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Protocol for Study M21-323

Platysma Prominence: Open-Label Extension Study of BOTOX® Treatment for Platysma Prominence

VERSION:	4.0	DATE:	22 November 2022
SPONSOR:	AbbVie*	PLANNED NUMBER OF SITES:	Up to 35
ABBVIE INVESTIGATIONAL PRODUCT:	BOTOX® (botulinum toxin type A)	EudraCT:	Not applicable

FULL TITLE: Phase 3, Multicenter Open-label Extension Study to Evaluate the Safety of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence

Incorporating Versions 1.0, 2.0, 3.0, and 4.0 and Administrative Change 1

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: Phase 3, Multicenter Open-label Extension Study to Evaluate the Safety of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence	
Background and Rationale:	BOTOX is approved for aesthetic treatment of glabellar lines, lateral canthal lines, and forehead lines. The purpose of this 8-month open-label extension study is to evaluate the long-term safety of repeated BOTOX treatment of platysma prominence in subjects who have previously completed a lead-in pivotal Phase 3 study.
Objective and Endpoint:	The study objective is to evaluate the long-term safety of repeat treatments of BOTOX in subjects with moderate to severe platysma prominence at maximum contraction. For both Food and Drug Administration (FDA) and European Union (EU) regulatory agencies, the primary endpoint of the study is incidence of adverse events (AEs).
Investigator(s):	Multicenter
Study Site(s):	Up to 35 study sites in the United States and Canada
Study Population and Number of Subjects to be Enrolled:	Approximately 270 subjects (or up to 400 adult subjects) from the lead-in Phase 3 study are anticipated to be enrolled into this study.
Investigational Plan:	8-month open-label extension study
Key Eligibility Criteria:	Adult male or female subjects who completed all phases of the lead-in Phase 3 study
Study Drug and Duration of Treatment:	Subjects in this study may receive up to 3 administrations of BOTOX (botulinum toxin type A), based on meeting treatment criteria, [redacted] The first administration of study drug may occur at the Day 1 visit. No treatment is allowed after the Day 180 visit (60 days prior to Day 240/study exit).
Date of Protocol Synopsis:	22 November 2022

2 INTRODUCTION

2.1 Background and Rationale

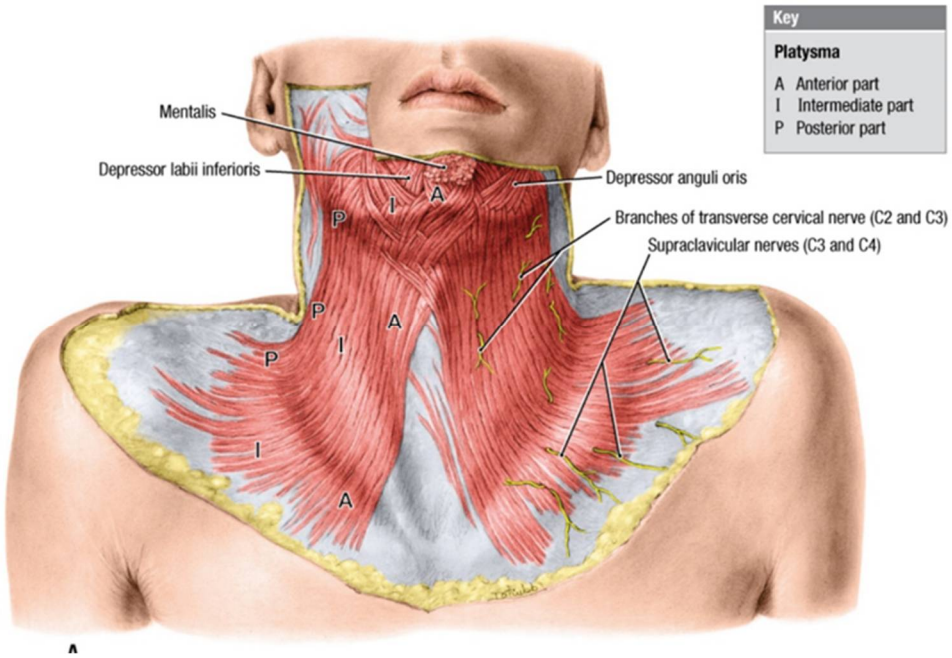
Why Is This Study Being Conducted?

BOTOX was first approved for aesthetic treatment of glabellar lines in 2001, lateral canthal lines (crow's feet lines) in 2013, and forehead lines in 2017. BOTOX is one of the most common nonsurgical procedures in aesthetic medicine.[1]

[redacted] the medical literature has described the use of BOTOX to improve the appearance of the lower face and neck.[2,3] Numerous publications specifically report the use of BOTOX to improve the appearance of the lower face by minimizing the effects of platysma muscle contraction.

The platysma muscle complex is composed of 2 separate, superficial muscle sheets that originate from the fascia of the upper thoracic region and pass upward over both sides of the neck, crossing over the mandibular border and inserting into the overlying skin of the neck and lower face. When relaxed, the platysma muscle smoothly drapes the jawline, neck, and clavicle to create a firm, fitted, and uniform appearance (Figure 1).

Figure 1. The Platysma Muscle: Anterior and Posterior Margins of the Platysma Muscle Sheets



Source: [4]

[redacted]

[redacted]

The purpose of this 8-month open-label extension study is to evaluate the long-term safety of repeated BOTOX treatment of platysma prominence in subjects who have previously completed a lead-in pivotal Phase 3 study.

2.2 Benefits and Risks to Subjects

[redacted]

BOTOX treatment of the platysma muscle has been reported as well tolerated, with adverse events (AEs) that are primarily local and expected based on the well-established safety profile of BOTOX and the muscles injected. Based on the literature review, treatment-related complications included transient edema or ecchymosis (both of which have been observed to resolve within 1-2 days), hematoma formation, muscle soreness, headaches, and stinging at injection sites.[5,11,12] [redacted]

From the literature and consultations with aesthetic physicians, BOTOX treatment complications in muscles adjacent to the platysma are considered technique- and dose-dependent.[11,14-17] [redacted]

[redacted]

Allergan sponsored a Phase 2 study (1936-201-008) designed to evaluate BOTOX for the treatment of platysma prominence. This was a 4-month, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study, comparing the efficacy and safety between a single treatment of BOTOX high dose [redacted] or BOTOX low dose [redacted] versus placebo in 171 subjects with moderate to severe platysma prominence.

Subjects were adults ≥ 18 years old [redacted] and moderate to severe platysma prominence, as rated at maximum contraction by both the investigator and subject using Allergan's platysma prominence scales. Subjects were excluded from the study if they [redacted] had increased medical risk with exposure to BOTOX. Subjects received a single treatment at baseline (Day 1) and were followed for approximately 120 days.

The primary and secondary efficacy endpoints, ≥ 1-grade improvement from baseline in platysma prominence severity at Day 14, assessed independently by Clinician Allergan Platysma Prominence Scale (C-APPS) and Participant Allergan Platysma Prominence Scale (P-APPS), respectively, were achieved. Both high and low dose BOTOX results were statistically significant compared with placebo ($p < 0.0001$). Similar results were observed with other study endpoints, which included patient reported outcome (PRO) measures [redacted] corroborating the C-APPS and P-APPS data. The safety profile observed was consistent with that reported in the medical literature and with the known pharmacological effects of BOTOX. The most frequently reported AEs related to the study procedure were balanced across all treatment groups and included injection site hemorrhage (6/169, 3.6%) and injection site bruising (11/169, 6.5%). [redacted]

[redacted].

While AbbVie does not consider coronavirus disease 2019 (COVID-19) to be a safety concern for BOTOX due to its mechanism of action and route of administration, the sponsor is monitoring COVID-19 events during the pandemic closely. A recent review of COVID-19 events for the periodic safety update report (PSUR) [redacted] did not identify any new or significant safety findings for the subjects receiving BOTOX treatment. Overall, the clinical course and presentation of patients with COVID-19 infection coincident with BOTOX is consistent with what has been described for the general population.

Considering the COVID-19 pandemic, based on the limited information to date, no additional risk to study participants is anticipated with the use of BOTOX.

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

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The study objective is to evaluate the long-term safety of repeat treatments of BOTOX in subjects with moderate to severe platysma prominence at maximum contraction.

The clinical hypothesis is that BOTOX is a safe treatment after repeat treatment in adult subjects with moderate to severe platysma prominence.

Secondary

There are no secondary objectives in the current study.

3.2 Primary Endpoint

For both FDA and European Union (EU) regulatory agencies, the primary endpoint of the study is incidence of AEs. No estimands are provided.

3.3 Secondary Endpoint(s)

There are no secondary endpoints in the current study.

3.4 Additional Efficacy Endpoints

[redacted]

3.5 Safety Endpoints

The safety endpoint evaluated in the current study is the primary endpoint of incidence of AEs (Section 3.2).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an 8-month, multicenter, open-label extension study to evaluate the long-term safety of BOTOX repeat treatment for platysma prominence. In this study, subjects may receive up to 3 administrations of study drug based on meeting treatment criteria (Section 5.7) [redacted]. The first administration of study drug may occur at the Day 1 visit, and the last administration of study drug may occur at the Day 180 visit (60 days prior to Day 240/study exit). No treatment is allowed after the Day 180 visit.

Subjects who complete all phases of the lead-in Phase 3 study may be eligible to enroll into this open-label extension study.

For subjects who choose to participate in this study and qualify for enrollment, Day 1 (study entry) must be same day as Day 120/study exit visit of the lead-in Phase 3 study. Once a subject is enrolled in this study, monthly follow-up visits will occur. During follow-up, if the subject meets treatment criteria, the subject will receive study drug. [redacted] Based on individual variability in time to meet treatment criteria, retreatment timepoints are not expected to be synchronized among all study subjects.

The total duration of study participation for each subject is approximately 8 months. Visits include study entry (Day 1), scheduled monthly visits (Days 30, 60, 90, 120, 150, 180, 210), Day 14 after each study drug administration, and study exit (Day 240 or premature discontinuation). Up to 12 scheduled visits are planned. Administration of study drug is not permitted after the Day 180 visit. Study exit (Day 240 visit/completion) or premature discontinuation must occur at least 60 days after the subject's last administration of study drug.

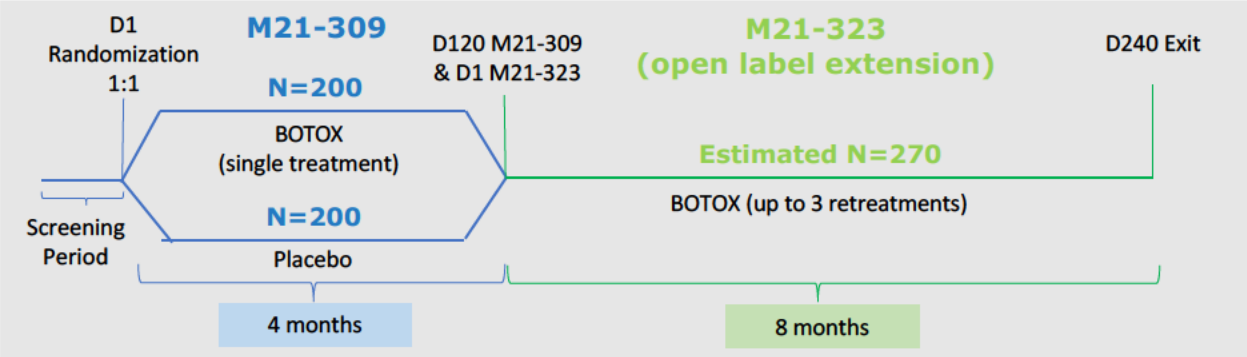
The total number of clinic visits will vary depending on the number and timing of the administration of study drug received by the subject:

- Study entry (Day 1) is a clinic visit (must be same day as the lead-in Phase 3 study Day 120/study exit)
- Study drug administration visits may occur at any scheduled monthly visit (Day 1 through Day 180) if treatment criteria are met
  - Prior to administering study drug, the investigator will assess if the subject meets treatment criteria. If the investigator determines the subject does not meet treatment criteria, the subject will return the following month to be reassessed using the treatment criteria.
  - If treatment criteria are not met on treatment day, the subject will return the following month and be reassessed using the treatment criteria
  - Follow-up visits at Day 14 will only occur after study drug administration at a Treatment visit
- Scheduled monthly visits (Days 30, 60, 90, 120, 150, 180, 210) will occur regardless of study drug administration
- No study drug is allowed after Day 180 visit
- Study exit (Day 240 visit, or premature discontinuation) is recommended to occur at least 60 days after the subject's last drug administration.

Subjects will be monitored for AEs in-clinic for at least 30 minutes after each administration of study drug.

Safety assessments include monitoring of AEs (including AESIs) and vital signs. [redacted]

Figure 2. Study Schematic



4.2 Discussion of Study Design

Choice of Control Group

This study is an open-label study with no control group.

Appropriateness of Measurements

The efficacy measure used in this study (C-APPS) was developed and validated by Allergan [redacted] supporting its acceptability for use in the present study. Allergan also developed and validated PROs for this program in accordance with global recommendations set forth by the United States Food and Drug Administration[18] and the European Medicines Agency.[19] These PROs include the P-APPS to assess platysma prominence severity, the BAS-PP to assess bother from vertical neck bands and jawline, and the ANLFQ: Satisfaction and Impacts modules to assess treatment expectations, satisfaction, and psychosocial impact related to platysma prominence. These PROs will be used to assess treatment efficacy from the patient perspective. All clinical procedures in this study are standard and generally accepted.

Suitability of Subject Population

The study population will include male and female adults with moderate to severe platysma prominence at maximum contraction who were previously enrolled in the Phase 3 lead-in study. Those subjects who have completed the Phase 3 lead-in study are eligible for the current study (M21-323). Eligibility criteria will be assessed at Day 1 of the current study to ensure subject safety.

[redacted]

[redacted]

[redacted]

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects who complete the lead-in Phase 3 study may be eligible to enroll into this 8-month open-label extension study.

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.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent**, approved by an Institutional Review Board (IRB), prior to the initiation of any study-specific procedures
- 2. Are willing and able to comply with procedures required in this protocol

Type of Subject and Characteristics

- 3. Completion of all phases of the lead-in Phase 3 study (Screening Period, Treatment Period [randomization/treatment with 4-month follow-up visit] and Study Exit visit)

Subject History

- [redacted]
- [redacted]
- 6. No medical condition that may put the subject at increased medical risk with exposure to BOTOX, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function

- [redacted]
- 8. No known immunization or hypersensitivity to any botulinum toxin serotype
- [redacted]
- 10. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months
- 11. No tattoos, jewelry, or clothing that cannot be removed, and that obscure the target area of interest
- [redacted]
- [redacted]

Concomitant Therapy

- 14. Subject does not have an anticipated need for treatment with botulinum toxin of any serotype for any indication during the study (other than study drug)
- [redacted]

Contraception

- [redacted]
- [redacted]
- 18. Female who is not **pregnant or breastfeeding, and is not considering becoming pregnant** or donating eggs during the study

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

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

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

     [redacted]

  2. Postmenopausal female

     [redacted]

- Females, of Childbearing Potential

  - Review and document pregnancy avoidance recommendations with females of childbearing potential
  - Females of childbearing potential must avoid pregnancy during the study.
  - Females must commit to one of the following methods of birth control:

    [redacted]

[redacted]

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

5.3 Prohibited Medications and Therapy

The decision to administer any prohibited medication/treatment during the study period is done with the safety of the study subject as the primary consideration. Additionally, the medication/treatment listed below are prohibitive due to the potential confounding impact to efficacy assessment and not due to any potential safety risk to the subject. When possible, the sponsor is to be notified before the prohibited medication/treatment is administered.

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

[redacted]

Site staff must notify the sponsor if a subject is administered or has taken any concomitant medications/procedures not permitted by the protocol.

5.4 Prior and Concomitant Therapy

Any medication or vaccine [redacted] that the subject is receiving at the time of enrollment or receives during the study must be recorded. See below for details on special handling for the COVID-19 vaccine.

The use of any medication during the study [redacted] is to be recorded on the subject's electronic case report form (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. 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. [redacted]

[redacted]

Any questions regarding concomitant or prior therapy should be raised to the AbbVie nonemergency contact. Information regarding potential drug interactions with BOTOX are in the BOTOX Investigator's Brochure.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during the treatment period, as long as components of the vaccine are not contraindicated.

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.

[redacted]

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 [redacted]

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

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. [redacted]

[redacted]

[redacted]

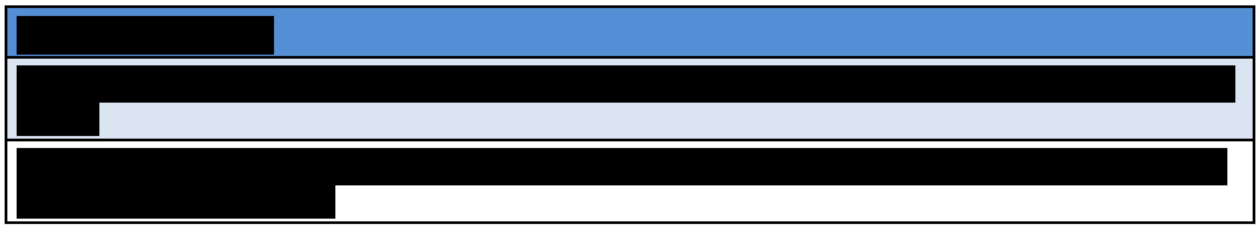
[redacted]

[redacted]

[redacted]

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.

[redacted]



[redacted]

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

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it may be necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. [redacted]

The investigator should contact the AbbVie nonemergency 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.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- [redacted]

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie nonemergency contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

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

To minimize missing data for safety and efficacy assessments, subjects should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely [redacted]

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, [redacted]

5.7 Study Drug

BOTOX will be packaged in vials with quantities sufficient to accommodate study design (Table 1). Study drug provided by AbbVie should not be substituted or alternately sourced unless otherwise directed by AbbVie. [redacted] Study drug will only be used for the conduct of this study.

Sites are responsible for maintaining the investigational study drug and devices according to the storage conditions specified [redacted]

During the treatment period of this study (Day 1 through Day 180), subjects may receive up to 3 administrations of study drug, if all the following treatment criteria are met:

- [redacted]
- No treatment is allowed in subjects who are experiencing active AESIs of any severity, or who, at the discretion of the investigator, are in a situation which may put the subject at increased medical risk with additional treatments
- [redacted]
- Subject has either moderate (Grade 3) or severe (Grade 4) platysma prominence [redacted] as determined at maximum contraction by the investigator using the C-APPS
- Subjects with confirmed (viral test positive) or suspected COVID-19 infection must meet COVID-19 viral clearance criteria before dosing (see Section 5.5)
- Females of childbearing potential must have a negative pregnancy test prior to treatment

If the subject does not meet treatment criteria, he/she will be assessed the following month for treatment eligibility. No treatment is allowed after the Day 180 visit. No treatment is allowed if subject has extreme (Grade 5) platysma prominence [redacted], as determined at maximum contraction by the investigator using the C-APPS. These subjects will return at the next monthly visit to be reassessed for treatment eligibility.

For each subject meeting treatment criteria, superficial intramuscular injections will be administered to [redacted] Dosing will be determined based on the baseline C-APPS score on treatment day [redacted]

[redacted]

Table 1. Study Formulations and Dilution Instructions

Investigational Medicinal Product	BOTOX
Dose Formulation	BOTOX (botulinum toxin type A) purified neurotoxin complex [redacted]
Dilution Instructions	[redacted]
Packaging and Labeling	[redacted]
Storage	[redacted]
Manufacturer	Allergan

[redacted]

[redacted]

5.8 Randomization/Drug Assignment

This is an open-label study with no randomization. Study drug will be unblinded.

The subject's identification number from the lead-in Phase 3 study will be used in this extension study. This will serve as the subject identification number on all study documents.

An automated IRT will be used to manage the study drug kit number(s) for each subject. Before the study is initiated, log-in information and directions for the IRT will be provided to each site.

[redacted]

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. [redacted]

[redacted]

5.10 Data Monitoring Committee

A data monitoring committee is not planned for this study.

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).

[redacted]

Product complaints concerning the investigational product and/or device must be reported to AbbVie [redacted]

Reporting will be done via electronic data capture (EDC). [redacted] A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. [redacted]

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

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. [redacted]

[redacted]

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.

[redacted]

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 as an SAE [redacted]

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. [redacted]

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 [redacted]

All AEs reported from the time of study drug administration [redacted] 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 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 investigational medicinal product 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 investigational medicinal product in accordance with global and local requirements.

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

[redacted]

[redacted]

[redacted]

Upon identification and awareness of 1 or more of these events, the investigator must document and report the event by completing an AE eCRF, and must notify the AbbVie nonemergency contact and assigned clinical research associate by email or telephone call within 72 hours of awareness (if non-serious). The SAE form is not needed unless the AESI is serious. If the AESI meets SAE criteria (which are listed above), it must be reported within 24 hours of awareness per the sponsor's SAE reporting requirements [redacted]

Adverse Event Severity and Relationship to Study Drug

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. [redacted]

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

Possible Distant Spread of Toxin

Possible distant spread of toxin (PDSOT) is defined as a possible pharmacologic effect of botulinum toxin at sites noncontiguous and distant from the site of injection. Utilizing a standardized methodology to assess for PDSOT, Medical Dictionary for Regulatory Activities PTs that may be associated with botulinum toxin effects have been prospectively identified [redacted]

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on the primary analysis. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

[redacted]

[redacted]

7.2 Definition for Analysis Populations

For United States (US) FDA analyses, efficacy variables will be analyzed based on the intent-to-treat (ITT) population. The ITT population consists of all subjects who enrolled in this study.

For EU regulatory agencies only, the efficacy analyses will be performed on the modified intent-to-treat (mITT) population, [redacted]

Safety analyses will be based on the ITT population. Subjects will be analyzed by actual study drug received.

Subject data from the current study will be integrated with the corresponding subject data from the lead-in study.

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

For the primary endpoint (Section 3.2), AEs will be reported as observed, without additional handling of potential intercurrent events.

There are no secondary endpoints in this study.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

The analyses related to the primary endpoint of incidence of AEs is described in Section 7.5.

Summary and Analysis of Additional Efficacy Endpoints

[redacted]

[redacted]

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population. The safety parameters will include incidence of AEs and change from baseline in vital signs. [redacted]

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug.

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 TEAE
- Any TEAE related to study treatment according to the investigator
  - Any TEAE related to study procedure according to the investigator
  - Any TEAE related to study drug according to the investigator
- Any severe TEAE
- Any serious TEAE
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to death
- Any AESIs
- 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 TEAEs 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.

[redacted]

Safety analyses will take into account both study drug groups (e.g., placebo or BOTOX in the lead-in Phase 3 study, BOTOX in this study) and BOTOX treatment cycles from both the lead-in Phase 3 study and this study. Adverse events will be summarized by treatment cycle and for the overall study.

[redacted]

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

7.6 Interim Analysis

Interim analyses are not planned for this study.

7.7 Overall Type I Error Control

Not applicable for this study.

7.8 Sample Size Determination

No formal statistical power or sample size calculation was performed for this study. Approximately 270 subjects (or up to 400 subjects) are anticipated to be enrolled into this study. [redacted]

Due to local guidelines to prevent and mitigate the effects of a pandemic or natural disaster, it is understood that some subjects may not be able to complete all visits in clinic as indicated per protocol.

8 ETHICS

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

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

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

10 DATA QUALITY ASSURANCE

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

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

A subject is considered to have completed the study if he/she has completed all phases of the study including the Study Exit Visit.

12 REFERENCES

[redacted]

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANLFQ	Appearance of Neck and Lower Face Questionnaire
BAS-PP	Bother Assessment Scale - Platysma Prominence
C-APPS	Clinician Allergan Platysma Prominence Scale
CI	confidence interval
COVID-19	Coronavirus Disease – 2019
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
GCP	good clinical practice
HA	hyaluronic acid
HRT	hormone replacement therapy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
mITT	modified intent-to-treat
P-APPS	Participant Allergan Platysma Prominence Scale
PDSOT	possible distant spread of toxin
PGIS	Participant Global Impression of Severity
PRO	patient reported outcome
PSUR	Periodic Safety Update Report
PT	preferred term
RSI	reference safety information
SAE	serious adverse event
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviation	Definition
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
US	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M21-323: Phase 3, Multicenter Open-label Extension Study to Evaluate the Safety of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence

Protocol Date: 22 November 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and 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 Independent Ethics Committee (IEC)/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., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly to AbbVie, the ethics committee/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Therapeutic Area
[redacted]	[redacted]	Statistics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the up to 12 potential subject encounters/visits (depending on subjects meeting treatment criteria). The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual.

Activity	All Subjects		Only Subjects Meeting Treatment Criteria		All Subjects
	Study Entry (Day 1)	Scheduled Monthly Visits: Days 30, 60, 90, 120, 150, 180, 210	Treatment Visit (Day 1 through Day 180)	Day 14 After Each Treatment	End of Study (Day 240 or Premature Discontinuation)
Visit Windows		± 5 days		± 5 days	± 5 days
INTERVIEWS					
Informed consent	✓				
Eligibility criteria	✓				
[redacted]					
AE assessment	✓	✓	✓	✓	✓
Concomitant therapy		✓	✓	✓	✓
EXAMS					
[redacted]					
LOCAL LABS					
Urine pregnancy test			✓		✓
PHOTOGRAPHY					
Standardized photography		✓	✓	✓	✓
SCALES					
P-APPS	[redacted]				
C-APPS					
QUESTIONNAIRES					
BAS-PP, ANLFQ: Impacts, ANLFQ: Satisfaction (follow-up), PGIS-Jawline					
TREATMENT					
Study drug administration			✓		

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	[redacted]
Administrative Change 1	
Version 2.0	
Version 3.0	

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

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