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Protocol for Study M21-310

Platysma Prominence: BOTOX® for the Treatment of 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:	2021-000240-22

FULL TITLE: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence

Incorporating Versions 1.0, 1.1 (Germany Only), 2.0, 3.0, and 4.0 and Administrative Changes 1 and 2

PRINCIPAL INVESTIGATORS: Investigator information on file at AbbVie.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy 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 placebo-controlled Phase 3 study is to evaluate the safety and efficacy of BOTOX for the temporary improvement in the appearance of moderate to severe platysma prominence in adults. The study is designed to meet registration requirements to seek marketing approval in multiple geographic regions.
Objectives and Endpoints:	**Objectives:** To compare the safety and efficacy of BOTOX with placebo for the treatment of platysma prominence in subjects with moderate to severe platysma prominence at maximum contraction

	Primary Endpoints:
	For United States (US) Food and Drug Administration (FDA):
	• Composite achievement of Grade 1 or 2 (Minimal or Mild) and at least a 2-grade improvement from baseline based on both investigator's assessment using Clinician Allergan Platysma Prominence Scale (C-APPS) and subject's self-assessment using Participant Allergan Platysma Prominence Scale (P-APPS) at maximum contraction at Day 14
	For European Union (EU) regulatory agencies:
	• Coprimary: Achievement of at least a 2-grade improvement from baseline based on the following:
	  • Investigator's assessment using C-APPS at maximum contraction at Day 14
	  • Subject's self-assessment using P-APPS at maximum contraction at Day 14
	For US FDA and EU regulatory agencies:
	Incidence of adverse events (AEs)
	Secondary Endpoints:
	For US FDA:
	• Achievement of Grade 1 or 2 (Minimal or Mild) according to investigator's assessment using C-APPS at maximum contraction over time[redacted]
	• Achievement of Grade 1 or 2 (Minimal or Mild) according to subject's self-assessment using P-APPS at maximum contraction over time[redacted]
	• Responses of *Satisfied* or *Very satisfied* on the Appearance of Neck and Lower Face Questionnaire (ANLFQ): Satisfaction (Follow-up) Item 5 (effect of treatment) at Day 14
	• Responses of *Not at all bothered* or *A little bothered* on the Bother

	Assessment Scale - Platysma Prominence (BAS-PP) Item 2 (jawline) at Day 14 • Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 1 (vertical neck bands) at Day 14 • Change from baseline on the ANLFQ: Impacts summary score at Day 14 • Achievement of at least a 1-grade improvement from baseline based on investigator's assessment using C-APPS at maximum contraction over time[redacted] • Achievement of at least a 1-grade improvement from baseline based on the subject's self-assessment using P-APPS at maximum contraction over time[redacted] [redacted] *For EU regulatory agencies:* • Achievement of a rating of Minimal or Mild according to subject's self-assessment using P-APPS at maximum contraction at Day 14 • Responses of *Satisfied* or *Very satisfied* on the ANLFQ: Satisfaction (Follow-up) Item 5 (effect of treatment) at Day 14 • Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 2 (jawline) at Day 14 • Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 1 (vertical neck bands) at Day 14 • Change from baseline on the ANLFQ: Impacts summary score at Day 14 • Change from baseline on the ANLFQ: Impacts summary score at Days 30, 60, and 90
Investigators:	Multicenter
Study Sites:	Up to 35 study sites globally.
Study Population and Number of Subjects to be Enrolled:	Approximately 400 adult subjects with moderate to severe platysma prominence.
Investigational Plan:	4-month, multicenter, randomized, double-blind, placebo-controlled Phase 3 study to assess the safety and efficacy of BOTOX treatment in adults with moderate to severe platysma prominence
Key Eligibility Criteria:	Adult male or female; ≥ 18 years of age; [redacted] moderate (Grade 3) or severe (Grade 4) platysma prominence [redacted]

Study Drug and Duration of Treatment:	BOTOX (botulinum toxin type A) [redacted] in a single treatment
Date of Protocol Synopsis:	22 November 2022

2 INTRODUCTION

2.1 Background and Rationale

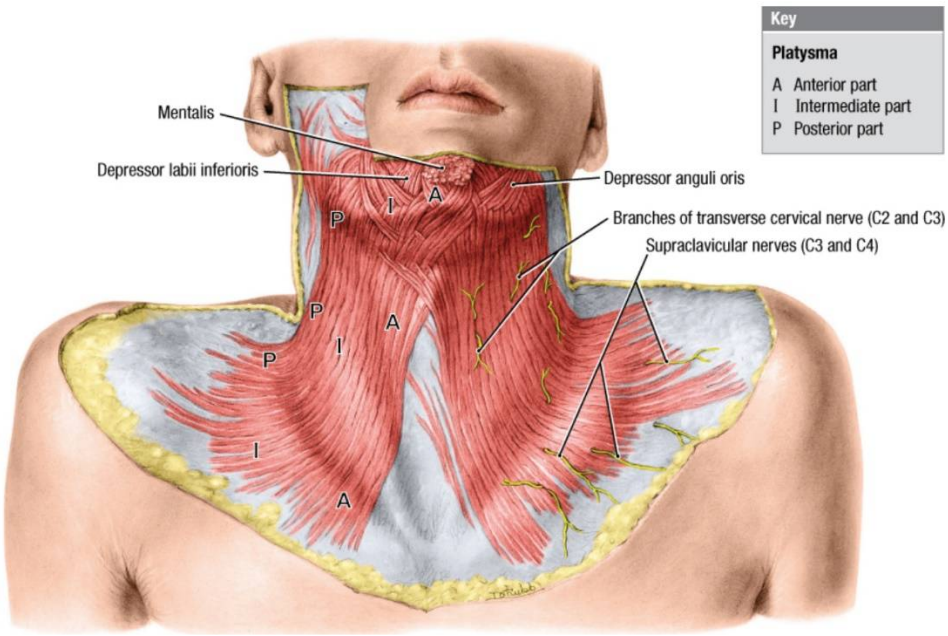
Why Is This Study Being Conducted?

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]

The purpose of this placebo-controlled Phase 3 study is to evaluate the safety and efficacy of BOTOX for the temporary improvement in the appearance of moderate to severe platysma prominence in adults. The study is designed to meet registration requirements to seek marketing approval in multiple geographic regions.

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

The study objective is to compare the safety and efficacy of BOTOX with placebo for the treatment of platysma prominence in adult subjects with moderate to severe platysma prominence at maximum contraction.

The clinical hypothesis is that BOTOX is a safe and effective treatment for the temporary improvement in the appearance associated with moderate to severe platysma prominence in adults.

Estimands: Primary Endpoints

The attributes of the estimands corresponding to the primary efficacy endpoints are summarized in Table 1.

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

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Variable (Endpoint)**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for primary endpoint [redacted]	Single dose of BOTOX [redacted] or placebo	Composite achievement of a Grade 1 or 2 (Minimal or Mild) and at least a 2-grade improvement from baseline based on both investigator's assessment using the C-APPS and subject's self-assessment using the P-APPS at maximum contraction at Day 14	Intent-to-treat (ITT) (all randomized)	Subjects who discontinue study prior to Day 14 assessments or who do not have Day 14 C-APPS or P-APPS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; Cochran-Mantel-Haenszel (CMH) test [redacted]
Hypothetical estimand for coprimary endpoints [redacted]	Single dose of BOTOX [redacted] or placebo	Achievement of at least a 2-grade improvement from baseline based on the following: • Investigator's assessment using C-APPS at maximum contraction at Day 14, and • Subject's self-assessment using P-APPS at maximum contraction at Day 14	Modified intent-to-treat (mITT) [redacted]	Subjects who discontinue study prior to Day 14 assessments or who do not have Day 14 C-APPS or P-APPS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]

Estimands: Secondary Endpoints

The attributes of the estimands corresponding to the secondary efficacy endpoints are summarized in Table 2. Treatment is the same as for the primary efficacy endpoints. For the US FDA variables/endpoints, the population is the ITT population (all randomized); for the EU

variables/endpoints, the population is the mITT population [redacted]. The variables/endpoints listed have the same handling of intercurrent events and statistical summary (including population-level summary and analysis methods) within their respective analysis populations for the US FDA and EU, as indicated in the estimand label.

Table 2. Summary of the Estimand Attributes of the Secondary Endpoints

	Attributes of the Estimand		
Estimand Label	**Variables (Endpoints)**	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for secondary categorical endpoint [redacted]	Achievement of a Grade 1 or 2 (Minimal or Mild) according to investigator's assessment using C-APPS at maximum contraction over time[redacted]	Subjects who discontinue study or who do not have C-APPS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]
Hypothetical estimand for secondary categorical endpoint [redacted]	Achievement of a Grade 1 or 2 (Minimal or Mild) according to subject's self-assessment using P-APPS at maximum contraction over time[redacted]	Subjects who discontinue study or who do not have P-APPS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted].

Estimand Label	Attributes of the Estimand		
	Variables (Endpoints)	Handling of Intercurrent Events	Statistical Summary
Hypothetical estimand for secondary categorical endpoint [redacted]	Achievement of a rating of Minimal or Mild according to subject's self-assessment using P-APPS at maximum contraction at Day 14	Subjects who discontinue study prior to Day 14 assessments or who do not have Day 14 P-APPS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]
Hypothetical estimand for secondary categorical endpoints [redacted]	Responses of S*atisfied* or *Very satisfied* on the ANLFQ: Satisfaction (Follow-up) Item 5 (effect of treatment) at Day 14	Subjects who discontinue study prior to Day 14 assessments or who do not have Day 14 ANLFQ: Satisfaction (Follow-up) Item 5 assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]
Hypothetical estimand for secondary categorical endpoints [redacted]	Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 2 (jawline) at Day 14	Subjects who discontinue study prior to Day 14 assessments or who do not have Day 14 BAS-PP Item 2 assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]
Hypothetical estimand for secondary categorical endpoints [redacted]	Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 1 (vertical neck bands) at Day 14	Subjects who discontinue study prior to Day 14 assessments or who do not have Day 14 BAS-PP Item 1 assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]

	Attributes of the Estimand		
Estimand Label	**Variables (Endpoints)**	**Handling of Intercurrent Events**	**Statistical Summary**
Hypothetical estimand for secondary continuous endpoints [redacted]	Change from baseline on the ANLFQ: Impacts summary score at Day 14	Subjects who discontinue study prior to applicable timepoints or who do not have Day 14 ANLFQ: Impacts summary score will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Mean change from baseline and mean differences between BOTOX and placebo treatment groups; analysis of variance [redacted]
Hypothetical estimand for secondary continuous endpoints [redacted]	Change from baseline on the ANLFQ: Impacts summary score at Days 30, 60, and 90	Subjects who discontinue study prior to applicable timepoints or who do not have Day 30, 60, and 90 ANLFQ: Impacts summary score will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Mean change from baseline and mean differences between BOTOX and placebo treatment groups; analysis of variance [redacted]
Hypothetical estimand for secondary categorical endpoint [redacted]	Achievement of at least a 1-grade improvement from baseline based on investigator's assessment using C-APPS at maximum contraction over time [redacted]	Subjects who discontinue study or who do not have C-APPS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]
Hypothetical estimand for secondary categorical endpoint [redacted]	Achievement of at least a 1-grade improvement from baseline based on subject's self-assessment using P-APPS at maximum contraction over time [redacted]	Subjects who discontinue study or who do not have P-APPS assessments will be included in the analysis as a hypothetical scenario in which the assessments were conducted as per protocol	Response rates and rate differences between BOTOX and placebo treatment groups; CMH test [redacted]

[redacted]

3.2 Primary Endpoints

For the FDA, the composite primary efficacy endpoint is achievement of a Grade 1 or 2 (Minimal or Mild) and at least a 2-grade improvement from baseline based on both investigator's assessment using the C-APPS and subject's self-assessment using P-APPS at maximum contraction at Day 14.

For EU regulatory agencies, the coprimary efficacy endpoints are the achievement of at least a 2-grade improvement from baseline based on the following: (1) investigator's assessment using C-APPS at maximum contraction at Day 14, and (2) subject's self-assessment using P-APPS at maximum contraction at Day 14.

3.3 Secondary Endpoints

For US FDA:

- Achievement of Grade 1 or 2 (Minimal or Mild) according to investigator's assessment using C-APPS at maximum contraction over time
- Achievement of Grade 1 or 2 (Minimal or Mild) according to subject's self-assessment using P-APPS at maximum contraction over time
- Responses of S*atisfied* or *Very satisfied* on the ANLFQ: Satisfaction (Follow-up) Item 5 (effect of treatment) at Day 14
- Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 2 (jawline) at Day 14
- Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 1 (vertical neck bands) at Day 14
- Change from baseline on the ANLFQ: Impacts summary score at Day 14
- Achievement of at least a 1-grade improvement from baseline based on investigator's assessment using C-APPS at maximum contraction over time
- Achievement of at least a 1-grade improvement from baseline based on subject's self-assessment using P-APPS at maximum contraction over time

For EU regulatory agencies:

- Achievement of a rating of Minimal or Mild according to subject's self-assessment using P-APPS at maximum contraction at Day 14
- Responses of *Satisfied* or *Very satisfied* on the ANLFQ: Satisfaction (Follow-up) Item 5 (effect of treatment) at Day 14
- Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 2 (jawline) at Day 14
- Responses of *Not at all bothered* or *A little bothered* on the BAS-PP Item 1 (vertical neck bands) at Day 14

- Change from baseline on the ANLFQ: Impacts summary score at Day 14
- Change from baseline on the ANLFQ: Impacts summary score at Days 30, 60, and 90

3.4 Additional Endpoints

[redacted]

3.5 Safety Endpoints

The safety endpoint is the incidence of AEs for the entire study population.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a 4-month, multicenter, randomized, double-blind, placebo-controlled Phase 3 study designed to assess the safety and efficacy of BOTOX treatment in adult subjects with moderate to severe platysma prominence.

To be eligible for enrollment, subjects must be at least 18 years of age, [redacted] and with either moderate (Grade 3) or severe (Grade 4) platysma prominence [redacted]

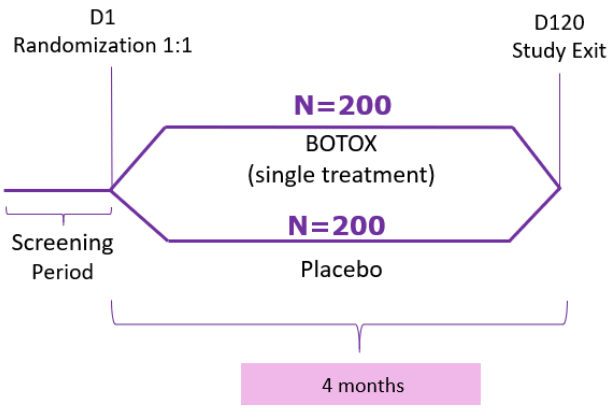
[redacted] Eligible subjects will be randomized on Day 1 in a 1:1 ratio to receive BOTOX or placebo.

Approximately 400 subjects will be randomized at up to 35 global study sites. [redacted]

Seven scheduled visits are planned: screening (Day -14 to Day -7), randomization/study drug (Day 1), follow-up visits (Days 14, 30, 60, 90), and study exit (Day 120). On Day 1, the study drug will be administered in the platysma muscle. Dosing will be determined based on the baseline C-APPS score on Day 1 (see Section 5.7).

The schematic of the study is shown in Figure 2. [redacted]

Figure 2. Study Schematic



4.2 Discussion of Study Design

Choice of Control Group

Placebo was chosen as a control because there are no FDA-approved drugs for platysma prominence.

Appropriateness of Measurements

The primary 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. Study subjects should be in good health

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the eligibility criteria in order to be included in the study. Screen failures can occur during the screening period up to the Day 1 Visit. [redacted] Any attempt to rescreen a subject must only occur after agreement with the sponsor.

[redacted]

Anything other than a positive response to the questions below will result in screen failure.

Consent

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

Demographics

- 3. Adult **male or female**, at least 18 years old at the time of signing the informed consent
- [redacted]

Condition

- [redacted]
- 6. Either moderate (Grade 3) or severe (Grade 4) platysma prominence [redacted] as determined at maximum contraction [redacted] by the investigator using the C-APPS
- 7. Either moderate (Grade 3) or severe (Grade 4) platysma prominence [redacted] as determined at maximum contraction [redacted] by the subject using the P-APPS
- [redacted]

- [redacted]
- [redacted]

Subject History

- 11. Good health as determined by medical history, physical examination, vital signs, and investigator's judgment
- 12. No abnormal variations and abnormal anatomical features in the lower face, neck, or décolletage area [redacted]
- 13. No history of dermatological disease [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- 15. 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
- 16. No lower facial and neck hair, scarring [redacted]
- 17. No tattoos, jewelry, or clothing that cannot be removed, and that obscure the target area of interest
- 18. No history of body weight change [redacted] prior to screening or anticipated body weight change [redacted] during the study period
- 19. No known immunization or hypersensitivity to any botulinum toxin serotype
- 20. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class
- 21. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** [redacted]
- 22. No plans for an extended absence away from the immediate area of the study site [redacted]
- 23. No history of clinically significant medical conditions [redacted]

- 24. No known active Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.
- [redacted]
- 26. Subject is not an employee or immediate relative of an employee of the sponsor, any of its affiliates or partners, or the study center or its affiliates

Concomitant Therapy

- [redacted]
- [redacted]
- 29. No anticipated need for treatment with botulinum toxin of any serotype for any indication during the study (other than study drug)
- 30. No anticipated need for surgery or overnight hospitalization during the study
- [redacted]
- 32. Subject must not have been treated with **any investigational drug or device** [redacted] prior to administration of study drug or is currently enrolled in another clinical study or was previously enrolled in this study

Contraception

- 33. For all females of childbearing potential, a **negative urine pregnancy test** [redacted] prior to the first dose of study drug

- 34. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth contro** [redacted]
- 35. [redacted]

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]
     - [redacted]
  2. Postmenopausal female
     - [redacted]
     - [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]

[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 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]

[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 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 [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., messenger RNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow-up, 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]

[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.

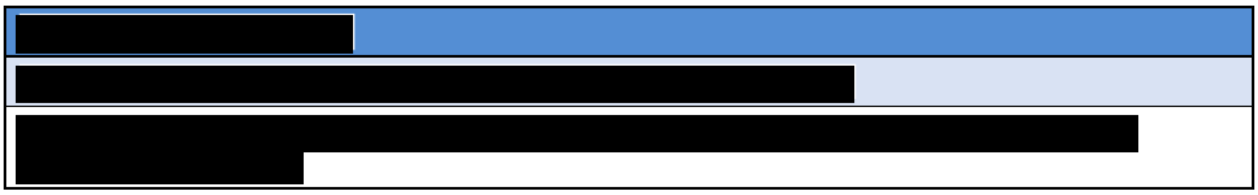
5.5 Withdrawal of Subjects and Discontinuation of Study

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

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

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]

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]

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.

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.

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

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,

5.7 Study Drug

BOTOX and matching placebo will be packaged in vials with quantities sufficient to accommodate study design (Table 3). Study drug provided by AbbVie should not be substituted or alternately sourced unless otherwise directed by AbbVie.

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

Dosing will be determined based on the baseline C-APPS score on Day 1

[redacted]

Table 3. Study Formulations and Dilution Instructions

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

[redacted]

[redacted]

5.8 Randomization/Drug Assignment

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

[redacted]

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

At each study site, designated staff member(s) will serve as the Independent Drug Reconstitutor (IDR). This person will be unblinded and will be responsible for study drug preparation and documentation.

[redacted]

[redacted]

Blinding is critical to the integrity of the clinical trial. The IRT will be programmed with blind-breaking instructions. [redacted] the investigator is to make every effort to contact AbbVie prior to unblinding a subject's study drug assignment unless this could delay emergency treatment of the subject. [redacted] The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

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]

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 evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

[redacted]

[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]
- [redacted]

[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 reaction (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 per the sponsor's SAE reporting requirements described above [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 per the SAE reporting requirements described above.

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 primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan.

7.2 Definition for Analysis Populations

The ITT population consists of all randomized subjects.

Baseline analyses and efficacy analyses for US FDA will be performed on the ITT population, consisting of all randomized subjects.

For EU regulatory agencies only, baseline analyses and efficacy analyses will be performed on the mITT populatio [redacted]

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. All safety analyses will be performed with subjects analyzed by their actual treatment received. The Safety Analysis Set will be used for all safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

The primary composite endpoint for the FDA and the coprimary endpoint for the EU regulatory agencies (defined in Section 3.2) will be analyzed based on the ITT population and the mITT population, respectively, and the following methods will be used to address potential intercurrent events:

- Subjects who did not receive any dose of study drug but are randomized will still be included in the ITT population. [redacted]
- Subjects who are randomized but prematurely discontinued the study before assessment of the primary endpoints will be considered as part of the ITT population. [redacted]
- Subjects who die before assessment of the primary endpoint will count as though they hypothetically continued in the study.
- Subjects who are lost to follow-up and are missing data for the primary endpoint will count as though they hypothetically continued in the study.
- Subjects who are missing assessments or data due to the COVID-19 pandemic and are missing data for the primary composite or coprimary endpoints will count as though they hypothetically continued in the study.
- Subjects who are missing data for any other reason for the primary endpoint will count as though they hypothetically continued in the study.

The efficacy analysis of secondary endpoints (defined in Section 3.3) will be analyzed based on the same populations as above with similar methods for addressing potential intercurrent events.

Missing values will be imputed per the below.

Missing data will be imputed using the following methods for the efficacy analyses:

- Multiple Imputation: The Multiple Imputation approach will be used as a primary analysis for the primary endpoint, as well as for all secondary endpoints. For the primary endpoint (US: composite endpoint; EU: coprimary endpoints) and the primary measure through Day 120 [redacted]

[redacted]

- Non-responder Imputation (NRI): The NRI analysis will categorize any subject who does not have evaluation during a specific visit window as a nonresponder for that visit. The NRI will be one of the sensitivity analysis approaches in the analyses of categorical variables for efficacy.
- As Observed (AO): The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study, and will be used for sensitivity analyses of efficacy endpoints.

7.4 Statistical Analyses for Efficacy

[redacted]

Summary and Analysis of the Primary Endpoints

Analysis of the primary endpoint will be conducted on the ITT population based on treatment as randomized for the US FDA analyses and on the mITT population based on treatment as randomized for the EU regulatory agencies.

US FDA: The composite responder endpoint for a Grade 1 or 2 (Minimal or Mild) and at least a 2-grade improvement will be analyzed using the CMH method [redacted]

EU regulatory agencies: In addition, the coprimary responder endpoints for at least a 2-grade improvement in the C-APPS and P-APPS separately will be analyzed using the CMH method [redacted]

The evaluation of the equality of the proportions of responders for the primary endpoint at Day 14 will be based on the CMH test stratified by baseline C-APPS score on Day 1 and by investigator site. A 2-sided p-value < 0.05 will be claimed as statistically significant. [redacted]

[redacted] The 95% CI for the treatment risk differences will be constructed using the normal approximation to the binary distribution.

Sensitivity analyses of the primary efficacy variables will be performed to establish their consistency and robustness as well as to further characterize the extent of subjects' responses. [redacted]

Summary and Analysis of Secondary Endpoints

Analysis of the secondary endpoints will be conducted on the ITT population based on treatment as randomized for the US FDA analyses and on the mITT population based on treatment as randomized for the EU regulatory agencies.

For the secondary endpoints, the proportion of responders will be analyzed using the CMH test [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 death
- Any AESI

- Any PDSOT AE
- 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]

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

Analyses will be conducted using a gated hierarchical testing procedure to preserve a familywise Type I error rate of $\alpha = 0.05$.

To control the family-wise Type I error rate at 0.05 for multiplicity across the primary and secondary analyses, a hierarchical testing strategy [23] will be used. [redacted] Nominal p-values will then be provided.

7.8 Sample Size Determination

Approximately 400 subjects will be randomized into the study in a 1:1 ratio yielding approximately 200 subjects in the BOTOX group and 200 subjects in the placebo group in the treatment period. [redacted]

For the US FDA primary analysis, an estimated sample size of 360 subjects will give a power of greater than 99% to detect a difference in responder rates between the BOTOX and placebo groups, assuming a 10% dropout rate by Day 14. [redacted]

The primary analysis for EU regulatory agencies only will be performed on the mITT population, [redacted] a sample size of 180 will result in a power of greater than 99% to detect a difference between BOTOX and placebo in the proportion of subjects achieving at least a 2-grade improvement from baseline according to both investigator's assessment using C-APPS and subject's self-assessment using P-APPS at maximum contraction at Day 14. [redacted]

All calculations are based on a 2-sided Type I error rate of 0.05. The power calculation is based on a 2-sample test of independent proportions, as implemented in the commercial software nQuery version 7.0.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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

For personal data that AbbVie controls and maintains, AbbVie has developed a robust security program to protect subject personal data focused on due diligence in design, managed change, and information security governance. Information security policies govern the information security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's information security policies taking into account the sensitivity of the data.

Before subject data is shared with AbbVie, the study doctor and staff will replace any information that could directly identify a patient (such as name, address, and contact information) with a generic code which AbbVie cannot link to that subject's identity to protect the confidentiality of the data.

AbbVie has a data protection impact assessment (DPIA) program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect the privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

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, IEC/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 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
AO	as observed
BAS-PP	Bother Assessment Scale - Platysma Prominence
BMI	body mass index
C-APPS	Clinician Allergan Platysma Prominence Scale
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
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
IDR	Independent Drug Reconstitutor
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
mITT	modified intent-to-treat
NRI	non-responder imputation
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

Abbreviation	Definition
PT	preferred term
RSI	reference safety information
SAE	serious adverse event
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
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 M21-310: A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy 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 (within 1 calendar day) 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 7 subject encounters/visits. The individual activities are described in detail in the **Operations Manual** (Appendix F). Allowed modifications due to COVID-19 are detailed within the Operations Manual.

Activity	Screening	Treatment/ Baseline	Follow-up				End of Study or Premature Discontinuation
	Visit 1 Day –14 to Day –7	Visit 2 Randomization/Day 1	Visit 3 Day 14 ± 5 days	Visit 4 Day 30 ± 5 days	Visit 5 Day 60 ± 5 days	Visit 6 Day 90 ± 5 days	Visit 7 Day 120 ± 5 days
INTERVIEWS							
Informed consent	✓						
Eligibility criteria	✓	✓					
Demographics	✓						
Fitzpatrick skin phototype	✓						
Medical/surgical history	✓	✓					
[redacted]							
AE assessment	✓	✓	✓	✓	✓	✓	✓
Prior/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 (baseline) (for baseline visit only), ANLFQ: Satisfaction (follow-up) (for all visits after baseline), PGIS-Jawline							

Activity	Screening	Treatment/ Baseline	Follow-up				End of Study or Premature Discontinuation
	Visit 1 Day –14 to Day –7	Visit 2 Randomization/Day 1	Visit 3 Day 14 ± 5 days	Visit 4 Day 30 ± 5 days	Visit 5 Day 60 ± 5 days	Visit 6 Day 90 ± 5 days	Visit 7 Day 120 ± 5 days
℞ TREATMENT							
Randomization		✓					
Study drug administration		✓					

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	[redacted]
Administrative Change 1	
Version 1.1 (Germany Only)	
Version 2.0	
Administrative Change 2	
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]
- [redacted]