CONFIDENTIAL

Protocol 1789-301-008

BOTOX

Title Page

Protocol Title: BOTOX® (onabotulinumtoxinA) Treatment of Masseter Muscle Prominence: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

Protocol Number: 1789-301-008

Product: OnabotulinumtoxinA

Brief Protocol Title: BOTOX Treatment of Masseter Muscle Prominence

Development Phase: 3

Sponsor Name and Legal Registered Address:

Allergan Sales LLC
5 Giralda Farms
Madison, NJ 07940
USA

and

Allergan Limited,
1st Floor Marlow International,
The Parkway, Marlow, Buckinghamshire SL7 1YL
United Kingdom

Regulatory Agency Identifying Number: IND 133,035

Emergency Telephone Number Refer to the Study Contacts List

SAE Reporting Fax Number/Email:

Business Unit /Legacy Organization	Email	Phone	Fax
Allergan	mail to: [redacted]	Not applicable	+1-714-796-9504 Backup: +1-714-246-5295

Sponsor Signatory:

[redacted]
Associate Vice President and Section Head
Medical Aesthetics

Refer to the final page of this protocol for electronic signature and date of approval.

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1. Synopsis

Protocol Title: BOTOX® (onabotulinumtoxinA) Treatment of Masseter Muscle Prominence: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

Protocol Number: 1789-301-008

Brief Title: BOTOX Treatment of Masseter Muscle Prominence

Study Rationale:

Based on the results of the Phase 2 Study 191622-130, this Phase 3 study is designed to further evaluate the efficacy and safety of BOTOX 72 U for the treatment of MMP in adults to support marketing authorization.

Objectives and Endpoints:

The primary and secondary objectives of this study are to compare the efficacy and safety of BOTOX versus placebo in participants with MMP.

Objectives	Endpoints
Primary	
• To compare the efficacy of BOTOX with placebo in participants with bilateral MMP	• Proportion of responders who achieve ≥ 2-grade improvement from baseline at Day 90, per investigator assessments of MMP using the MMPS (5 severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked)
• To compare the safety of BOTOX with placebo in participants with MMP	• Incidence of AEs and change from baseline in vital signs
Secondary	
• To compare the efficacy of BOTOX with placebo in participants with MMP	• Proportion of responders who achieve MMPS Grade ≤ 3 at Day 90, according to investigator • Proportion of responders who achieve MMPS-P Grade ≤ 3 at Day 90, according to participant • Proportion of responders who achieve ≥ 2-grade improvement from baseline at Day 90 using the MMPS-P • Proportion of responders who achieve PSAC Grade ≥ 1 (at least minimally improved from baseline) at Day 90 • Change from baseline in lower facial width (mm) at Day 90, calculated from standardized images

Objectives	Endpoints
	• Duration of effect for BOTOX-treated MMPS responders
Other (COA)	
• [redacted]	[redacted]

Overall Study Design:

This is an 18-month, multicenter study consisting of 2 periods, a double-blind placebo-controlled single-treatment period and an open-label period in which a maximum of 2 further study treatments can be received. Up to 20 scheduled visits are planned: screening (Day -14 to Day -1), baseline (Day 1), follow-up monthly thereafter (Days 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510), and study exit (Day 540).

Period 1 (Days 1 through 180) will be a double-blind, randomized, placebo-controlled, single-treatment design, which will assess the safety and efficacy of BOTOX treatment of MMP. On Day 1, participants will be randomized in a 3:1 ratio to receive BOTOX 72 U or placebo. Randomization will be stratified at each investigator site by the participant's baseline MMPS Grade (4 or 5). On Day 180, final Period 1 assessments will be collected, after which all participants will continue into Period 2, the open-label treatment portion of the study.

Period 2 (Days 180 through 540) will be open-label. All BOTOX and placebo-treated participants from Period 1 are eligible to receive up to 2 open-label treatments of BOTOX 72 U in Period 2 if they meet protocol-specified retreatment criteria on or after the Day 180 visit. If the participant does not meet the retreatment criteria at the Day 180 visit, he or she will be reassessed at the next visit. For Treatment 2, participants who qualify can be retreated from the Day 180 visit through the Day 420 visit. For Treatment 3, the earliest visit that participants may qualify and receive the third treatment is the Day 270 visit (3 months after the earliest visit for Treatment 2 [Day 180 visit]). The last visit that participants may qualify and receive treatment

BOTOX

(either Treatment 2 or Treatment 3) is [redacted]

Retreatment Criteria:

- Participant has presence of MMP of at least *marked* (Grade 4) on each side, as assessed by the investigator using the MMPS, AND
- Females of childbearing potential must have a negative pregnancy test prior to treatment, AND
- If it is the third treatment, at least 3 months have lapsed since the previous study treatment [redacted]

If a participant qualifies for retreatment in Period 2 and declines it, retreatment will not be administered at that visit and the participant's reason for declining retreatment will be captured on the eCRF. If the participant still meets retreatment criteria at the next visit (up to Day 420), he or she may receive retreatment at that time.

Number of Participants:

Approximately 360 participants will be enrolled in order to have 306 participants complete the study based on an anticipated dropout rate of 15%.

- Approximately 235 participants will be enrolled from China (mainland).
- Approximately 75 participants will be enrolled from Canada.
- Approximately 50 participants will be enrolled from Taiwan.

Number of Sites:

Approximately 30 sites in China (mainland), Canada, and Taiwan

Intervention Groups and Study Duration:

In Period 1 (Days 1 through 180), participants will be randomized 3:1 to treatment with BOTOX 72 U or placebo, administered on Day 1. Period 2 (Days 180 through 540) will be an open-label period during which participants meeting retreatment criteria will receive up to 2 open-label treatments with BOTOX 72 U.

Treatments will be administered intramuscularly to the bilateral masseter muscles as 6 total injections (0.3 mL per injection), with 3 injections administered per masseter in the area of maximal muscle bulge, for a total injection volume of 1.8 mL. Each 0.3 mL injection will contain BOTOX 12 U or placebo.

The total study duration is approximately 18 months.

Data Monitoring Committee: No

1.3. Schedule of Activities (SoA)

Study procedures are recommended to be done in sequence as listed in the below schedule (with exceptions described in a footnote); however, the sequence is not mandatory.

Table 1–1 Schedule of Visits and Procedures

[redacted]

[redacted]

[redacted]

2. Introduction

BOTOX has been used for therapeutic and aesthetic purposes for 3 decades, with its first therapeutic approval (treatment of facial spasmodic disorders) in 1989 and first aesthetic approval (treatment of glabellar lines) in 2002. Since the first reports of clinical results with botulinum toxin type A treatment of MMH (Moore 1994, Smyth 1994), numerous publications in the medical literature suggest BOTOX may be a locally applied, well-tolerated, and predictable treatment to improve the appearance of the masseter muscles in the lower face. Compared with conservative approaches, BOTOX may produce a relatively rapid, predictable, and desired effect of reducing the size and shape of the masseter muscles; compared with surgical treatment, BOTOX injections may be less invasive, may lead to fewer side effects and a shorter recovery time, and the chemical denervation of the masseter muscle is temporary.

2.1. Study Rationale

The masseter muscle is 1 of 4 muscles used for mastication. Prominence of the masseter muscle can appear as a widened and square lower face shape, which is an aesthetic concern for individuals who prefer a narrower and more ovoid lower face shape.

When BOTOX is injected into a muscle, it interferes with neuromuscular transmission, producing temporary chemical denervation resulting in localized relaxation of the muscle and reduction in muscle activity. When injected into a masseter muscle, BOTOX treatment has been observed to reduce the size of the muscle (Moore 1994), producing an effect perceived as lower facial shaping or slimming (Wu 2010).

Study 191622-130 was the first Allergan-sponsored study of BOTOX for the treatment of MMP, as an aesthetic indication. This was a 12-month, multicenter, double-blind, randomized, placebo-controlled, dose-escalation, Phase 2 study in which BOTOX treatment of MMP was shown to be safe at doses ranging from 24 U (12 U/masseter) to 96 U (48 U/masseter). Participants were adults < 50 years with BMI $\leq$ 30 kg/m^2 and who had *marked* to *very marked* MMP, assessed by the investigator using the MMPS. For the primary and key secondary endpoints (at Day 90), statistically significant positive efficacy results were demonstrated for all 4 BOTOX doses compared with placebo, with a dose-dependent trend favoring the higher 2 doses (72 U and 96 U). The benefit of 72 U and 96 U was similar for duration, volume reduction, MMPS change, facial width, facial angle and facial shape with no significant additional benefit consistently demonstrated with 96 U over 72 U. There were no safety trends or patterns identified with a dose increase, although facial paresis (including reports of weak or altered smile) was reported in the highest dose group (96 U) only, as a local effect. For details of dose selection and justification for the current Phase 3 study, see Section 4.3.

Study 191622-130 safety measures included standardized dental and CT exams with the goal to identify and characterize BOTOX treatment effects on dentition, masseter muscle volume, and the mandible. Dental data yielded no abnormal clinically meaningful posttreatment findings for any participant in the study. No safety signal or unexpected new pathological development was detected from any exploratory radiologic CT measure. There were no dose-related trends, AE reports, or abnormal clinically relevant findings on dental examination.

Based on the results of the Phase 2 Study 191622-130, this Phase 3 study is designed to further evaluate the safety and efficacy of up to 3 treatment cycles with BOTOX 72 U for the treatment of MMP in adults to support marketing authorization as there is no neurotoxin currently approved for treatment of this indication worldwide. Exploratory CT and dental examinations developed by Allergan in Study 191622-130 did not identify any additional potential safety and/or efficacy signals; thus, this Phase 3 study uses routine AE monitoring to characterize safety. Similarly, several exploratory efficacy endpoints and responder definitions used in Study 191622-130 were demonstrated to be less reliable; therefore, this Phase 3 study proposes efficacy endpoints that are most reliable and limited in number for meaningful clinical and statistical analysis.

2.2. Background

The masseter muscle functions to protract and elevate the mandible for mastication. Prominence of the masseter muscle can appear as a widened lower face, which is an aesthetic concern for individuals who prefer a narrower lower face shape. Individuals who deem this masseter prominence as aesthetically undesirable may seek medical treatment to decrease a wide, bulky, or square-appearing lower face (Ahn 2004, Chai 2011, Jin 2005, Klein 2014, Liew 2008, Morris 2007, Mu 2010, Pu 2009, Shim 2010).

In medical literature, MMH can be defined as encompassing both functional and aesthetic symptoms of an enlarged masseter muscle (Fedorowicz 2013). Allergan's focus is the aesthetic indication; to clarify this, the term MMP is now being used instead of MMH, to reflect this focus.

MMP may be unilateral or bilateral. It may be idiopathic or may occur in association with conditions such as bruxism, occlusal and muscular imbalances, TMJD, or particular chewing habits and/or diets (eg, unilateral chewing, chewing gum or hard foods) (Aydil 2012, Choe 2005, Mischkowski 2005). The highest incidence of MMP is believed to occur in the second and third decades of life, and there is no gender predilection (Smyth 1994). Patients with MMP may also have mandibular bony prominence (eg, a prominent mandibular angle) that may contribute to the appearance of a wide lower face.

BOTOX has been used to treat MMP in clinical practice for 3 decades, predominantly in Asian countries where aesthetics favor a slender ovoid facial shape (Ahn 2004, Chang 2016, Liew 2008, Moore 1994). There is growing interest in MMP treatment among non-Asian populations (Liew 2008) and published reports characterize the patient population (Asian and non-Asian), injection techniques utilized, clinical results achieved, and AEs (Ahn 2004, Aydil 2012, Choe 2005, Liew 2008, Peng 2017). As a potentially lower-risk alternative to surgical intervention, the aesthetic procedure of treating the masseter muscle with botulinum toxin has gained popularity among physicians and patients (Ahn 2004, Xie 2014).

2.3. Benefit/Risk Assessment

Current treatment options for MMP include conservative (nonsurgical) as well as invasive treatment modalities. Conservative treatments include reducing the muscular function and activity by behavioral modification, occlusal splints, and/or muscle relaxants (Ahn 2004, Aydil 2012, Mischkowski 2005, Rauso 2010, Tartaro 2008, To 2001). These methods have not been rigorously studied for this indication and are believed to have limited efficacy. Invasive therapies for treating a wide lower face include surgical procedures such as osteotomy, ostectomy, and corticectomy to change the shape of the jawline targeting the mandible and/or including excision of the masseter (Baek 1989, Chai 2011, Deguchi 1997, Jin 2004, Jin 2005, Kim 2001, Kim 2003, Lee 2003, Lee 2006, Mu 2010, Onizuka 1983, Sumiya 2004, Yang 1991), and radiofrequency volumetric reduction of the masseter (Park 2007). Risks of surgical reduction of the mandible and/or masseter muscle include those of a general anesthetic, pain and discomfort, postoperative hemorrhage, edema, hematoma, infection, scarring, injury to the alveolar nerve, fracture of the ramus, condyle, or subcondyle mandibular bone structures, asymmetric result, and facial nerve damage (Baek 1989, Chai 2011, Choe 2005, Deguchi 1997, Jin 2005, Morris 2007, Mu 2010, Pu 2009, Yang 1995). BOTOX for MMP represents a potentially lower-risk alternative to surgical intervention and higher efficacious alternative to other conservative nonsurgical treatment options.

In general, data from the completed Phase 2 clinical study of BOTOX treatment of MMP and from the medical literature show that BOTOX treatment of MMP has been well tolerated with AEs that were primarily local and expected, based on the well-established safety profile of BOTOX and the muscles injected. In the Phase 2 Study 191622-130, the most frequently-reported treatment-related AEs included commonly occurring conditions in the general population (eg, headache [2.0%, 3/150]), events associated with the injection procedure (eg, injection site pain [3.3%, 5/150]), or events related to local muscle weakness that impact smiling or chewing that are consistent with the known BOTOX pharmacological effects following injection into the masseter (eg, mastication disorder [5.3%, 8/150] and facial paresis [2.7%, 4/150; reported verbatim terms: weakness when smiling, altered smile, right depressor

labia inferior paresis, and subject noticed possible loss of movement along jawline]). In addition, there was no safety risk identified in participants who received 2 BOTOX treatments for MMP within 1 year.

Similar safety results have been described in the medical literature following BOTOX treatment of MMP in 1178 participants with various doses (ranging from 10 to 100 U/masseter) and numbers of treatment cycles (Section 5.2.2 of the BOTOX MMP investigator brochure). The most frequently reported AEs were pain, discomfort, or muscle ache at the sites of injection. Because the masseter muscle is 1 of the primary muscles of mastication, its treatment resulted in some reports of transient masticatory difficulties (ie, weakness chewing), which was the next most frequently reported AE in these publications. BOTOX injection of the masseter and/or adjacent facial muscles also resulted in some cosmetic complaints, which were reported less frequently. In general, adverse reactions occur within the first few days to weeks following injection of BOTOX and, while generally transient, may have a duration of several months or, in rare cases, longer. More detailed information about the known and expected benefits and risks and reasonably expected AEs with BOTOX treatment may be found in the investigator's brochure and package insert.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of BOTOX with placebo in participants with bilateral MMP	• Proportion of responders who achieve ≥ 2-grade improvement from baseline at Day 90, per investigator assessments of MMP using the MMPS (5 severity grades: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked)
• To compare the safety of BOTOX with placebo in participants with MMP	• Incidence of AEs and change from baseline in vital signs
Secondary	
• To compare the efficacy of BOTOX with placebo in participants with MMP	• Proportion of responders who achieve MMPS Grade ≤ 3 at Day 90, according to investigator • Proportion of responders who achieve MMPS-P Grade ≤ 3 at Day 90, according to participant • Proportion of responders who achieve ≥ 2-grade improvement from baseline at Day 90 using the MMPS-P • Proportion of responders who achieve PSAC Grade ≥ 1 (at least minimally improved from baseline) at Day 90 • Change from baseline in lower facial width (mm) at Day 90, calculated from standardized images • Duration of effect for BOTOX-treated MMPS responders
Other (COA)	
[redacted]	[redacted]

4. Study Design

4.1. Overall Design

This is an 18-month, multicenter study consisting of 2 periods (see schema, Section 1.2). Period 1 (Days 1 through 180) is a double-blind, randomized, placebo-controlled, single-treatment design, which will assess the safety and efficacy of BOTOX treatment of MMP. Period 2 (Days 180 through 540) is open-label with up to 2 BOTOX retreatments if the participant meets retreatment criteria (Section 6.6). Over the duration of the study, a maximum of 3 study treatments will be administered to each study participant.

Approximately 360 participants will be enrolled at approximately 30 sites in order to have 306 participants complete the study based on an anticipated dropout rate of 15%. Of the enrolled participants, approximately 235 will be enrolled from China (mainland), approximately 75 will be enrolled from Canada, and approximately 50 will be enrolled from Taiwan region.

On Day 1, participants will be randomized in a 3:1 ratio to receive BOTOX 72 U or placebo. Randomization will be stratified at each investigator site by the participant's baseline MMPS Grade (4 or 5). Following completion of Period 1, all participants will continue in Period 2, which will assess the efficacy and safety of repeat administration of BOTOX for the treatment of MMP.

Up to 20 scheduled visits are planned: screening (Day -14 to Day -1), baseline (Day 1), follow-up monthly thereafter (Days 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510), and study exit (Day 540).

After verification that the participants meet all inclusion and exclusion criteria and completion of all baseline study procedures, participants will be randomized and enrolled. Once enrolled, participants will spend approximately 18 months in the study.

Period 1 (Days 1 through 180)

Treatment will be administered intramuscularly to the bilateral masseter muscles as 6 total injections (0.3 mL per injection), with 3 injections administered per masseter in the area of maximal muscle bulge (Figure 6-1, Section 6.1), for a total injection volume of 1.8 mL. Each 0.3 mL injection will contain BOTOX 12 U or placebo. In Period 1, treatment will be administered on Day 1, and participants will return for follow-up assessments (see Table 1–1) on Days 30, 60, 90, 120, 150, and 180. On Day 180, final Period 1 assessments will be collected, after which all participants will continue into Period 2, the open-label treatment portion of the study.

Period 2 (Days 180 through 540/Study Exit)

Day 180 is considered both the end of Period 1 and the beginning of Period 2. After Period 1 assessments are collected, the participant will enter Period 2 and will be assessed for retreatment. If the participant does not meet the retreatment criteria at Day 180, he or she will be reassessed at the next visit. All BOTOX and placebo-treated participants from Period 1 are eligible to receive up to 2 open-label treatments of BOTOX 72 U in Period 2 *if* they meet the following retreatment criteria (also see Section 6.6) on or after the Day 180 visit.

- Participant has bilateral *marked* (Grade 4) or *very marked* (Grade 5) MMP, as assessed by the investigator using the MMPS, AND
- Females of childbearing potential must have a negative pregnancy test prior to treatment, AND
- If it is the third treatment, at least 3 months have lapsed since the previous study treatment (no retreatment earlier than 84 days)

During Period 2, participants will attend all follow-up visits (Days 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, and 540). For Treatment 2, participants who qualify can be retreated from the Day 180 visit through the Day 420 visit. For Treatment 3, the earliest visit that participants may qualify and receive the third treatment is Day 270 (3 months after the earliest visit for Treatment 2 [Day 180]). The last day that a participant can receive either Treatment 2 or 3 is Day 420; this ensures a 120-day safety and efficacy follow-up period by Day 540/study exit. A participant who meets retreatment criteria may decline retreatment if they choose, and their reason will be captured on the eCRF. If the participant still meets retreatment criteria at the next visit (up to Day 420), he or she may receive retreatment at that time.

In Period 2, participants will receive up to 2 additional treatments. Based on individual variability in time to meet retreatment criteria noted in the Phase 2 Study 191622-130, retreatment timepoints are not expected to be synchronized among the participants in the study.

4.1.1. Clinical Hypotheses

BOTOX treatment of MMP is more effective than placebo as measured by investigator assessment of MMP severity using the MMPS.

BOTOX has an acceptable safety profile after single and repeat MMP treatment.

4.2. Scientific Rationale for Study Design

In the current study, all participants will be assessed for a minimum of 180 days after double-blind treatment on Day 1 (Period 1). A randomized double-blind design in Period 1 minimizes investigator and participant bias and the placebo control provides a comparator. After

1 blinded cycle of treatment in Period 1, open-label treatment of BOTOX will be administered to all participants who meet retreatment criteria on or after Day 180 in Period 2. The open-label treatment of BOTOX in Period 2 will assess the efficacy and safety of repeat administration of BOTOX (up to 2 treatments) for the treatment of MMP. Thus, a maximum of 3 treatments will be administered in this study and all participants in this study will have the opportunity to receive at least 1 treatment with BOTOX.

Previous studies, including Allergan's Phase 2 Study 191622-130, reported peak efficacy of botulinum toxin treatment of MMP at 3 months (Hong 2005; Kim 2003; Kim 2007; Park 2003), therefore, Day 90 has been chosen as the primary timepoint in the present study.

Allergan developed the MMPS, a clinician's assessment tool for evaluation of MMP. In the present study, the MMPS is to be used by trained clinicians to evaluate and grade the prominence of the masseter muscle on the left and right sides of the face as the primary endpoint measure. The MMPS is a static measurement encompassing both visual and palpable examination of the masseter muscle at rest and at jaw-clench state. The MMPS showed substantial inter- and intra-rater reliability in the non-treatment scale validation Study 191622-128, confirming its acceptability for use in the present study. Study 191622-130 was the first study to use the MMPS to assess the treatment effect of BOTOX, and it demonstrated statistically significant greater proportions of responders in achieving both a MMPS Grade ≤ 3, and ≥ 1-grade or ≥ 2-grade improvements from baseline, as assessed by the investigator at the primary timepoint. Results from Study 191622-130 support a clinician tool (MMPS) that can immediately assess the relevant masseter prominence without requiring radiological exposure from CT scans or 3D standardized imaging that requires a trained analyst to confirm the aesthetic complaint described by the participant. Therefore, the MMPS has been confirmed as an validated efficacy measure based upon the results of Studies 191622-128 and 191622-130.

In the medical literature, various imaging methods have been used to assess effects of botulinum toxin on masseter muscle size and lower facial shape (refer to the investigator's brochure). Technologies used to measure quantitative changes in masseter muscle volume have included ultrasound, CT, and MRI. Photographic technologies developed to provide 3D quantitative analysis of facial morphology include image subtraction technique, moire topography, liquid crystal scanning, light luminance scanning, laser scanning, stereo-lithography, and passive stereophotogrammetry (Adriaens 2012; Kim 2005; Tzou 2011), which all measure change to the lower facial contour.

A VECTRA Stereophotogrammetry system (Canfield Scientific, Inc.; Fairfield, New Jersey, USA) will be used to quantify the effect of BOTOX on lower facial volume as an other endpoint measure in the current study. This system has previously been validated for use in the facial region (de Menezes 2010), and the lower facial area encompassing the masseter muscle

(MV-Report#1832, MV-Report#1832-Addendum). The efficacy measures used to quantitate volume in Study 191622-130 demonstrated that lower facial volume reductions using 3D images (primary endpoint) correlated well with volume reductions in masseter muscle in a defined region using CT scans. Similarly, decreases in lower facial width using 2D image projections showed improvements comparable with the 3D image and CT volume results. Lower facial width is a secondary efficacy endpoint in the current study.

[redacted]

Safety assessments include AEs and vital signs. In the Phase 2 Study 191622-130, the most frequently reported AEs included commonly-occurring conditions in the general population (eg, nasopharyngitis [8.0% of all BOTOX-treated participants], headache [5.3%], and upper respiratory tract infection [4.0%]) or events related to chewing that are not unexpected following injection into the masseter (eg, mastication disorder [6.0%]) Of the reported AEs among the 1178 participants treated with BOTOX for MMP in the published medical literature, the most frequently reported AEs were pain, discomfort, or muscle ache at the sites of injection. Because the masseter muscle is 1 of the primary muscles of mastication, its treatment resulted in some reports of transient masticatory difficulties (ie, weakness chewing), which was the next most frequently reported AE in these publications. BOTOX injection of the masseter and/or adjacent facial muscles also resulted in some cosmetic complaints, which were reported less frequently. In general, these AEs have been reported as mild and resolved without treatment.

Study 191622-130 yielded no new or meaningful safety findings from dental or CT exams; rather, analysis of AEs provided the most sensitive assessment of safety. Thus, this Phase 3 study uses routine AE monitoring (as well as vital sign monitoring) to characterize safety.

4.3. Justification for Dose

A review of the medical literature of BOTOX treatment of MMP found a mean dose of approximately 38 U per masseter (range: 10 U to 100 U/masseter) administered into 1 to 6 injection sites/masseter (refer to the investigator's brochure). In Allergan's Phase 2 Study 191622-130, participants received total doses ranging from BOTOX 24 U to 96 U (Section 2.1).

Analyses of the data from Study 191622-130 provide evidence to support selection of a 72 U BOTOX dose (36 U administered per masseter muscle) for treatment of MMP. Efficacy of BOTOX treatment of MMP persisted at least 6 months with a median time to loss of response using the MMPS up to 9 months in some participants. BOTOX administration was shown to be safe through Day 360 for all doses (24 U, 48 U, 72 U, and 96 U).

The 72 U dose performed as well as 96 U on multiple measures of efficacy (eg, MMPS responder analyses and changes in lower facial volume); therefore, there was no advantage associated with the higher dose. Similarly, the 72 U dose demonstrated a good safety profile and did not have any incidence of facial paresis, in contrast to the 96 U dose.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant.

A participant is considered to have completed the study if he/she is a randomized participant who was treated in Period 1 and retreated in Period 2 if eligible, has not been discontinued for any reason, and attends/completes the study exit visit.

5. Study Population

The study population will be adult participants with *marked* (Grade 4) or *very marked* (Grade 5) MMP, as determined by the investigator using the MMPS AND with *pronounced* (Grade 4) or *very pronounced* (Grade 5) MMP, as determined by the participant using the MMPS-P, and who meet eligibility criteria for this protocol as specified in Section 5.1 and Section 5.2.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be at least 18 years of age (or older if legal age of adulthood is > 18 as per local regulations), at the time of signing the informed consent
2.	**Type of Participant and Masseter Characteristics**
2.01	Participant must be healthy as assessed by the investigator.
2.02	Participant has a *marked* (Grade 4) or *very marked* (Grade 5) bilateral MMP (identical grades for left and right masseter), as determined at the Day 1 visit by the investigator using the MMPS
2.03	Participant has a pronounced (Grade 4) or very pronounced (Grade 5) MMP, as determined at the Day 1 visit by the participant using the MMPS-P
3.	**Body Mass Index**
3.01	BMI ≤ 30 kg/m^2 using the calculation: BMI = weight (kg)/[height (m)]^2
4.	**Sex**
4.01	Male or female
5.	**Contraceptives**
5.01	A female participant must be willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up periods.

5.02	A female participant is eligible to participate if she is not pregnant (has a negative pregnancy result prior to randomization; see Appendix 6), not breastfeeding, and at least one of the following conditions applies: a. Not a WOCBP as defined in Appendix 6 OR b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 during the treatment and follow-up period
6.	**Informed Consent**
6.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
6.02	Written informed consent from the participant has been obtained prior to any study-related procedures.
6.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable.
7.	**Other**
7.01	Able, as assessed by the investigator, and willing to follow study instructions and likely to complete all required study visits.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Any medical condition that may put the participant 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
1.02	Any uncontrolled medical condition
1.03	An anticipated need for surgery or overnight hospitalization during the study
2.	**Prior/Concomitant Therapy**
2.01	An anticipated need for treatment with botulinum toxin of any serotype for any indication during the study (other than study intervention)
2.02	History of dental or surgical procedure for lower facial shaping or masseter muscle reduction

2.03	Prior mid-facial and/or lower facial treatment with nonpermanent soft tissue fillers, synthetic implantations, autologous fat transplantation, fat-reducing injectables, and/or skin-tightening laser treatments within 6 months prior to Day 1
2.04	Current or planned dental or facial procedures during the study period (eg, braces, dental implants, and reconstructive or aesthetic surgery) that could interfere with MMPS, as determined by the investigator
2.05	Facial hair or scarring (eg, acne) significant enough to interfere with the 3D clinical imaging assessment, as determined by Canfield Scientific, Inc.
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
3.02	Prior exposure to botulinum toxin of any serotype to the masseter muscle or lower face at any time, or to any other part of the body within the 6 months prior to Day 1
4.	**Diagnostic Assessments**
4.01	Current intraoral infection, including infection of the mouth or gums, or facial skin infection requiring medical treatment in the opinion of the investigator
4.02	History of or current TMJD, or presence of signs/symptoms of possible TMJD (see Section 8.2.3) in the opinion of the investigator
4.03	Weakness of the masseter, pterygoid, or temporalis muscles due to trauma, facial nerve injury, or other condition that could interfere with normal chewing and jaw clenching, as determined by the investigator
4.04	Excess lower facial fat, loose or lax skin in lower face, or parotid gland prominence that could interfere with MMPS, as determined by the investigator
4.05	Significant asymmetry of left and right sides of the face that could prevent identical MMPS grading on both sides of the face, as determined by the investigator
4.06	[redacted]
4.07	Masseter prominence due to other etiologies (eg, parotid gland infection, parotiditis, malignancy).
5.	**Other**
5.01	A female who is pregnant, nursing, or planning a pregnancy during the study OR who is of childbearing potential and will not follow the contraceptive guidance in Appendix 6
5.02	Known immunization or hypersensitivity to any botulinum toxin serotype

5.03	Known allergy or sensitivity to any of the components of the study treatments or any materials used in the study procedures
5.04	History of alcohol or drug abuse within 12 months of Day 1
5.05	Any condition or situation which, in the investigator's opinion, precludes the participant's ability to comply with study requirements, including completion of the study visits or an inability to read, or that may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study

5.3. Lifestyle Considerations

Not applicable; no restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. All investigators and site staff involved with injection of study interventions will receive training that is appropriate to their role, and the training will be documented.

6.1. Study Interventions Administered

The study interventions administered are summarized in Table 6-1.

Table 6-1 Study Interventions Administered

Study Intervention Name	BOTOX	Placebo
Dosage Formulation	BOTOX [redacted]	Placebo [redacted]
Unit Dose Strength(s)/Dosage Level(s)	[redacted]	[redacted]

Study Intervention Name	BOTOX	Placebo
Route of Administration	Intramuscular	Intramuscular
Dosing Instructions	BOTOX will be administered on Day 1 [redacted]	Placebo will be administered on Day 1 [redacted]
Packaging and Labeling	Study intervention will be provided in vials containing 100 U of vacuum-dried powder. Each vial will be labeled as required per country requirement.	Placebo is supplied in vials with identical appearance to vials containing BOTOX. Each vial will be labeled as required per country requirement.
Manufacturer	Allergan	Allergan

[redacted]

To identify the masseter muscle treatment area [redacted]

With the participant no longer clenching his/her jaw, the investigator will inject the needle tip into the first marked injection site perpendicularly to the full depth of the muscle. For each

injection, the needle direction within the muscle bulk sh ɔuld be per ɔendicular and not oblique, and the ɾolume should be distributed within the deeper ɯnd more su perficial muscle layers. For each inj ɔction site, an equal volume will be administere l (see Table 6-2).

After co mpleting the 3 injections of the masseter muscle on 1 side of the face, the investigator should apply direct ɾressure to the treatment area for approximately 30 seconds. If there is evidence of cutaneo ɯs bleeding or emerging hematoma, continued direct pressure should be applied until the ble ɔding stops. The same procedure wi l be follow ɔd for injection to the contralateral masset ɾr muscle. The participant should be observed f ɾr at least 30 minutes after the injections for A s.

[redacted]

Immedi tely before ɾispensing the study intervention, the investigator (or appropriately trained designee) will write the participant's identification num ɔer and the late on the label.

6.1.1. Other Study Supplies

The foll ɔwing will be provided by the sponsor or designee:

- emperature recording device for monitoring re rigerator temperature
- Imaging equipment (supplied by a third-party ve ɯdor)
- eCOA devic s (supplied by a third-party vendor)

The foll ɔwing will be provided by the study site:

- cotton pads and makeup remover
- alcohol wipes
- ɯedical gloves

- serum or urine pregnancy tests in accordance with the local institutional requirements. If urine pregnancy test kits are to be used, a minimum sensitivity of 25 IU/mL is required
- sterile surgical marker pens
- appropriately-sized sterile needles and syringes for study treatment reconstitution and injection
- [redacted]
- lockable refrigerator, to store study treatment kits according to the Study Manual
- covered container for discarded medical waste materials (sharps box)
- internet connection (high-speed connection for eCRF completion)

6.2. Preparation/Handling/Storage/Accountability

In order to ensure injector blinding during Period 1, an unblinded IDR will be identified prior to study initiation, who will not be involved with other study activities. The dedicated IDR will be responsible for preparation of blinded study interventions for Period 1 while maintaining the blind for all other study personnel and the study participants.

For Period 2, open-label study interventions (BOTOX) will be prepared by assigned study personnel, which may be the IDR or another designee.

Study interventions will be reconstituted with 0.9% sodium chloride (preservative free).

Table 6-2 Injection Volume

Study Intervention	Total Dose (U); Total Volume (mL)	Masseter Dose (U); Volume per Masseter (mL)	Volume per Injection (mL)
BOTOX	[redacted]	[redacted]	[redacted]
Placebo			

Detailed instructions on reconstitution and syringe preparation are provided in the Study Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All used and unused study intervention must be stored secured, with limited access to a designated unblinded site member, and returned to the sponsor or designee once expired or at the termination of study. Unit counts will be performed when the study intervention is returned, and all study intervention must be accounted for.

6.3. Measures to Minimize Bias: Randomization and Blinding

At the Screening Visit, after the participant signs the ICF, the site will log on to the IWRS to obtain a participant number. On Day 1, the IWRS will be used to manage the randomization and assignment of participants into one of the 2 study intervention groups based on a randomization schedule prepared the sponsor's Biostatistics department. The randomization will occur after all baseline procedures have been completed and the investigator has verified that the participant has met all inclusion and exclusion criteria. Randomization will be stratified at each investigator site by the participant's baseline (Day 1) MMPS Grade (4 or 5), as assessed by the investigator.

For the double-blind Period 1, all study interventions will be provided in identical vials and cartons to maintain blinding. In addition, the injection volume and study intervention administration will be identical for both groups.

For open-label Period 2, all study intervention will be provided in cartons, each containing one open-label vial.

Study intervention will be labeled with kit numbers. The IWRS will provide the site with the specific kit number for each randomized participant at the time of randomization (Day 1). The IWRS will also issue the specific kit number for each participant who qualifies for retreatment. Sites will dispense study intervention according to the IWRS instructions. Sites will receive the IWRS confirmation notifications for each transaction and will maintain these with the study source documents.

At each study site, a designated staff member will serve as the IDR for the double-blind Period 1. This person will be responsible only for blinded study intervention preparation during Period 1. This person will be a staff member with no study responsibilities that require interaction with participants and with participant efficacy or safety data. For Period 2, site personnel other than the IDR may be assigned to prepare open-label study interventions (BOTOX).

For Period 1, the IDR will prepare the vial of study intervention as described in Section 6.2 and the Study Manual. Once the study intervention vial is reconstituted, the IDR will draw the required volume into an appropriately sized syringe and label the syringe with the participant's ID number. The IDR will then provide the filled syringes to the investigator. The investigator will inject the participant according to the study intervention administration instructions in Section 6.2. In Period 1, only the IDR will be unblinded to the study treatment; all other site personnel and study participants will be blinded.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4. Study Intervention Compliance

The study investigator will administer all study intervention injections to the participants.

The study site will keep an accurate study intervention disposition record.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, cannabis [in regions where its use is legal], vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication/reason for medication use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.5.1. Prohibited Treatments and Washout Before the Study

[redacted]

[redacted]

[redacted]

[redacted]

6.6. Dose Modification

Dose modification is not applicable.

6.6.1. Retreatment Criteria

All participants entered into the study will be treated at Day 1. A participant will receive 1 additional treatment if she/he meets retreatment criteria, as determined by the investigator. To be eligible for retreatment at the Day 180, 210, 240, 270, 300, 330, 360, 390, or 420 visits, the participant must meet all the following criteria:

- Participant has presence of MMP of at least *marked* (Grade 4) on each side, as measured by the investigator using the MMPS, AND
- Females of childbearing potential must have a negative pregnancy test prior to treatment, AND
- [redacted]

A second treatment is only allowed on or between the Day 180 and Day 420 visits. [redacted] Retreatments must

occur during normally scheduled visit windows and are prepared and administered as described in Section 6.2 for BOTOX.

Treatment	Study Visit	Description
Treatment 1	Day 1 (Visit 2)	Double blind, randomized
Treatment 2 (Retreatment 1)	Days 180 to 420 (Visit 8 to 16)	Open-label; participant must qualify for retreatment
Treatment 3 (Retreatment 2)	Days 270 to 420 (Visits 11 to 16)	Open-label; participant must qualify for retreatment; must be 84 days from the previous treatment

If a participant qualifies for retreatment in Period 2 and declines it, retreatment will not be administered at that visit and the participant's reason for declining retreatment will be captured on the eCRF. If the participant still meets retreatment criteria at the next visit (up to Day 420), he or she may receive retreatment at that time.

6.7. Intervention after the End of the Study

No interventions after the end of the study are planned.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants may voluntarily withdraw from the study at any time. A premature discontinuation will occur if a participant who signs the ICF and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

Reasons for discontinuation from the study treatment and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Lack of efficacy	
Lost to follow-up	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

Definitions of the standard terms are provided in Appendix 4.

7.1. Discontinuation of Study Intervention

See the SoA [redacted] for data to be collected at the time of discontinuation from the study intervention and follow-up and for any further evaluations that need to be completed.

If a pregnancy is confirmed after the participant has received study intervention, the participant will not receive additional treatment and may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the end-of-study visit.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant exits the study early, every effort should be made to ensure a Study Exit Visit and associated procedures are performed - see the SoA [redacted] for data to be collected at the time of study discontinuation.
- Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- [redacted]

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Evaluations are to be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the participant, then evaluations should overlap (examine the participant together and discuss findings) for at least 1 visit.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (see Section 1.3). The measures are described in detail in Appendix 7 and Appendix 8.

8.1.1. Primary Efficacy Assessment

The primary efficacy assessment is to be completed at screening, baseline, and at each scheduled visit thereafter until study exit.

Note: The Day 1 images will be used as baseline images. If the baseline images are not of acceptable quality, the screening images will be used instead. Canfield Scientific, Inc. must approve each participant's screening images to ensure a quality baseline image is available if the Day 1 images are not of acceptable quality. If the screening images are not acceptable, 1 retake is permitted and must be taken before Day 1.

Masseter Muscle Prominence Scale – Investigator (MMPS)

The primary efficacy assessment is masseter muscle prominence assessed by the investigator using the MMPS (1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = very marked [redacted]

8.1.2. Secondary Efficacy Assessments

MMPS-P and lower facial width assessments will be completed at screening, baseline, and at each scheduled visit thereafter until study exit. The PSAC will be completed at all scheduled postbaseline visits. Participants will be trained on how to properly complete the MMPS-P and PSAC assessments using images, at the Screening Visit (and at other visits if needed).

Masseter Muscle Prominence Scale – Participant (MMPS-P)

MMP assessed by the participant is a secondary efficacy assessment developed by the sponsor through concept elicitation and cognitive debriefing. Participants will be asked to assess the severity of their masseter prominence using a single question composed of 5 grades (1 = not at all pronounced, 2 = mildly pronounced, 3 = moderately pronounced, 4 = pronounced, 5 = very pronounced; [redacted]

Participant Self-Assessment of Change (PSAC)

The PSAC is a commonly used assessment of change scale that has been adapted for use with MMP by the sponsor using concept elicitation and cognitive debriefing. Participants will be asked to assess change of their lower face shape using 2D images collected before study intervention (ie, baseline, or screening if the baseline image is not of acceptable quality) and after study intervention (ie, the current study visit) [redacted]

The participant will answer the questions on the accompanying assessments via electronic tablet that will be provided to the study participant at the study site.

Lower Facial Width

The lower facial width (mm) will be calculated from 2D projections of 3D images.

8.1.3. Other Efficacy Assessments

[redacted]

[redacted]

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Section 1.3).

8.2.1. Vital Signs

Vital signs will be assessed as follows:

- Pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with participants in a sitting position after sitting for at least 5 minutes; use of either a manual or automated device is acceptable. Manual techniques will be used only by trained personnel; whenever possible, the same person should perform all manual assessments as much as possible.
- Height and weight will also be measured and recorded, and BMI calculated at the screening visit.

8.2.2. Pregnancy Testing

Pregnancy testing will be conducted at the screening, baseline retreatment, and study exit visits. Urine pregnancy tests will be used unless the study site requires the use of serum testing, in which case serum testing will be used. Females of childbearing potential must have a negative test result before receiving study treatment/retreatment. This test may also be performed at any other visit, at the investigator's discretion. At each visit, the investigator should discuss contraceptive use compliance with females of childbearing potential.

8.2.3. Screening for TMJD

Screening for signs/symptoms of possible TMJD will be conducted by the investigator at the screening visit, as described in the Study Manual. Depending on the findings, the investigator may decide to exclude the participant from the study, or may refer the participant to a dentist for further TMJD screening, to be completed prior to Day 1. The participant may complete the rest of the planned activities and procedures for the screening visit, with the dentist examination occurring at a later time. If, based on findings from a dental examination, the dentist diagnoses the participant with TMJD, the participant will be considered a screen failure.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (ie, repeat treatment) or study (see Section 7).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs from the signing of the ICF will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

All AEs from the signing of the ICF will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent, will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The methods of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and any AESI as defined in Appendix 2 will be followed

until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a participant dies during participation in the study, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- If a pregnancy is confirmed after the participant has received the study intervention, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the end-of-study visit.
- Details of all pregnancies in female participants will be collected from the signing of the ICF and through the duration of the pregnancy.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.6. Adverse Events of Special Interest

AESIs will be recorded as indicated in Appendix 2.

8.3.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol, for example:

- Wrong study drug
- Wrong dose (including dosing regimen, concentration, amount)
- Wrong participant (ie, not administered to the intended participant)

8.4. Treatment of Overdose

The LD50 for BOTOX in humans is estimated from primate studies to be approximately 3000 U. This makes accidental injection of a lethal dose highly unlikely, but significant AEs may still occur at doses below the LD50 (Herrero 1967, Scott 1989).

Excessive doses may produce local or distant, generalized, and profound neuromuscular paralysis. Should accidental injection or oral ingestion occur, or overdose be suspected, the participant should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness that could be local or distant from the site of injection, and which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness, or respiratory failure. Please refer to the general Section 6.5 of the BOTOX MMP investigator's brochure for further details.

In the event of an overdose, the investigator should:

1. Contact the medical safety physician immediately.
2. Closely monitor the participant for AEs and SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF as well as other details that led to the overdose.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The following set of hypotheses will be used to compare the BOTOX 72 U group with placebo:

- Null hypothesis: BOTOX and placebo are equally effective in reducing MMP as measured by the proportion of responders achieving ≥ 2-grade improvement from baseline at Day 90 using the MMPS.
- Alternative hypothesis: BOTOX and placebo are not equally effective in reducing MMP as measured by the proportion of responders achieving ≥ 2-grade improvement from baseline at Day 90 using the MMPS.

9.2. Sample Size Determination

[redacted] approximately 360 participants (270 BOTOX and 90 placebo) will provide > 90% power [redacted].

9.3. Populations for Analyses

The analysis populations will consist of participants as defined in below:

- The mITT population includes all randomized participants with ≥ 1 postbaseline MMPS assessment. Participants will be summarized according to the randomized study intervention.
- The safety population includes all treated participants who receive ≥ 1 administration of study intervention. Participants will be summarized according to the study intervention they received.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and unblinding and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Planned analyses of other efficacy endpoints and other collected clinical and safety data from this study will be fully documented in the study SAP.

9.4.1. Efficacy Analyses

The efficacy analyses will be based on the mITT population. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the first dose of study intervention. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects.

The overall familywise error rate will be controlled at $\alpha = 0.05$ for the set of primary and secondary endpoint comparisons between BOTOX 72 U vs placebo. The overall serial gatekeeping MCP is defined in Table 9-1.

[redacted]

9.4.1.1. Analysis Endpoints

The primary and secondary efficacy endpoints are listed below, and analyses will be defined in the following sections. All analyses for other efficacy endpoints listed below will be defined in the SAP.

Primary efficacy endpoint:

- Proportion of responders who achieve ≥ 2-grade improvement from baseline at Day 90, per investigator assessments of MMP using the MMPS

Secondary efficacy endpoints:

- Proportion of responders who achieve MMPS Grade ≤ 3 at Day 90, according to investigator
- Proportion of responders who achieve MMPS-P Grade ≤ 3 at Day 90, according to participant
- Proportion of responders who achieve ≥ 2-grade improvement from baseline at Day 90 using the MMPS-P
- Proportion of responders who achieve PSAC Grade ≥ 1 (at least minimally improved from baseline) at Day 90
- Change from baseline in lower facial width (mm) at Day 90
- Duration of effect for BOTOX-treated MMPS responders [redacted]

Other endpoints:

[redacted]

9.4.1.2. Primary Analyses

The primary efficacy endpoint will be the proportion of responders who achieve ≥ 2-grade improvement from baseline at Day 90, per investigator assessments of MMP using the MMPS and will be analyzed using CMH model stratified by baseline MMPS Grade (4 or 5). Missing MMPS values in Period 1 will be imputed using multiple imputation methods. A sensitivity analysis will be based on observed data.

9.4.1.3. Secondary Analyses

MMPS responders will be defined as participants who achieve MMPS Grade ≤ 3.

MMPS-P responders will be defined as:

1. Participants who achieve MMPS-P Grade ≤ 3
2. Participants who achieve ≥ 2-grade MMPS-P improvement from baseline

The proportion of MMPS and MMPS-P responders as defined above and PSAC Grade ≥ 1 responders will be analyzed using CMH model stratified by baseline MMPS Grade (4 or 5).

The change from baseline in lower facial width will be analyzed using ANCOVA [redacted]

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs and vital signs. For vital signs data, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if:

- The AE began on or after the date of the first dose of study intervention; or
- The AE was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first dose of study intervention

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criteria.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants reporting treatment-related TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with SAEs and participants with AEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Appendix 2.

9.4.2.2. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate) at baseline and changes from baseline at each assessment will be presented by study intervention.

[redacted]

9.5. Interim Analyses

Interim analyses are not planned for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH/ISO/GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study, if applicable.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Posting Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.
- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and must follow ALCOA, ie, records must be attributable, legible, contemporaneous, original, and accurate.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. **AESI** An AESI is an AE of scientific and medical concern specific to the sponsor's study drug/device or program, which may warrant ongoing monitoring. Such an event might warrant further investigation in order to characterize and understand it. Facial muscle paralysis (NOT including a weak or altered smile) has been identified as an AESI for the study intervention in this protocol. Suspected AESIs should be reported to the sponsor as a typical adverse event. No AESI form is needed. If the AESI meets SAE criteria (which are listed below), it should be reported within 24 hours.

Events Meeting the AE Definition
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE

should be considered serious.

Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Allergan in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Allergan. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Allergan.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Allergan. However, **it is very important that the investigator always make an assessment of causality for**

every event before the initial transmission of the SAE data to Allergan.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
• Email is the preferred method to transmit SAE information. The email address is [redacted] • Facsimile transmission of the SAE information is also acceptable. The fax number is [redacted] (backup number is [redacted]). • Contacts for SAE reporting can be found on the protocol title page.

10.3. Appendix 3: Abbreviations

Abbreviation/Term	Definition
2D	2-dimensional
3D	3-dimensional
AE	adverse event
AESI	adverse event of special interest
ALCOA	attributable, legible, contemporaneous, original, and accurate
ANCOVA	analysis of covariance
BMI	body mass index
BOTOX	Botulinum toxin type A purified neurotoxin
CDISC	Clinical Data Interchange Standards Consortium
CFB	change from baseline
CIOMS	Declaration of Helsinki and Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment (formerly described as patient-reported outcomes [PRO])
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CT	computed tomography
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council on Harmonisation
IDR	independent drug reconstitutor
IEC	independent ethics committee
IRB	institutional review board
ISO	International Organization for Standardization
IUD	intrauterine device
IUS	intrauterine system
IWRS	interactive web response system
LD50	lethal dose, 50%

[redacted]	
MCP	multiple comparisons procedure
mITT	modified intent-to-treat
MMH	masseter muscle hypertrophy
MMP	masseter muscle prominence
MMPS	Masseter Muscle Prominence Scale
MMPS-P	MMPS-participant
MRI	magnetic resonance imaging
NCI	National Cancer Institute
No.	number
PCS	potentially clinically significant
[redacted]	[redacted]
PSAC	Participant Self-assessment of Change
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMJD	temporomandibular joint disorders
U	unit
WOCBP	woman of childbearing potential

10.4. Appendix 4: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.5. Appendix 5: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	BOTOX® (onabotulinumtoxinA) Treatment of Masseter Muscle Prominence: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study
	Clinical Study Sponsor	Allergan Sales, LLC / Allergan Limited
	Trial Phase Classification	Phase 3 Trial
	Trial Indication	Masseter Muscle Prominence
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	540 days plus the 14-day screening period
	Planned Country of Investigational Sites	Country/Region: Canada, China (mainland), Taiwan
	Planned Number of Subjects	360
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Participant information	Diagnosis Group	Masseter Muscle Prominence
	Healthy Subject Indicator	Yes
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	Not specified
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not specified

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	OnabotulinumtoxinA
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Neurotoxin
	Dose per Administration	72 (total dose)
	Dose Units	U
	Dosing Frequency	Up to 3 treatments [redacted]
	Route of Administration	Intramuscular
	Current Therapy or Treatment	No
	Added on to Existing Treatments	No
	Control Type	Placebo (Period 1 only)
	Comparative Treatment Name	Placebo
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Trial is Randomized	Yes
	Randomization Quotient	3:1 (BOTOX:placebo)
	Trial Blinding Schema	Double blind (Period 1) and Open-label (Period 2)
	Stratification Factor	Day 1 MMPS Grade (4 or 5)
	Adaptive Design	No
	Study Stop Rules	None

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Contraception Guidance:

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-1.

Contraceptive methods using Chinese traditional medicine or other herbal remedies are not considered acceptable methods of contraception in this study.

Table 10-1 Highly Effective and Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg. Essure, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test at screening and also a negative test at baseline.

- Additional pregnancy testing should be performed prior to retreatment and at study exit, and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Urine pregnancy testing will be used unless the study site requires the use of serum testing, in which case serum testing will be used.

Collection of Pregnancy Information:

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Allergan within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to Allergan. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to Allergan as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- If a pregnancy is confirmed after the participant has received study intervention, the participant may choose to exit the study after appropriate safety follow-up or to remain in the study for all safety and efficacy follow-up assessments through the end-of-study visit.

10.7. Appendix 7: Efficacy Measures

10.7.1. Masseter Muscle Prominence Scale – Investigator Assessment

Instructions

[redacted]

10.7.2. Facial Width Measurement

[redacted]

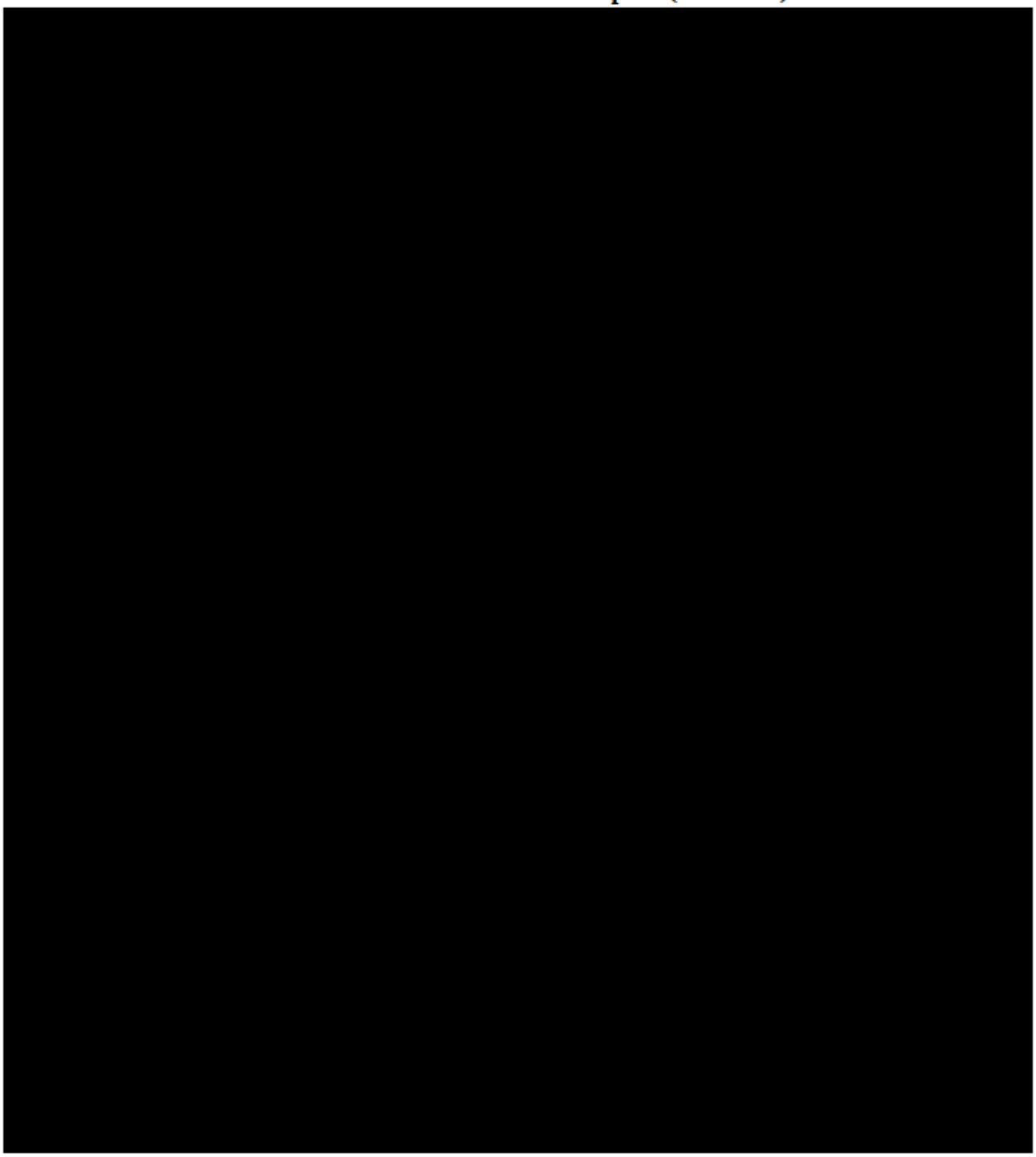
[redacted]

[redacted]

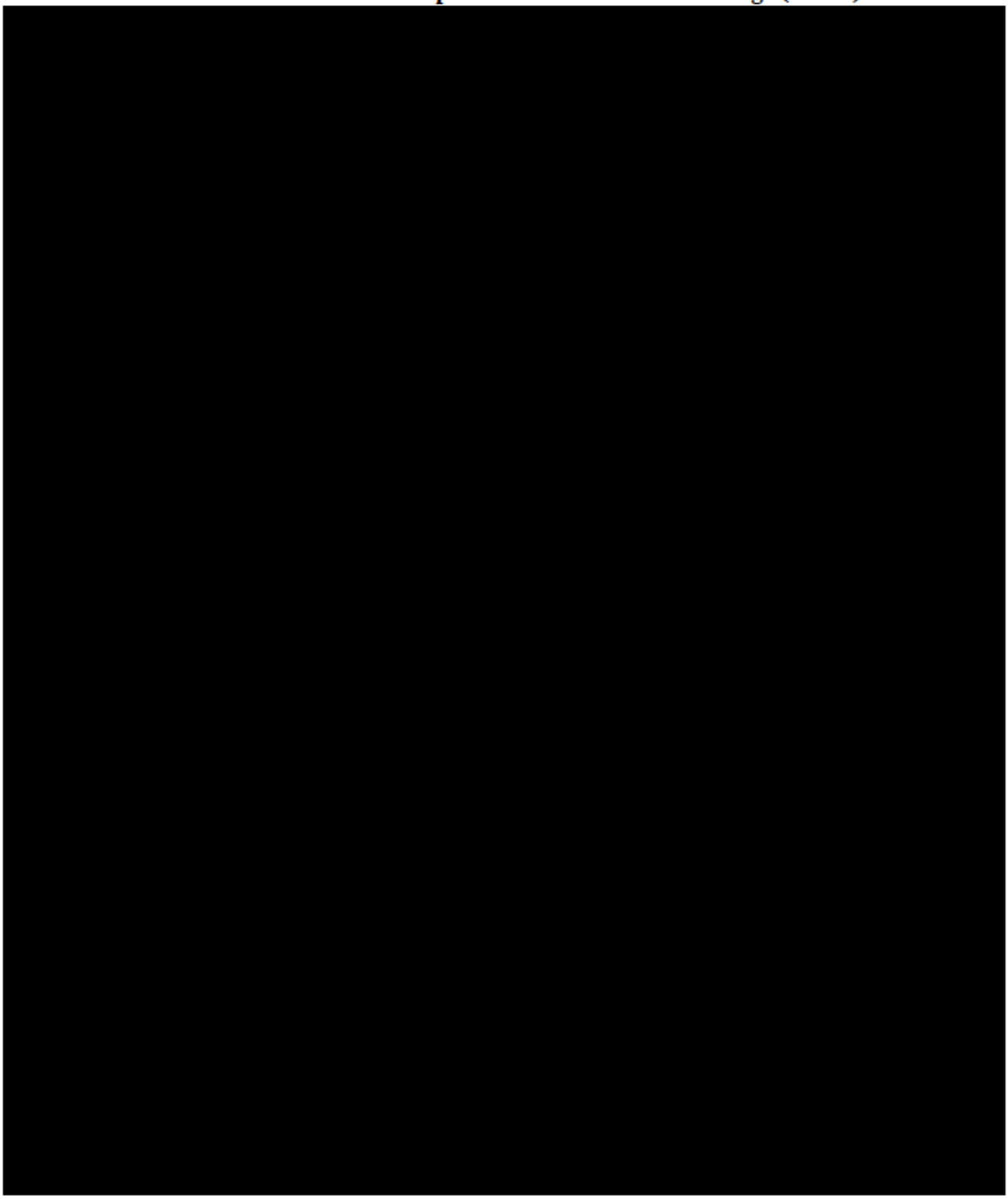
10.8. Appendix 8: Example Clinical Outcome Assessment Questionnaires, Descriptions, and Instructions

This appendix provides complete samples of each COA questionnaire; however, participants will provide responses in electronic tablets (ie, eCOA) at the study site.

10.8.1. Massete · Muscle Prominence Scale – Participant (M ,IPS-P)

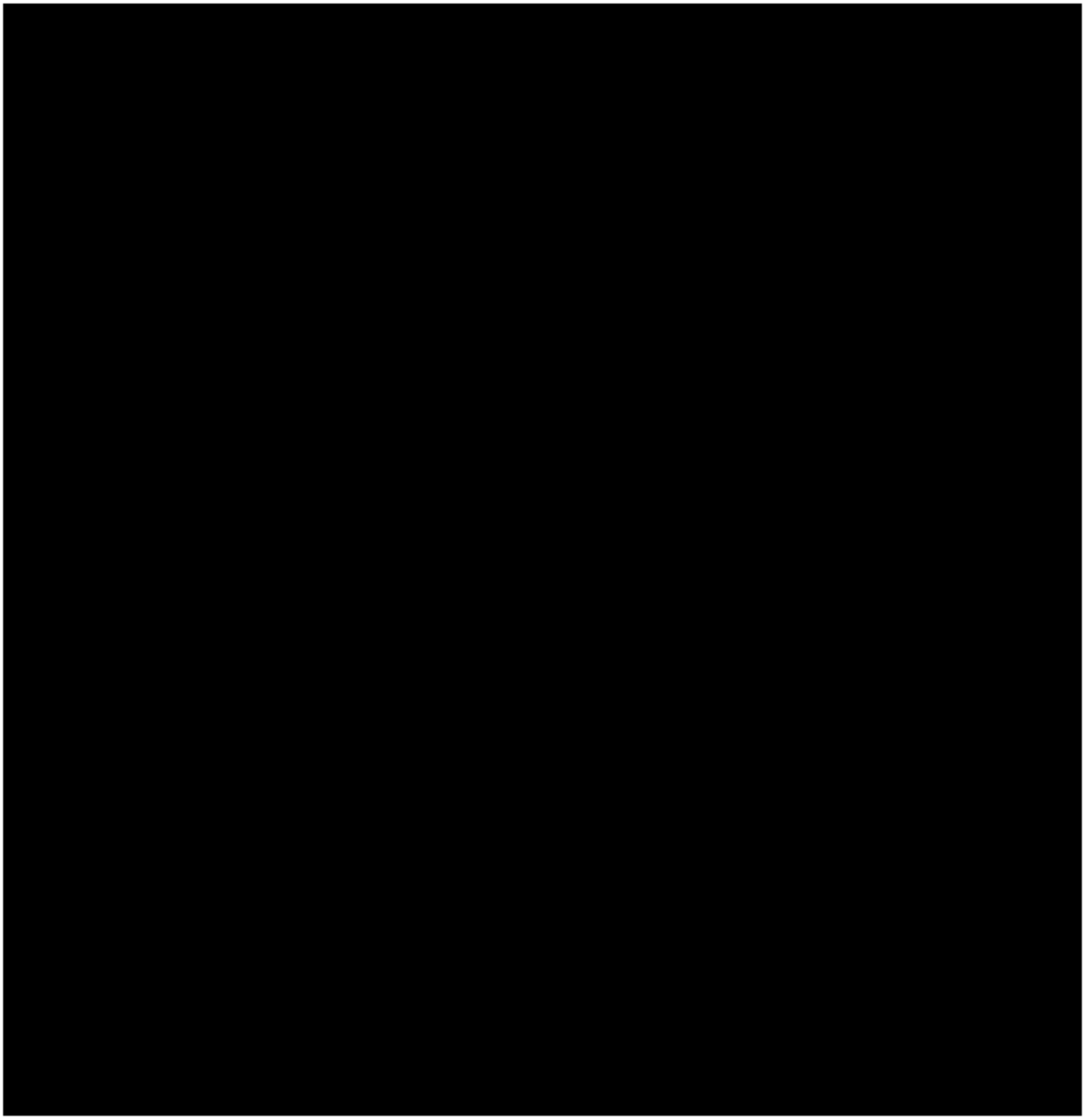


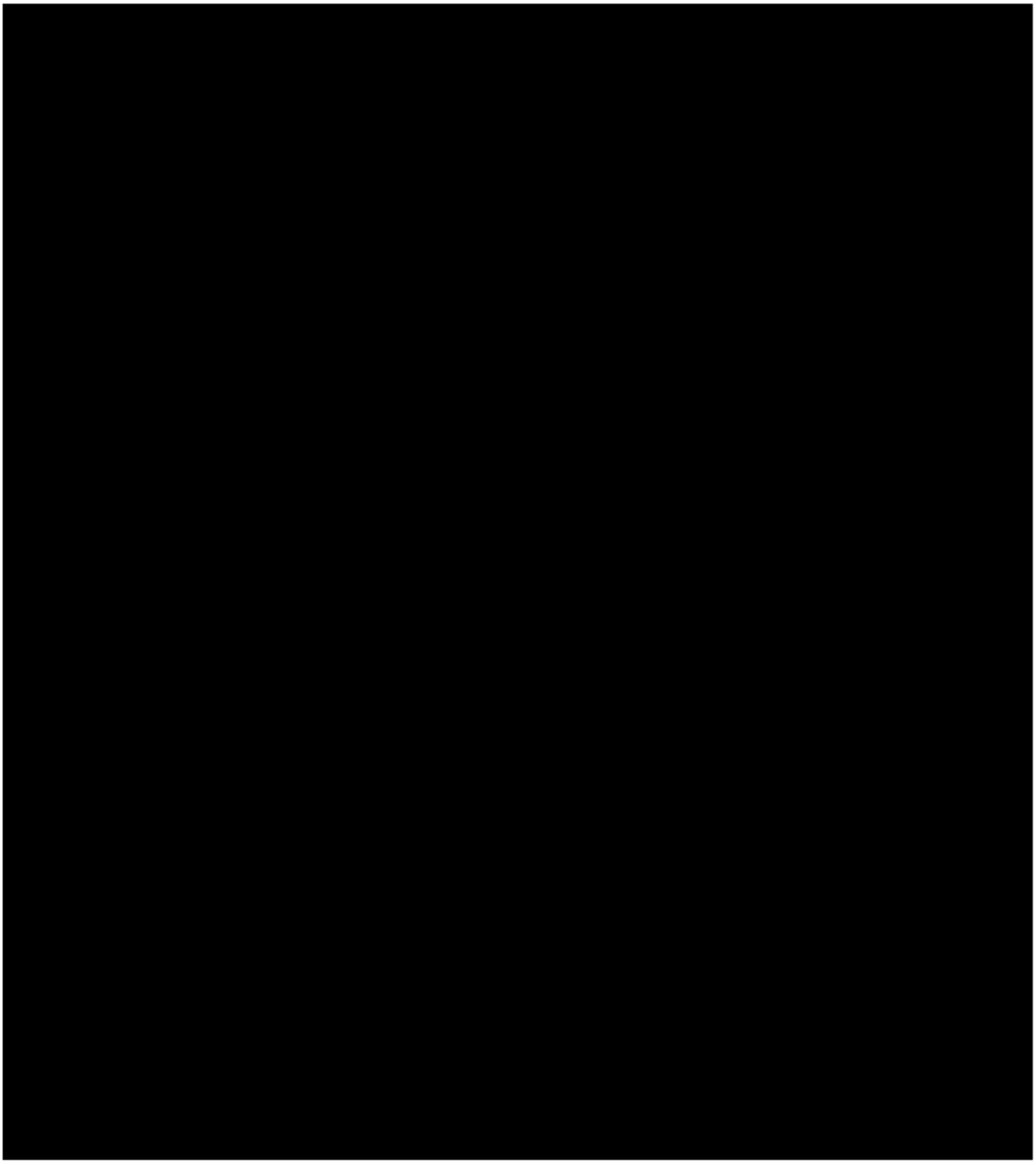
10.8.2. Massete · Prominence Participant Self-Assessment of Change (PSAC)

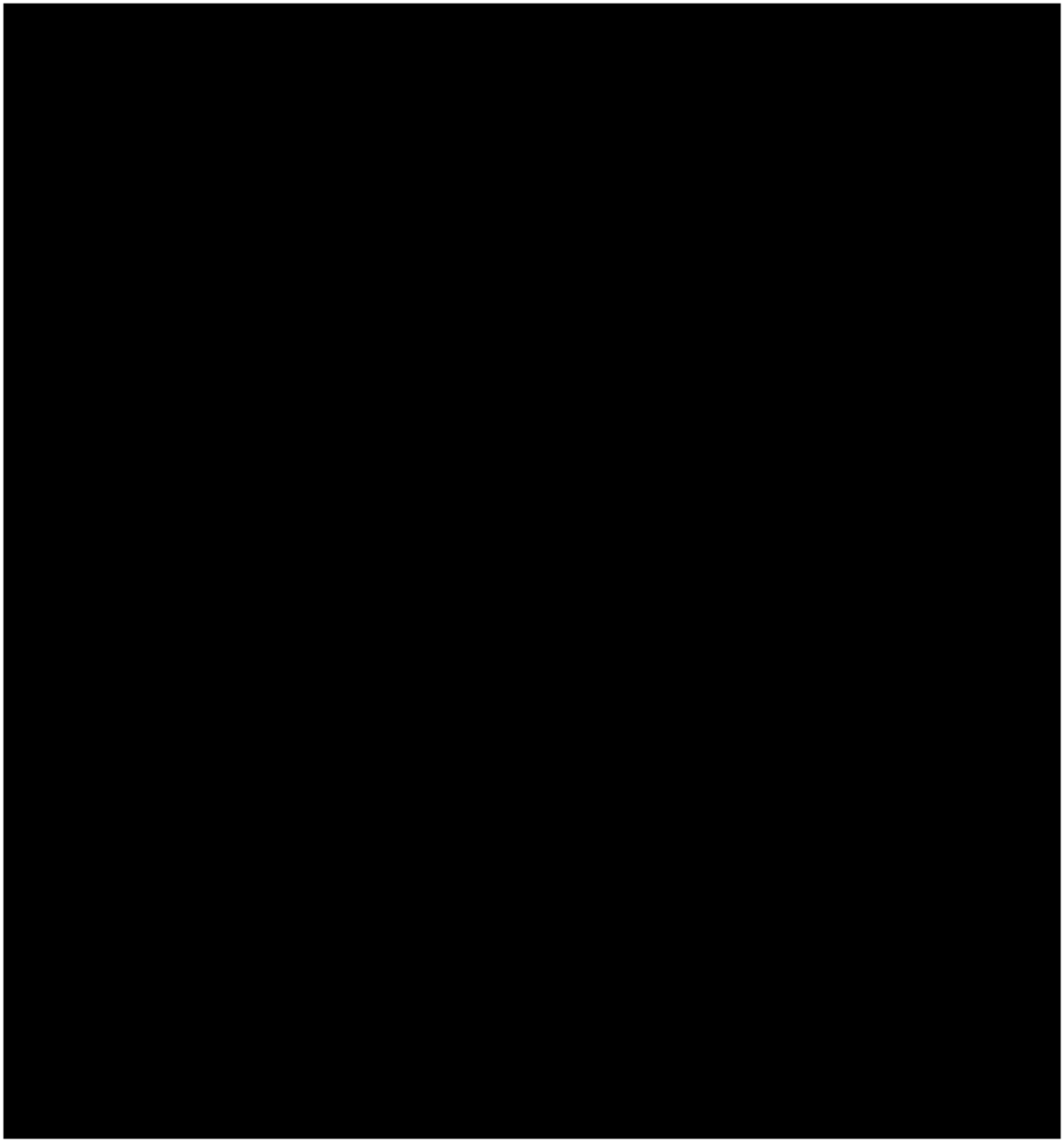


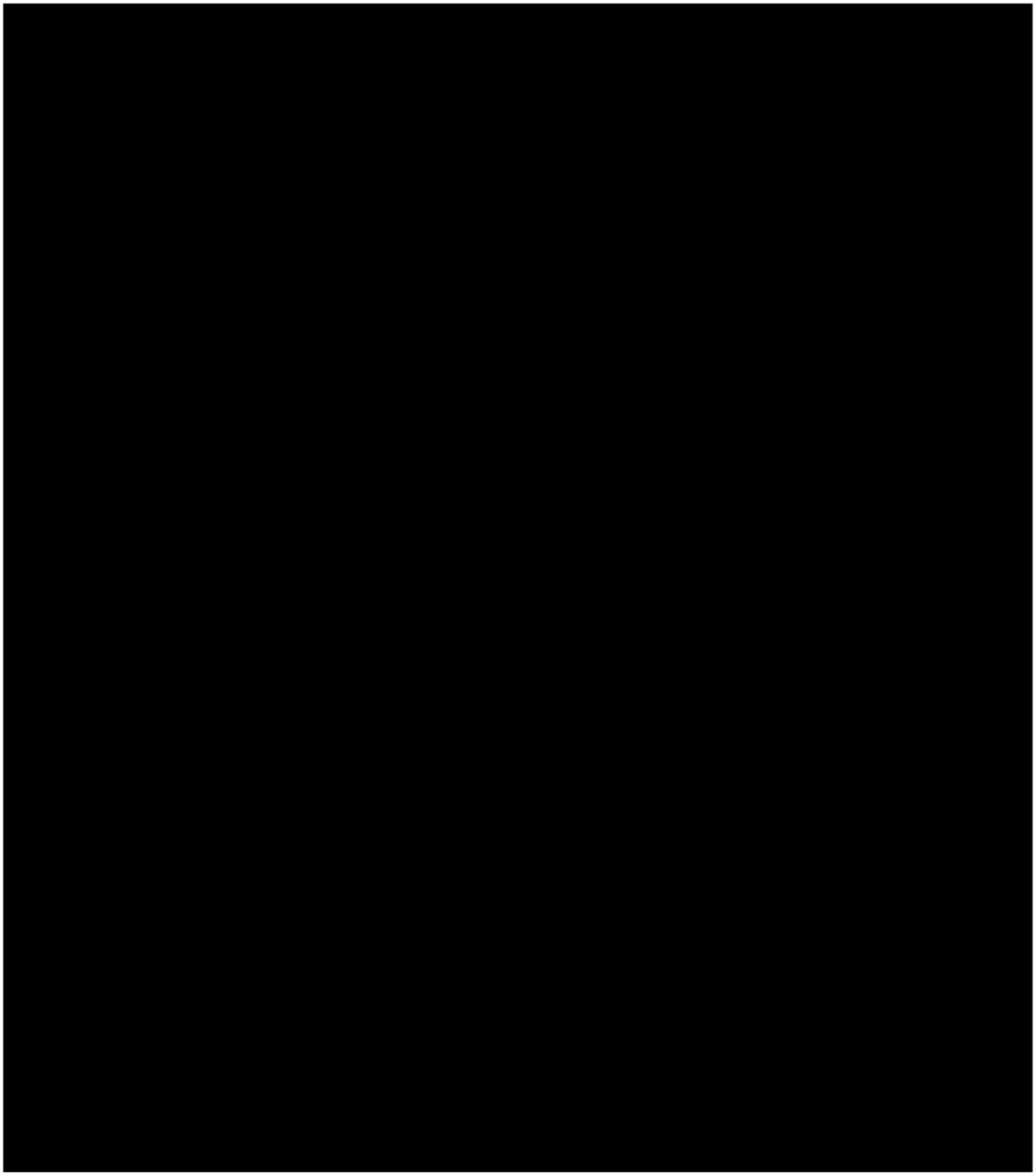
[redacted]

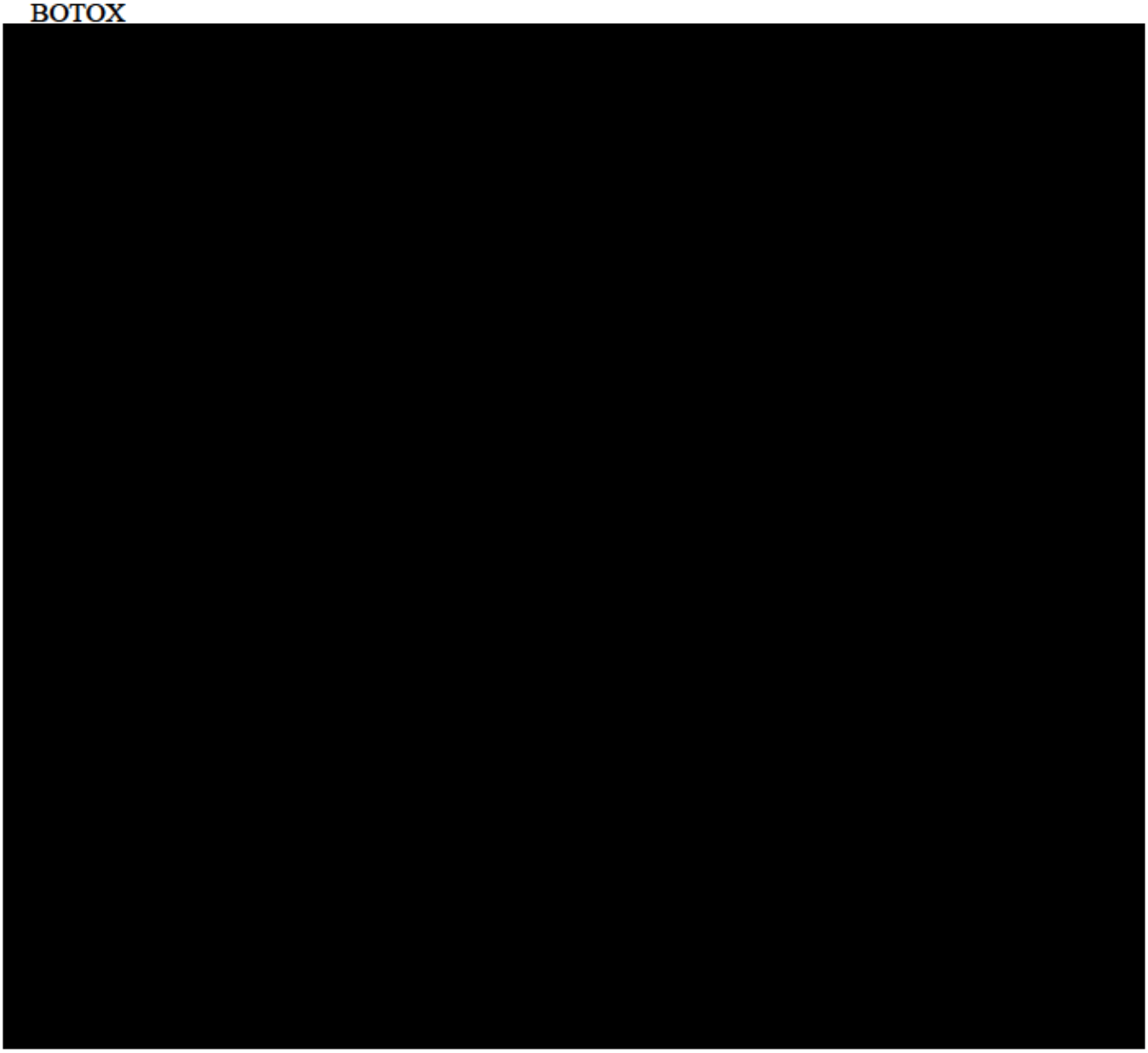
[redacted]











11. References

Adriaens J, van Loon B, Ingels KJ, Berge SJ, Maal TJ. Three-dimensional stereophotogrammetric method of quantifying the effect of botulinum toxin type A injections on masseter hypertrophy. Plast Reconstr Surg. 2012;130(2):376e-378e.

Ahn J, Horn C, Blitzer A. Botulinum toxin for masseter reduction in Asian patients. Arch Facial Plast Surg. 2004;6(3):188-191.

Aydil B, Basaran B, Unsaler S, Suoglu Y. The use of botulinum toxin type A in masseteric muscle hypertrophy: long-term effects and lasting improvement. Kulak Burun Boggaz Ihtis Derg (Journal of Ear, Nose and Throat). 2012;22(5):249-253. [English translation from Turkish]

Baek SM, Kim SS, Bindiger A. The prominent mandibular angle: preoperative management, operative technique, and results in 42 patients. Plast Reconstr Surg. 1989;83:272-278.

Chai G, Zhang Y, Zhu M, Ma X, Yu Z, Mu X, Qi Z. Evaluation of dynamic morphologic changes in the masseter muscle in patients undergoing mandibular angle sagittal split osteotomy. Arch Facial Plast Surg. 2011;13:301-304.

Chang CS, Kang G C-W. Achieving ideal lower face aesthetic contours: combination of tridimensional fat grafting to the chin with masseter botulinum toxin injection. Aesthetic Surgery Journal, 2016;36(10):1093–1100.

Choe SW, Cho WI, Lee CK, Seo SJ. Effects of botulinum toxin type A on contouring of the lower face. Dermatol Surg. 2005;31(5):502-508.

de Menezes M, Rosati R, Ferrario VF, Sforza C. Accuracy and reproducibility of a 3-dimensional stereophotogrammetric imaging system. J Oral Maxillofac Surg. 2010;68:2129-2135.

Deguchi M, Iio Y, Kobayashi K, Shirakabe T. Angle-splitting ostectomy for reducing the width of the lower face. Plast Reconstr Surg. 1997;99:1831-1839.

Fedorowicz Z, van Zuuren EJ, Schoones J. Botulinum toxin for masseter hypertrophy. Cochrane Database Syst Rev. 2013;(9):CD007510. Review.

Herrero BA, Ecklung AE, Streett CS, Ford DF, King JK. Experimental botulism in monkeys: a clinical pathological study. Exp Mol Pathol. 1967;6:84-95.

Hong HS, Kang SC, Kim C-Y, Kim ST. Long-term evaluation of the effect of botulinum toxin A injection in patients with masseteric hypertrophy. Korean J Oral Med. 2005;30(1):121-129.

Jin H. Misconceptions about mandible reduction procedures. Aesthetic Plast Surg. 2005;29:317-324.

Jin H, Kim BG. Mandible reduction versus mandibular angle reduction. Plast Reconstr Surg. 2004;114:1263-1269.

Kim HJ, Yum K-W, Lee S-S, Heo M-S, Seo K. Effects of botulinum toxin type A on bilateral masseteric hypertrophy evaluated with computed tomographic measurement. Dermatol Surg. 2003;29:484-489.

Kim J-H, Shin JH, Kim ST, Kim C-Y. Effects of two different units of botulinum toxin type A evaluated by computed tomography and electromyographic measurement of human masseter muscle. Plast Reconstr Surg. 2007;119(2):711-717.

Kim N-H, Chung J-H, Park R-H, Park J-B. The use of botulinum toxin type A in aesthetic mandibular contouring. Plast Reconstr Surg. 2005;115(3):919-930.

Kim SK, Han JJ, Kim JT. Classification and treatment of prominent mandibular angle. Aesthetic Plast Surg. 2001;25:382–387.

Klein FH, Brenner FM, Sato MS, Robert FM, Helmer KA. Lower facial remodeling with botulinum toxin type A for the treatment of masseter hypertrophy. An Bras Dermatol. 2014;89(5):878-884.

Lee JG, Park YW. Intraoral approach for reduction malarplasty: a simple method. Plast Reconstr Surg. 2003;111:453-460.

Lee KC, Ha SU, Park JM, Kim SK, Park SH, Kim JH. Reduction malarplasty by 3-mm percutaneous osteotomy. Aesthetic Plast Surg. 2006;30:333–341.

Liew S, Dart A. Nonsurgical reshaping of the lower face. Aesthet Surg J. 2008;28(3):251-257.

Mischkowski RA, Siessegger M, Lazar F, Zoller JE. [Chemodenervation with botulinum toxin in masseteric hypertrophy]. Mund-, Kiefer-und Gesichtschir. 2005;9(2):101-108.

Moore AP, Wood GD. The medical management of masseter hypertrophy with botulinum toxin type A. Br J Oral Maxillofac Surg. 1994;32(1):26-28.

Morris DE, Moaveni Z, Lo L-J. Aesthetic facial skeletal contouring in the Asian patient. Clin Plastic Surg. 2007;34:547–556.

Mu X. Experience in East Asian facial recontouring: reduction malarplasty and mandibular reshaping. Arch Facial Plast Surg. 2010;12:222-229.

Onizuka T, Watanabe K, Takasu K, Keyama A. Reduction malar plasty. Aesthetic Plast Surg. 1983;7:121-125.

Park MY, Ahn KY, Jung DS. Botulinum toxin type A treatment for contouring of the lower face. Dermatol Surg. 2003;29:477-483.

Park YJ, Jo YW, Bang SI, Kim HJ, Lim SY, Mun GH, et al. Radiofrequency volumetric reduction for masseteric hypertrophy. Aesthetic Plast Surg. 2007;31:42-52.

Peng H-L P, Peng J-H. Complications of botulinum toxin injection for masseter hypertrophy: incidence rate from 2036 treatments and summary of causes and preventions. J Cosmet Dermatol. 2017;00:1-6

Pu Z, Zhang Y, Yang J, Liu T, Zhang Y, Yang Q, et al. Mandibular angle ostectomy for Chinese women: approaches and extent determined by cephalometric analysis. J Craniofac Surg. 2009;20:105-110.

Rauso R, Santagata M, Colella G. Can occlusal devices prolong the effect of botulinum toxin type A in the contouring of the lower face? Eur J Plast Surg. 2010;33:35-40.

Scott AB. Clostridial toxins as therapeutic agents. In: Simpson LL, editor. Botulinum neurotoxin and tetanus toxin. New York, Academic Press. 1989;399-412.

Shim WH, Yoon SH, Park JH, Choi Y-C, Kim ST. Effect of botulinum toxin type A injection on lower facial contouring evaluated using a three-dimensional laser scan. Dermatol Surg. 2010;36(Suppl 4):2161-2166.

Smyth AG. Botulinum toxin treatment of bilateral masseteric hypertrophy. Br J Oral Maxillofac Surg. 1994;32:29-33.

Sumiya N, Yoshinori I, Ozumi K. Reduction malarplasty. Plast Reconstr Surg. 2004;113:1497–1499.

Tartaro G, Rauso R, Santagata M, Santillo V, Itro A. Lower facial contouring with botulinum toxin type A. J Craniofac Surg. 2008;19:1613-1617.

To EWH, Ahuja AT, Ho WS, King WWK, Wong WK, Pang PCW, et al. A prospective study of the effect of botulinum toxin A on masseteric muscle hypertrophy with ultrasonographic and electromyographic measurement. Br J Plast Surg. 2001;54:197-200.

Tzou C-H J, Frey M. Evolution of 3D surface imaging systems in facial plastic surgery. Facial Plast Surg Clin North Am. 2011;19:591-602.

Wu WTL. Botox facial slimming/facial sculpting: the role of botulinum toxin-A in the treatment of hypertrophic masseter muscle and parotid enlargement to narrow the lower facial width. Facial Plastic Surgery Clinics of North America 2010;18(1):133-140.

Xie Y, Zhou J, Li H, Cheng C, Herrler T, Li Q. Classification of Masseter Hypertrophy for Tailored Botulinum Toxin Type A Treatment. Plast Reconstr Surg. 2014;134:209e-218e.

Yang DB, Park CG. Mandibular contouring surgery for purely aesthetic reasons. Aesthetic Plast Surg. 1991;15:53–60.

Yang DB, Song HS, Park CG. Unfavorable results and their resolution in mandibular contouring surgery. Aesthetic Plast Surg. 1995;19:93-102.