal fillers, synthetic implantation, and/or autologous fat transplantation

Contraception

- 21. For all females of child-bearing potential, a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Day 1 prior to the first dose of study drug.
- 22. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is effective from Study Day 1 through study exit. Female subjects of non-childbearing potential do not need to use birth control.
- 23. Female who is not pregnant or breastfeeding, and is not considering becoming pregnant or donating eggs during the study.

Concomitant Therapy

- 24. Subject must not have been treated with any investigational drug within 30 days prior to the first dose of study drug or is currently enrolled in another clinical study or was previously enrolled in this study.
- 25. Subject must not have received any live vaccine within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.

5.2 Contraception Recommendations

Contraception Requirements

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:

- Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
- Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

2. Postmenopausal female
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level ≥ 30 International Unit/L.

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy throughout the duration of the study
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system.
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
    - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1.
    - Male or female condom with or without spermicide.
    - Cap, diaphragm, or sponge with spermicide.
    - A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

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. 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 drug)
- Medium depth to deep facial chemical peels (i.e., TCA above 35% and phenol) to the face
- Energy-based treatments (e.g., intense pulsed light, Clear + Brilliant®, monopolar radiofrequency, microfocused ultrasound) to the face
- Microneedling to the face
- Facial lift (partial or full face) or cosmetic/surgical suspension threads
- Rhinoplasty
- Blepharoplasty
- Synthetic implantation (e.g., Gore-Tex) to the mid or upper face
- Autologous fat transplantation to the mid or upper face
- non-HA soft tissue/dermal fillers to the mid or upper face
- HA soft tissue/dermal fillers to the mid or upper face
- Permanent make-up to the mid or upper face

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.

Co-administration of aminoglycosides or agents that could interfere with neuromuscular transmission (e.g., curare-like agents) or muscle relaxants are to be used with caution as the effects of the toxin, theoretically, could be potentiated.

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 and estrogens and their derivatives, dehydroepiandrosterone (DHEA), etc.
- Topicals (anywhere on the body) including testosterone & estrogens and their derivatives, DHEA, etc.
- Androgel, Axiron, Testim, Fortesta, Vogelxo
- Emepelle (methyl estradiolpropanoate), Rejuvenate, All Natural Bioidentical Estradiol, Emerita Phytoestrogen

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 may be found in the 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

The potential impact of OnabotA X on SARS-CoV-2 vaccination is unknown. If the subject has received a SARS-CoV-2 vaccination, the subject must have completed their final dose at least 7 days prior to Day 1.

Following Day 1, the decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

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:

- Clinically significant abnormal laboratory results or AEs, as determined by the investigator or sponsor.
- The investigator believes it is in the best interest of the subject.
- 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.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- Subject is significantly noncompliant with study procedures.

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.

Refer to the Operations Manual in Appendix F, Section 2 and Section 3, for details on how to handle study activities/procedures.

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 (SAEs) have been resolved.

5.7 Study Drug

[redacted]

Table 1. Study Drug Identification

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
[redacted]				

N/A = not applicable; U = unit(s)

[redacted]

Immediately before dispensing the study drug, the investigator (or appropriately trained designee) will write the subject's identification number and the date on the label. Further details are provided in the pharmacy manual.

5.8 Randomization/Study 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 (1:1:1).

Randomization will be central by block randomization. The same block will not be shared across investigative sites.

All subjects will be treated with OnabotA X (Formulation A, B, or C) in an unblinded, open-label manner.

Study drug will be labeled with study kit numbers. The IRT system will provide the designated site personnel with the specific study kit number for each subject after eligibility is confirmed on Day 1. The designated site personnel will receive and maintain the IRT confirmation notifications for each transaction. The designated, qualified site personnel will prepare the study drug per the instructions in the pharmacy manual and per subject randomization, and will draw up the required administration volume into an appropriately sized syringe(s) and label the syringe(s) with the subject's assigned identification number (and other information as specified in the pharmacy manual for a given formulation). At the time of study drug administration, the designated site personnel will provide the labeled dosing syringe(s) to the trained qualified physician who will inject the subject according to the study drug administration instructions.

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 the IRB, regulatory authorities (as applicable), and AbbVie.

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.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

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 drug, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

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 contract 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 until 30 days after the last dose of study drug or until completion of the study or the last follow-up visit, whichever is longer, will be collected, 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.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an investigational medicinal product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

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

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

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. To assess possible local and distant spread of toxin, Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) that may be associated with botulinum toxin effects have been identified, and the final terms will be listed in the statistical analysis plan. All AEs will be medically reviewed by the Sponsor on a regular basis throughout the duration of the study to identify PDSOT events, which will be assessed for severity, frequency, and trending and will be summarized in study 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.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

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.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy and baseline analyses. Subjects in this population will be analyzed per randomization, regardless of actual treatment received.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. The Safety Analysis Set will be used for all safety analyses. Subjects in this population will be analyzed according to the actual treatment received.

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

Not applicable.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

Not applicable.

Summary and Analysis of Secondary Endpoints

Not applicable.

Summary and Analysis of Additional Efficacy Endpoints

The number and percentage (or proportion) of the subjects who are responders will be summarized, 95% confidence interval will be calculated with an exact method based on the binomial distribution for percentage (or proportion) of the subjects. Observed data without imputation will be used.

For efficacy endpoints using AGLSS, subsets of subjects will be used as follows:

- 1-grade improvement from baseline at maximum frown or at rest: only subjects with corresponding baseline score being at least mild are included
- 2-grade improvement from baseline at maximum frown: only subjects with corresponding baseline score being at least moderate are included
- Achieving none or mild at maximum frown: only subjects with corresponding baseline score being at least moderate are included

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population. The safety parameters will include incidence of AEs and change from baseline in vital signs, laboratory assessments, and ECG. 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 level of 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 and laboratory measurements will be summarized for changes from baseline at each assessment timepoint.

Analyses for ECGs and other safety endpoints will be addressed in the SAP.

Statistical Analyses for Immunogenicity and Hypersensitivity

Samples from subjects treated with OnabotA X will be analyzed for anti-drug antibodies using validated assays. Immunogenicity results, manifested as the binding antibodies and neutralizing antibodies, will be summarized in a table for each sampling timepoint.

Results from hypersensitivity evaluations, if any are conducted, will be listed.

7.6 Overall Type I Error Control

Not applicable.

7.7 Sample Size Determination

This is a proof-of-concept study with a primary objective of evaluating safety. A sample size of 90 (30 per treatment group) subjects will provide sufficient data for safety evaluations of OnabotA X to support future placebo-controlled studies in larger sample sizes, powered for efficacy evaluations.

8 ETHICS

8.1 Institutional Review Board (IRB)

The protocol, investigator brochure, informed consent form(s), recruitment materials, and all subject materials will be submitted to the 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 IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be 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.

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. 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, 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
COVID-19	Coronavirus Disease – 2019
CRF	case report form
DAS	Digit Abduction Score
DHEA	dehydroepiandrosterone
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FWS-GL	Facial Wrinkle Scale – Glabellar Lines
GCP	Good clinical practice
GL	glabellar lines
[redacted]	[redacted]
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IM	intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	interactive response technology
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
OnabotA X	onabotulinumtoxinA X
PCR	polymerase chain reaction
PDSOT	possible distant spread of toxin
POC	proof-of-concept
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

Abbreviation	Definition
QTcF	QT interval corrected for heart rate using Fridericia's formula
RSI	reference safety information
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	unit(s)
WOCBP	woman of childbearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-324: A Phase 2a Multicenter Open-label Study to Evaluate the Safety and Efficacy of OnabotulinumtoxinA X in Subjects with Glabellar Lines

Protocol Date: 07 September 2021

Clinical research studies sponsored by AbbVie are subject to the ICH 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), 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., 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, 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]	Director, Clinical Program Development	Clinical Study Leadership
[redacted]	Principal Medical Writer	Medical Writing
[redacted]	Vice President, Head of Clinical Development, Aesthetic Medicine	Therapeutic Area
[redacted]	Vice President, Non-Clinical and Translational Science	Therapeutic Area
[redacted]	Executive Director, 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), Section 2 and Section 3.

Study Activities Table

	Screening	Baseline/ Treatment	Follow-up							
Activity	Day –14 to Day –7	Day 1	Day 3 (± 1 day)	Day 7 (± 3 days)	Day 14 (± 3 days)	Day 30 (± 7 days)	Day 60 (± 7 days)	Day 90 (± 7 days)	Day 120 (± 7 days)	Day 180 (± 7 days) or Premature Discontinuation
INTERVIEWS										
Informed consent/Privacy authorization	✓									
Eligibility criteria	✓	✓								
Demographics including Fitzpatrick skin phototype	✓									
Medical/surgical history	✓	✓								
Prior/concomitant therapy and procedures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Subject training on FWS-GL	✓	✓								
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
QUESTIONNAIRES										
FWS-GL – Investigator assessment; at rest and maximum contraction (independent evaluator)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
FWS-GL – Subject assessment; at rest and maximum contraction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AGLSS – Investigator assessment; at rest and maximum contraction		✓				✓				
PHOTOGRAPHY										
Standardized facial photography		✓	✓	✓	✓	✓	✓	✓	✓	✓
EXAMINATIONS										
Abbreviated physical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital sign measurements	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neurologic assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LABS										
12-lead ECG	✓					✓	✓		✓	✓

	Screening	Baseline/ Treatment	Follow-up							
Activity	Day –14 to Day –7	Day 1	Day 3 (± 1 day)	Day 7 (± 3 days)	Day 14 (± 3 days)	Day 30 (± 7 days)	Day 60 (± 7 days)	Day 90 (± 7 days)	Day 120 (± 7 days)	Day 180 (± 7 days) or Premature Discontinuation
Serum pregnancy test (WOCBP)	✓									
Urine pregnancy test (WOCBP)		✓								✓
Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis	✓				✓	✓	✓	✓	✓	✓
Collection of blood samples for immunogenicity testing		✓				✓		✓		✓
℞ TREATMENT										
Randomization and study drug administration		✓								
Injector Experience Survey		✓								

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 2.0	07 June 2021
Version 1.0	19 March 2021

Version 3.0

The primary purpose of the version update to 3.0 is to incorporate ECGs into the study design, per FDA feedback. Edits were made in Section 1. Synopsis; Section 4.1 Overall Study Design and Plan; Section 5.1 Eligibility Criteria; Section 7.5 Statistical Analyses for Safety; Appendix D, Activity Schedule; Appendix F, Operations Manual.

Additional edits were made, as follows:

Instructions to collect concomitant medications and concurrent procedures at each visit were added to Section 5.4 Prior and Concomitant Therapy.

For the definition of PDSOT, the word "potential" was corrected to "possible" (Section 6.1 Complaints and Adverse Events).

The following verbiage in Section 6.1 Complaints and Adverse Events was copied verbatim into Appendix F, Operations Manual (Section 4.1): "All AEs reported from the time of study drug administration until 30 days after the last dose of study drug or until completion of the study or the last follow-up visit, whichever is longer, will be collected, 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."

Categories of study drug-related AEs and study procedure-related AEs were added to the overview of AEs analysis described in Section 7.5 Statistical Analyses of Safety.

Protocol signatories were updated to be current (Appendix C List of Protocol Signatories).

In Appendix F, Operations Manual, the Fitzpatrick Skin Phototype scale was added, COVID-19-related acceptable protocol modifications were deleted for standardized facial photography, paper forms were removed from the procedures for SAE reporting, and height and weight were added to the Baseline collection of vital signs.

Version 2.0

[redacted]

Edits to align with these study design updates were made in the following sections of the protocol: Section 1. Synopsis; Section 2.1 Background and Rationale; Section 3.1 Objectives, Hypotheses, and Estimands; Section 4.1 Overall Study Design and Plan; Section 4.2 Discussion of Study Design; Section 5.1 Eligibility Criteria; Section 5.8 Randomization/Study Drug Assignment; Section 7.2 Definition for Analysis Populations; Section 7.7 Sample Size Determination; Appendix D, Activity Schedule; Appendix F, Operations Manual.

Additional edits were made, as follows:

The non-emergency medical contact was changed (Cover page and Appendix F, Operations Manual).

The AGLSS endpoints were edited to specify which subjects were included in each analysis, based on baseline AGLSS grades (Section 3.4 Additional Efficacy Endpoints)

A study schematic was added to Section 4.1 Overall Study Design and Plan.

An Injector Experience Survey was added to the study, to be completed by the Investigator following study drug administration on Day 1 (Section 4.1 Overall Study Design and Plan; Appendix D, Activity Schedule; Appendix F, Operations Manual).

Eligibility criteria that, if failed, would preclude a subject from being permitted to rescreen for the study, were identified at the beginning of Section 5.1 Eligibility Criteria.

Diluent was added to the list of Investigational Products in Section 5.7 Study Drug and Appendix F, Operations Manual. Allergan (rather than Allergan Pharmaceuticals Ireland) was listed as the manufacturer in Section 5.7 Study Drug. The verbiage "Formulations A, B, or C" was included in Section 5.7 Study Drug, Section 5.8 Randomization/Study Drug Assignment, and Appendix F, Operations Manual.

Updated verbiage was incorporated to align with other aesthetic toxin protocols, in Section 5.4 Prior and Concomitant Therapy and Section 5.5 Withdrawal of Subjects and Discontinuation of Study.

The FWS-GL Investigator assessment was changed to be completed at all timepoints by an independent evaluating sub-investigator; the AGLSS will now be completed by the principal investigator (Appendix D, Activity Schedule; Appendix F, Operations Manual).

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M21-324

Glabellar lines: Safety and Efficacy of OnabotulinumtoxinA X in Subjects with Glabellar Lines

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	OnabotA X

FULL TITLE: A Phase 2a Multicenter Open-label Study to Evaluate the Safety and Efficacy of OnabotulinumtoxinA X in Subjects with Glabellar Lines

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] Allergan Aesthetics, an AbbVie company 2525 Dupont Drive Irvine, CA 92612 **EMERGENCY 24-hour Number:** **+1 (973) 784-6402**	Mobile: [redacted] Email:
Sponsor/Non-Emergency Medical Contact:	[redacted] Allergan Aesthetics, an AbbVie Company 2525 Dupont Drive Irvine, CA 92612	Mobile: [redacted] Email:
Safety Concerns	Aesthetics Safety Team 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 (833) 942-2226 Email: SafetyManagement_Aesthetics_Devices@abbvie.com
SAE Reporting outside of EDC	Email: IR-Clinical-SAE@allergan.com	Fax: +1 (714) 796-9504 Backup fax: +1 (714) 246-5295
Certified Central Clinical Lab	LabCorp Drug Development 8211 SciCor Drive Indianapolis, IN 46214	Phone: +1 (317) 271-1200 Toll free: +1 (800) 462-8885 Fax: +1 (317) 273-4030
ECG vendor	ERT 1818 Market Street 10th floor Philadelphia, PA 19103	Phone: +1 (215) 282-5583 Mobile: +1 (215) 960-5834
Immunogenicity Sample Labs	BAB: BioAgilytix Labs 2300 Englert Dr Durham, NC 27713	Phone: +1 (919) 381-6097 Fax: +1 (919) 381-6099
	NAB: Battelle Memorial Institute 1425 Plain City-Georgesville Road (FedEx/UPS Only S.R. 142 NE) West Jefferson, OH 43162	Phone: +1 (800) 201-2011; +1 (614) 424-5833 Fax: +1 (614) 458-5833
Photography	Canfield Scientific, Inc. 4 Wood Hollow Road Parsippany, NJ 07054	Phone: +1 (973) 434-1200

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent sections. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed with agreement from the sponsor:

- If permitted by local regulations, the IRB, and the subject, postbaseline visits may be conducted virtually, including only prior/concomitant therapy, AE assessment, and partial neurologic assessment.
- During a virtual visit, the following activities do not need to be performed: abbreviated physical examination, vital signs, FWS-GL assessments by investigator and subject, AGLSS (independent evaluating investigator assessment), standardized facial photography, immunogenicity blood sampling, urine pregnancy testing.
- Clinical laboratory assessments and ECGs may be skipped, unless the investigator has a significant concern and it is possible to arrange for the subject to have laboratory work and/or ECG done at an appropriate local facility. The local laboratory draw and/or ECG should be scheduled within 7 days of the missed scheduled visit, if possible.
- Study Visits should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modification is allowed with sponsor approval:
  - If the Day 1 visit cannot occur within 30 days of Screening, then the subject will be considered a screen failure and must be rescreened to participate in the study.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Activity Schedule.

Activities are grouped by category (Interview, Examinations, etc.). Further information about each activity is provided in Section 3.

All Screening and Baseline visit procedures must be performed onsite.

SCREENING (Day -14 to -7):

INTERVIEW	• Informed consent/privacy authorization • Eligibility criteria • Demographics • Fitzpatrick Skin Phototype	• Medical/surgical history • Prior/concomitant therapy and procedures • Subject training on FWS-GL • Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment
LABS	• 12-lead ECG • Serum pregnancy test (women of childbearing potential; WOCBP)	• Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis

BASELINE/TREATMENT (DAY 1):

INTERVIEW	• Eligibility criteria • Medical/surgical history	• Prior/concomitant therapy and procedures • Subject training on FWS-GL • Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction • AGLSS – Investigator assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs (including height and weight at baseline)	• Neurologic assessment
LABS	• Urine pregnancy test (WOCBP)	• Collection of blood sample for immunogenicity testing
TREATMENT	• Randomization • Study drug administration	• Injector Experience Survey

On Day 1, all assessments and sample collections need to be done prior to randomization. After receiving study drug on Day 1, the subject must remain in the office for at least 2 hours for observation of AE. In suspected cases of anaphylaxis, blood samples should be collected within 2 hours or as soon as possible.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Activity Schedule.

Activities are grouped by category (Interview, Examination, etc.). Further information about the activities is presented in Section 3.

If permitted by local regulations, the IRB, and the subject, postbaseline visits may be conducted virtually. See Section 2 for additional detail on COVID-19 pandemic-related protocol modifications.

DAY 3 (± 1 DAY):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment

DAY 7 (± 3 DAYS):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment

DAY 14 (± 3 DAYS):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment
LABS	• Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis	

DAY 30 (± 7 DAYS):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction • AGLSS – Investigator assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment
LABS	• 12-lead ECG • Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis	• Collection of blood sample for immunogenicity testing

DAY 60 (± 7 DAYS):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment
LABS	• 12-lead ECG	• Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis

DAY 90 (± 7 DAYS):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment
LABS	• Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis	• Collection of blood sample for immunogenicity testing

DAY 120 (± 7 DAYS):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment
LABS	• 12-lead ECG	• Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis

DAY 180/PREMATURE DISCONTINUATION (± 7 DAYS):

INTERVIEW	• Prior/concomitant therapy and procedures	• Adverse event assessment
QUESTIONNAIRES	• FWS-GL – Investigator assessment; at rest and maximum contraction (by an independent evaluating sub-investigator)	• FWS-GL - Subject assessment; at rest and maximum contraction
PHOTOGRAPHY	• Standardized facial photography	
EXAMINATIONS	• Abbreviated physical examination • Vital signs	• Neurologic assessment
LABS	• 12-lead ECG • Urine pregnancy test (WOCBP) • Collection of nonfasting blood and urine samples for hematology/chemistry/urinalysis	• Collection of blood sample for immunogenicity testing

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject, the benefits and risks anticipated from participation in the study and will answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Photographs will be taken for research purposes, and may also be used for education, commercial, and/or marketing purposes. To participate in this study, the subject must consent to having photographs taken for research but may still participate if he/she declines use of the photographs for other purposes. The sponsor shall have full ownership rights to any photographs derived from the study.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed because of participation in the study can be found in the informed consent form.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional temporary verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

3.2 Medical/Surgical History

A complete medical history including demographics; history of tobacco, alcohol, and drug use; and Fitzpatrick skin phototype will be taken at screening.

Fitzpatrick skin phototypes are defined as follows[1]:

I = Always burns, never tans
II = Always burns easily, tans minimally
III = Burns moderately, tans uniformly
IV = Burns minimally, always tans well
V= Rarely burns, tans profusely
VI = Never burns

The subject's medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment. Any abnormal findings from screening assessments (e.g., laboratory assessments, ECG, neurologic assessment) should be captured as medical history.

3.3 Subject Training on FWS-GL

At the Screening and Day 1 visits, subjects will view a training video on how to assess their GL severity using the FWS-GL-Subject. At any time during the study, subjects may view the training video again, if the site considers it to be necessary or helpful.

3.4 Adverse Event Assessment

Please refer to Section 4.1.

3.5 Immunogenicity and Hypersensitivity Sampling

Immunogenicity Sampling

Blood samples for immunogenicity testing will be collected from all subjects according to the Study Activities Table (Protocol, Appendix D) at Day 1 (Baseline), Day 30, Day 90, and End-of-Study (Day 180 or Premature Discontinuation) visits. Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory. Collected samples will be processed to yield serum for analysis.

A 2-tier assay approach will be used for the detection of binding and neutralizing antibodies to OnabotulinumtoxinA in human serum. In Tier 1, serum samples will be screened using a validated enzyme-linked immunosorbent assay (ELISA). The positive samples will subsequently be immunodepleted to confirm that the antibodies were specifically binding to OnabotulinumtoxinA and then titered to assess the magnitude of antibodies present. In Tier 2, only samples that are confirmed positive in the ELISA will be tested for neutralizing antibodies to OnabotulinumtoxinA using a validated assay.

Samples collected will also be used for investigative purpose in characterizing the assay.

There are no pandemic or natural disaster-related protocol modifications for immunogenicity samples. If a site visit is missed at which immunogenicity samples were planned to be collected, this assessment will be skipped for that timepoint.

Hypersensitivity Assessments

In suspected cases of anaphylaxis or systemic hypersensitivity reactions (see Appendix 7.2), blood samples for testing of biomarkers (i.e., tryptase) should be collected within 2 hours after dosing or as soon as possible after the event. The sponsor may require additional testing be conducted. Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

Subjects who experience anaphylaxis (regardless of seriousness) or serious systemic hypersensitivity will be managed per standard of care and referred to an allergist/immunologist for further assessment.

Subjects who experience systemic hypersensitivity reactions will be followed until stabilization or resolution of the event.

3.6 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 2; height and weight will also be collected, at the baseline visit. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 5 minutes.

Measurements should be assessed consistently throughout the study. Vital signs measurements determined prior to dosing on Day 1 will serve as baseline.

There are no pandemic or natural disaster-related protocol modifications for vital signs. If a site visit is missed at which vital signs were planned to be collected, this assessment will be skipped for that timepoint.

3.7 Abbreviated Physical Examination

An abbreviated physical examination, including general appearance, head, ears, eyes, nose, throat, and neck, will be performed at the designated study visits as specified in Section 2. The physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at the Baseline Visit prior to the first dose of study drug should be recorded in the subject's medical history. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

There are no pandemic or natural disaster-related protocol modifications for physical examinations. If a site visit is missed at which a physical examination was planned, this assessment will be skipped for that timepoint.

3.8 Clinical Laboratory Tests

The blood samples for serum chemistry tests will be collected nonfasting. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

If a laboratory test value at Screening is outside the reference range and the investigator considers the laboratory result to be clinically significant, the subject will be a screen failure and will be referred for follow-up with their physician. Laboratory abnormalities at Screening will be captured as medical history for enrolled subjects.

If a post-baseline laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will record the result as an AE, repeat the test to verify the value, and:

- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment

<table>
<tr><th colspan="2">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th></tr>
<tr><td>Hematocrit
Hemoglobin
Red blood cell (RBC) count
White blood cell (WBC) count
Neutrophils
Bands
Lymphocytes
Monocytes
Basophils
Eosinophils
Platelet count (estimate not acceptable)
International normalized ratio (INR)</td><td rowspan="3">Blood urea nitrogen (BUN)
Creatinine
Total bilirubin
Direct and indirect bilirubin
Gamma-glutamyl transferase (GGT)
Albumin
Alanine transaminase (SGPT/ALT)
Aspartate transaminase (SGOT/AST)
Alkaline phosphatase
Sodium
Potassium
Calcium
Inorganic phosphorus
Uric acid
Cholesterol
Total protein
Glucose
Triglycerides
Bicarbonate/CO_2
Chloride</td></tr>
<tr><th>Urinalysis</th></tr>
<tr><td>Specific gravity
Ketones
pH
Protein
Blood
Glucose</td></tr>
</table>

Pregnancy Tests

Serum pregnancy tests will be performed at Screening and urine pregnancy tests will be performed at Day 1 prior to treatment, for all female subjects of childbearing potential. Females of child-bearing potential must have a negative pregnancy test result at Day 1 prior to administration of study drug.

Additional urine pregnancy tests will be performed at the exit visit, and may be conducted at any visit, if deemed necessary by the investigator.

There are no pandemic or natural disaster-related protocol modifications for urine pregnancy testing. If a site visit is missed at which a urine pregnancy test was planned, this assessment will be skipped for that timepoint. (Screening and Day 1 visits are mandatory to occur onsite.)

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations due to a pandemic or natural disaster prevent the subject from having blood drawn for laboratory testing at the study site, it may be skipped unless the investigator has a significant concern and it is possible to arrange for the subject to have laboratory work done at a local laboratory, hospital, or other facility. The local laboratory draw should be scheduled within 7 days of the missed scheduled visit, if possible. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. The investigator should review local laboratory results as soon as possible.

3.9 Neurologic Assessment

[redacted]

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations due to a pandemic or natural disaster prevent the subject from completing an in-person visit, a partial neurologic assessment could be conducted remotely, to the best of ability by observing the subject via video call, if subject is in good health and a

video call is possible to arrange. In this case, the missing components of the neurologic assessment must be documented as not performed.

3.10 12-Lead Electrocardiogram

12-Lead Electrocardiogram (ECG)

All subjects will undergo conventional 12-lead ECG using standardized equipment and electrode placement at the visits outlined in the study activities table (Protocol Appendix D). Subjects are to be in a semirecumbent position for at least 10 minutes prior to starting the tracing. Single, legible/readable ECG tracings will be taken at all timepoints. When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection.

A qualified third-party vendor will read the ECGs and report the findings as normal, abnormal, or unable to evaluate.

For screening ECGs, prespecified significant abnormal findings will be flagged as exclusion alerts, and a third-party vendor will generate an exclusion alert for the site and the sponsor. For all subsequent ECGs, a qualified third-party vendor will also report the appearance of any new, prespecified significant abnormal findings and generate a protocol alert for the site and the sponsor.

The cardiologists will be blinded to participant study intervention assignments. If the ECG finding is abnormal, they will specify the abnormality or give a diagnosis, whenever it is possible. ECG reports will be provided to the investigator and the sponsor via a secure portal within 24 hours of screening and within 72 hours for all other visits.

Before study intervention, if the ECG finding is clinically significant, the investigator must capture the finding in the medical history eCRF. After study intervention, if the pre-existing finding becomes worse and is clinically significant or the new ECG finding is clinically significant, the investigator must capture the AE in the AE eCRF. Hard copies of the ECG tracings will be kept in the study files at the investigator's site.

The ECG will be assessed for the following measures: heart rate, QRS duration, QT interval, QTcB interval, QTcF interval, ST segment, RR interval, PR interval, and qualitative results.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event the ECG may not be performed due to study modifications related to the COVID-19 pandemic, it may be skipped for that timepoint unless the investigator has a significant concern and an arrangement can be safely made to have an alternative acceptable local facility perform the ECG.

3.11 Facial Wrinkle Scale – Glabellar Lines (FWS-GL)

Investigators' and subjects' assessments of the severity of GL at rest and maximum contraction using the FWS-GL are based on the following scale:

0 = None

1 = Mild

2 = Moderate

3 = Severe

The FWS-GL scales will be provided by the sponsor to each study site. Both versions of the scale provide photographic examples of GL severity at rest and at maximum contraction. Prior to enrolling subjects, physician investigators will be trained in grading GL severity using the FWS-GL to ensure that severity is graded consistently at each site and across all sites. For this training, the same set of images will be used for all raters and all sites.

The FWS-GL must be evaluated by a qualified, trained, physician sub-investigator other than the principal investigator who administers the study drug and who completes all other assessments (described in Section 2 as an "independent evaluating investigator"). The FWS-GL is the only assessment in the study that this sub-investigator will complete. The FWS-GL assessment is to be performed by the same sub-investigator throughout the study whenever possible. If it is not possible to use the same assessor to follow the subject, it is recommended that the FWS-GL assessments overlap (assess the subject together and discuss findings) for at least 1 visit for a given subject. The sub-investigator who performs the FWS-GL assessment must do so independent of the investigator who completes the AGLSS, and the results of the FWS-GL and AGLSS assessments must not be discussed.

Subjects will also be provided standardized training in grading GL severity using the FWS-GL to ensure that severity is scored consistently. Instructions on using the FWS-GL will be provided prior to performing the assessment. Standard mirrors (non-magnifying mirrors) will be used by the subject to aid in self-assessments.

Investigators and subjects will assess GL severity using the FWS-GL at the same time. However, assessments must be independent of each other, and the results of the assessments must not be discussed. The investigator and subject must grade the severity of GL first at rest and then at maximum contraction, using the FWS-GL.

There are no pandemic or natural disaster-related protocol modifications for the FWS-GL scale. If a site visit is missed at which this assessment was planned, the assessment will be skipped for that timepoint.

3.12 Allergan Glabellar Line Severity Scale (AGLSS)

Similar to the FWS-GL, the AGLSS assessments are to be conducted at rest and maximum contraction. The scale provides photographic examples of GL severity at rest and at maximum contraction; it uses a different set of photographs than the FWS-GL scales.

The AGLSS uses the following scale:

0 = None

1 = Mild

2 = Moderate

3 = Severe

The AGLSS will be provided by the sponsor to each study site. Prior to enrolling subjects, physician investigators will be trained in grading GL severity using the AGLSS to ensure that severity is graded consistently across all sites. For this training, the same set of images will be used for all raters and all sites. The AGLSS assessment is to be performed by the principal investigator; it must not be conducted by the sub-investigator who conducts the FWS-GL assessments (see Section 3.10). These 2 investigators must perform the assessments independently of each other, and the results of the assessments must not be discussed.

The investigator must grade the severity of GL first at rest and then at maximum contraction, using the AGLSS.

There are no pandemic or natural disaster-related protocol modifications for the AGLSS. If a site visit is missed at which this assessment was planned, the assessment will be skipped for that timepoint.

3.13 Standardized Facial Photography

Standardized digital facial photography will be performed prior to injection of study drug for all subjects at the times described in Section 2. Images will be taken by study site staff of each subject's face from the front at rest and at maximum contraction. Each site will receive documented training and instructions on taking photographs.

Conditions of photography will be standardized across all photographs, including camera equipment, exposure, background, lighting, and focal length. Ideally, the same photographer will take all required photographs. A qualified third-party vendor will provide instructions for taking photographs and processing digital photographs. All digital images will be transferred to the sponsor at the end of the study.

Photographs may be used for education, commercial, and/or marketing purposes. To participate in this study, the subject must consent to having photographs taken for research but may still participate if he/she declines use of the photographs for other purposes. The sponsor shall have full ownership rights to any photographs derived from the study.

There are no pandemic or natural disaster-related protocol modifications for standardized facial photography. If a site visit is missed at which photography was planned, it will be skipped for that timepoint.

3.14 Study Drug Adminstration

Study drug will be dispensed to site personnel at Baseline (Day 1), as specified in Section 2.1, and will be administered after all other baseline (Day 1) procedures are completed.

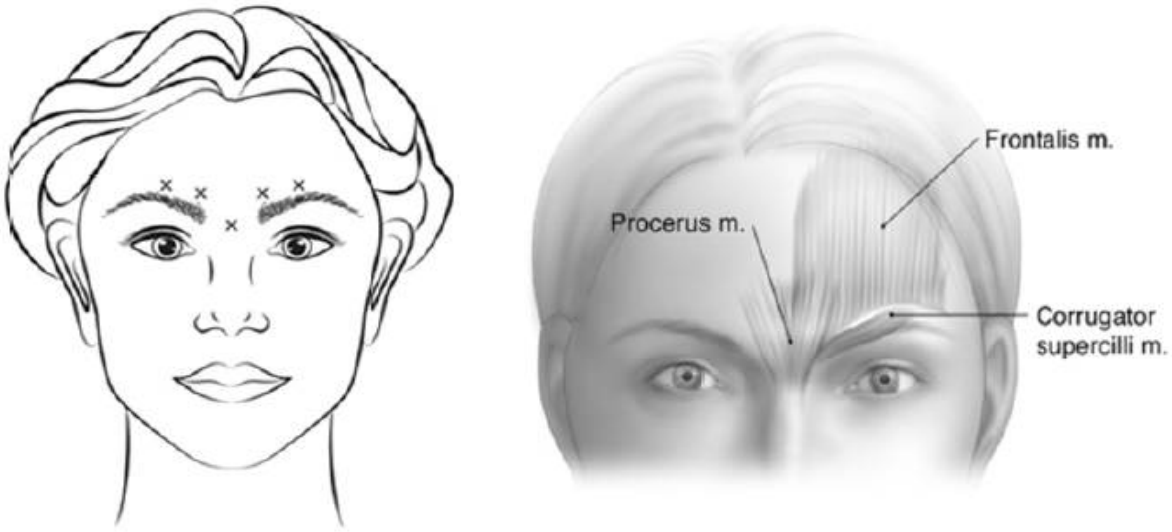
Only the principal investigator as a trained and medically qualified physician is authorized to administer the study drug. Study-specific training for GL injections is provided to investigators via a video with injection demonstration, and review of injection techniques as outlined in the protocol. The video is available on the training portal for injectors to access at any time as a refresher course.

The study intervention will be administered as intramuscular (IM) injections at 5 different injection sites in the glabellar complex (Figure 1).

Glabellar Line (GL) Injection Technique

Prior to injection, the skin at the injection sites and surrounding areas will be cleansed with antimicrobial solution. Injections will be given using a sterile needle. Each injection will contain 0.1 mL. Injections must be given with the bevel oriented superiorly and laterally. The first injection will be made to the midline at the base of the procerus muscle. The next 4 injections will be made bilaterally (i.e., 2 injections per side) into each corrugator muscle (Figure 1). The corrugators will be injected inferomedially near the origin of the supratrochlear nerve and superolaterally to the superior middle aspect ≥ 1 cm above the bony orbital rim.

Figure 1. Glabellar Line Injection Paradigm



m = muscle

Subjects must remain in the investigator's office for a minimum of 2 hours following the injection and be observed clinically during this time for any AEs. The subject should be instructed to avoid rubbing or massaging the injection area for the next 24 hours.

3.15 Injector Experience Survey

Following study drug administration on Day 1, the investigator will complete the Injector Experience Survey, which collects information about the investigator's experiences with administering the treatment (e.g., ease of injection).

3.16 Subject Withdrawal from Study

All attempts must be made to determine the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

3.17 Unscheduled Visits

An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3, or for other tests, at the investigator's discretion.

Visits to only retest a lab will not be considered an Unscheduled Visit.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All AEs reported from the time of study drug administration until 30 days after the last dose of study drug or until completion of the study or the last follow-up visit, whichever is longer, will be collected, 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.

4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system (RAVE) within 24 hours of the site being made aware of the SAE. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF form and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE and entered into RAVE system as soon as it becomes available.

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Email: IR-Clinical-SAE@allergan.com
FAX to: +1 (714) 796-9504; Backup fax: +1 (714) 246-5295

For safety concerns, contact the Aesthetics Safety Team at:

Aesthetics Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: SafetyManagement_Aesthetics_Devices@abbvie.com

For any subject safety concerns, please contact the physician listed below:

EMERGENCY MEDICAL CONTACT:
[redacted]
Allergan Aesthetics, an AbbVie company
2525 Dupont Drive
Irvine, CA 92612

Contact Information:

Mobile: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary emergency medical contact is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie contact:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

For non-emergencies, please contact:

[redacted]
Allergan Aesthetics, an AbbVie Company
2525 Dupont Drive
Irvine, CA 92612

Contact Information:

Mobile: [redacted]
Email: [redacted]

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations due to a pandemic or natural disaster prevent the subject from in-person visits, AEs may be collected via phone or video conference.

Supplemental study CRFs should be completed in the event of COVID-19 related missed/virtual visits, or AEs (including capture of specific signs/symptoms of infection and testing results).

SARS-CoV-2 infections should be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID -19 Supplemental Signs/ Symptoms
- COVID-19 Status Form

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All AEs associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 Sample Retention Requirements

Samples for immunogenicity and hypersensitivity (as needed) testing may be stored for a maximum of 5 years from application approval or 5 years from study completion (if not approved) at a facility selected by the sponsor to enable further characterization if necessary.

5.2 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI

during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6 STUDY DRUG

6.1 Treatments Administered

The study drug (OnabotA X Formulations A, B, and C) will be dispensed, prepared, and administered as an IM injection at the Baseline/Day 1 visit as described in Section 5.7 of the study protocol.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system.

6.2 Packaging and Labeling

[redacted]

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

This is a randomized, open-label study. All eligible subjects will receive the same [redacted] dosage of OnabotA X; however, 1 of 3 different formulations (A, B, or C) will be administered to subjects based on randomization.

At the screening visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

[redacted] Subjects must remain at the site for observation for at least 2 hours following administration.

6.5 Preparation/Reconsitution of Dosage Form

Written instructions for the preparation of OnabotA X Formulations A, B, and C for injection will be provided in the pharmacy manual.

7 Appendices

7.1 Focused Neurological Examination Sheet

[redacted]

7.2 Anaphylaxis and Systemic Hypersensitivity

The National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) diagnostic criteria serve as a rapid and simplified method to make an accurate clinical diagnosis of anaphylaxis.[2] Investigators should utilize these criteria to recognize any early signs and symptoms of anaphylaxis and practice clinical judgement for acute treatment and referral to emergency care. The NIAID/FAAN diagnostic criteria for anaphylaxis are outlined below.

Table 1. National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Criteria for Anaphylaxis

National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Criteria for Anaphylaxis
Anaphylaxis is likely when any one of these 3 criteria is fulfilled: Acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue, or uvula) and at least one of the following: a. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin or mucosal tissue (e.g., generalized hives, itch or flush, swollen lips, tongue, or uvula) b. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal tract symptoms (e.g., crampy abdominal pain, vomiting) Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic blood pressure (age-specific) or > 30% decrease in systolic blood pressure[a] b. Adults: systolic blood pressure < 90 mm Hg or > 30% decrease from that person's baseline

a. Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 x age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

Source: [2]

8 References

1. ARPANSA. Fitzpatrick Skin Phototype [Available from: https://www.arpansa.gov.au/sites/default/files/legacy/pubs/RadiationProtection/FitzpatrickSkinType.pdf.

2. Manivannan V, Decker WW, Stead LG, et al. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. Int J Emerg Med. 2009;2(1):3-5.