NCT02833077

Study ID: VOLUMA-006

Title: A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for chin augmentation

Protocol Amendment 4 Date: 01 Mar 2017

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Study Title:	A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for chin augmentation
Protocol Number:	VOLUMA-006 Amendment 4
Protocol Date	01 Mar 2017
Product Name:	JUVÉDERM VOLUMA XC Injectable Gel
Development Phase:	Pivotal
Sponsor:	Allergan, Inc. 2525 Dupont Drive Irvine, CA 92612
[redacted]	[redacted]
[redacted]	[redacted]

Names and contact information of Allergan study personnel are provided in the supplementary Study Contacts page.

INVESTIGATOR SIGNATURE PAGE

Study Title:	A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for chin augmentation
Protocol Number:	VOLUMA-006 Amendment 4
Protocol Date:	01 Mar 2017
Product Name:	JUVÉDERM VOLUMA XC Injectable Gel
Investigator:	
Study Location:	

I agree to:

- Implement and conduct this study diligently and in strict compliance with this protocol, good clinical practices (GCP), and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethics Committee (EC), or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

RETURN TO ALLERGAN

Synopsis

NUMBER AND TITLE OF STUDY: VOLUMA-006: A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for chin augmentation
DEVELOPMENT PHASE: Pivotal
STUDY CENTERS: Up to 15 United States (US) centers
NUMBER OF SUBJECTS: Up to 224 subjects will be enrolled
OBJECTIVES: The objectives of this study are to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC injectable gel for chin augmentation to correct volume deficit in adult subjects seeking correction of chin retrusion.
STUDY DESIGN: This is a prospective, multicenter, evaluator-blinded, randomized, controlled study to evaluate the safety and [redacted] **Treatment Group:** For subjects randomized to the treatment group, the TI will use [redacted]

[redacted]

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION:
Adults with chin retrusion who are seeking to increase facial volume in the chin area

INCLUSION:

1. Age 22 or over and in good general health
2. [redacted]
3. Treating Investigator considers the subject's chin retrusion to be amenable to temporary correction
4. Ability to follow study instructions and likely to complete all required visits
5. Written informed consent has been obtained

EXCLUSION:

1. Has ever received permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
2. Has ever undergone fat injections below the subnasale or is planning to undergo this procedure during the study
3. Has tattoos, piercings, facial hair (ie, beard, mustache), or scars below and including the subnasale that would interfere with visual assessment of the chin, jowls, or jawline
4. Has undergone semipermanent dermal filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) in the chin or jaw within 36 months before enrollment or is planning to undergo such treatment during the study
5. Has undergone dermal filler injections, or has undergone any surgery in the chin or jaw area (including marionette lines, pre-jowl sulci, mandibular body, or masseter muscles) within 24 months before enrollment or is planning to undergo any of these procedures during the study
6. Has undergone dermal filler injection in the lips or perioral area within 12 months before enrollment or is planning to undergo such treatment during the study
7. [redacted]
8. [redacted]
9. [redacted]
10. Has undergone mesotherapy or cosmetic treatment (laser, photomodulation, intense pulsed light, radio

frequency, dermabrasion, moderate or greater depth chemical peel, liposuction, lipolysis, or other ablative procedures) anywhere in the face or neck, or botulinum toxin treatment below the subnasale (including injections to the masseter muscles) within 6 months before enrollment or is planning to undergo any of these procedures during the study

[redacted]

TEST PRODUCT, DEVICE VOLUME, AND MODE OF ADMINISTRATION:

[redacted] Appropriate injection volume for the chin and chin area will be determined by the Treating Investigator but is not to exceed a maximum total volume of 4.0 mL for initial and touch-up treatments combined, and 4.0 mL for repeat treatment.

DURATION OF STUDY: Treatment Group: Initial treatment period: up to 30 days; Follow-up period: 12 months following last treatment (initial or touch-up), and 1 month following optional repeat treatment. Control Group: Control period: 6 months; Initial treatment period: up to 30 days; Follow-up period: 6 months following last treatment (initial or touch-up)

RESPONSE MEASURES:

Effectiveness: The primary effectiveness measure is the EI's photo assessment of chin retrusion using the ACRS at month 6 based on 2D profile images of the left side of the chin rendered by the Canfield image analysis technician from the 3D images. Secondary effectiveness measures include EI and subject assessments of global aesthetic improvement in the chin area using the 5-point GAIS, and subject responses on the Satisfaction with Chin module of the validated FACE-Q questionnaire. [redacted].

[redacted]

STATISTICAL METHODS:

Sample Size Calculation: Sample size is determined to provide adequate power to demonstrate that the product is effective as well as safe. A sample size of 120 subjects in the treatment group and 40 subjects in the control group will provide > 99% power to detect a difference of at least 40% in the responder rates between the groups. This calculation is based on a 2-sided Fisher's exact test at the 5% level. The treatment group is assumed to have at least 80% responder rate and the control group will have at most 40% responder rate. Assuming a screen fail rate of 15% and a drop-out rate of 15% between randomization and the month 6 visit, up to 224 subjects will be enrolled, resulting in up to 168 subjects randomized to the treatment group and up to 56 subjects to the control group (3:1 ratio). Assuming a screen fail rate of 15% and an overall drop-out rate of 20% between randomization and study completion, an estimated 152 subjects will complete the study.

With up to 168 subjects randomized to the treatment group and an estimated screen fail rate of 15%, it is estimated that at least 143 subjects will be treated in the study. With 143 treated subjects, there is at least an 88% power to detect an AE related to treatment with an incidence rate of 1.5% in the population using a 1-sided exact binomial test at the 2.5% level.

Due to an estimated 15% of subjects having a baseline photo assessment of 1 or 4, up to 36 additional subjects may be randomized to ensure sufficient power for sensitivity analyses, resulting in a total of up to 260 subjects enrolled.

The commercial software, [redacted] was used for the power calculation. The sample size calculation used an inequality test for 2 proportions to demonstrate that the treatment group is superior to the control group. The safety calculation used an inequality test for 1 proportion.

Effectiveness: The primary effectiveness endpoint will be met if the responder rate at month 6 for the treatment group is statistically greater than that for the control group at month 6 and the responder rate at month 6 for the treatment group is greater than 50%. Responder rate is the percentage of subjects who show at least 1-point improvement on the ACRS from baseline based on EI assessment of 2D renderings of the chin profile. Baseline is defined as the EI assessment of the 2D image at randomization (or screening if no usable randomization photo is available). The primary effectiveness analysis will be performed on the modified intent-to-treat (mITT) population, which includes subjects who are randomized to study treatment (treatment group) and receive at least 1 study device treatment or are randomized to the control group. A sensitivity analysis will be performed on the intent-to-treat (ITT) population, which includes all randomized subjects. For the primary effectiveness analysis, a 2-sided, Fisher's exact test at the 5% level will be used to test whether the responder rate from baseline for the treatment group is significantly greater than that for the control group at month 6 in the control

period.

The secondary effectiveness analyses will include the responder rates with 95% confidence intervals for the treatment group based separately on the EI and subject assessments of GAIS, where a "responder" is a subject who shows improvement in the overall aesthetic assessment in the chin area (Improved or Much Improved on GAIS) at the month 6 visit and descriptive summary of the change in overall score of subject's satisfaction with chin since baseline at the month 6 visit based on the treatment group subjects' responses on Satisfaction With Chin FACE-Q questionnaire and a 2-sided paired t-test at the 5% level to demonstrate that the mean overall satisfaction score at month 6 visit is statistically greater than that at baseline for the treatment group. Other effectiveness analyses will include [redacted]

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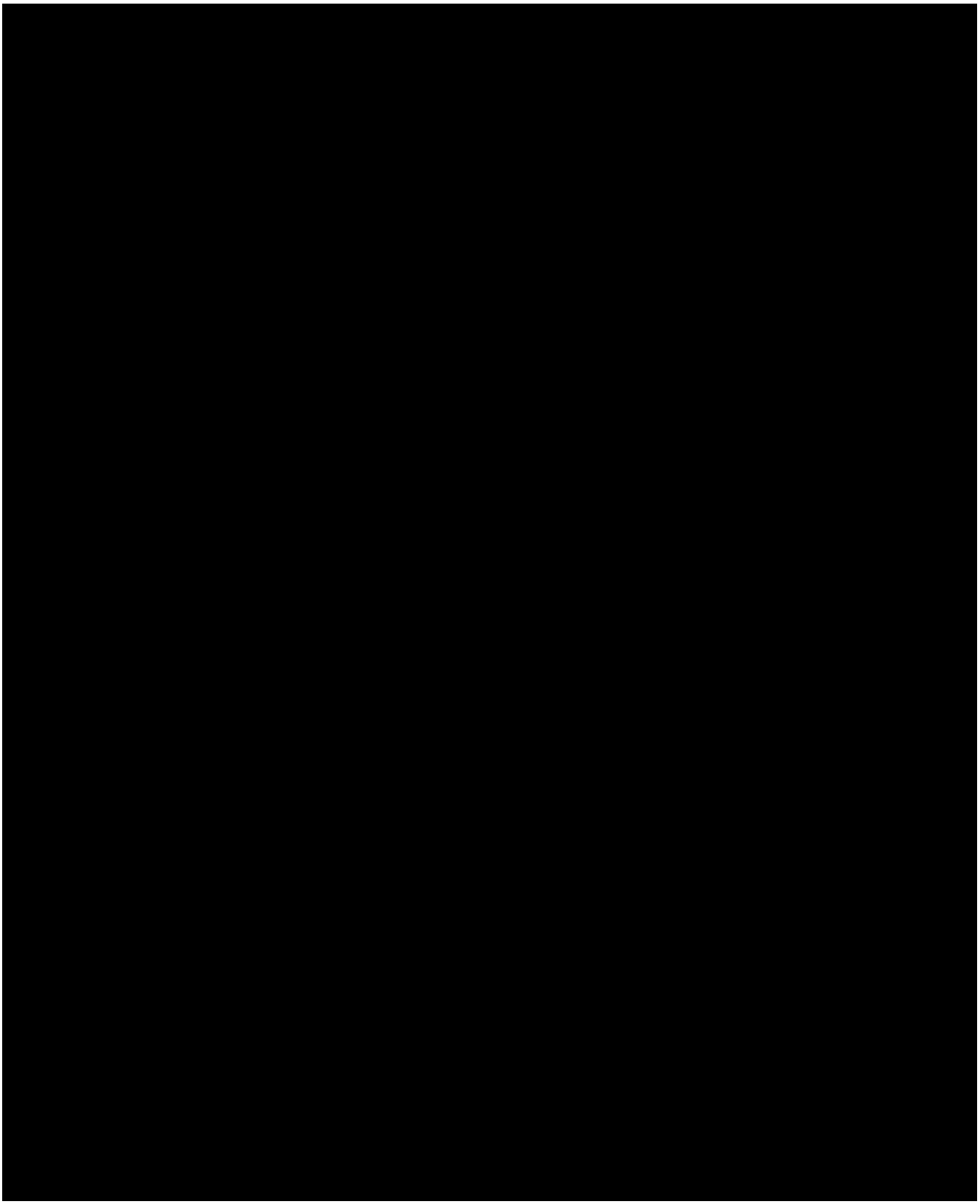
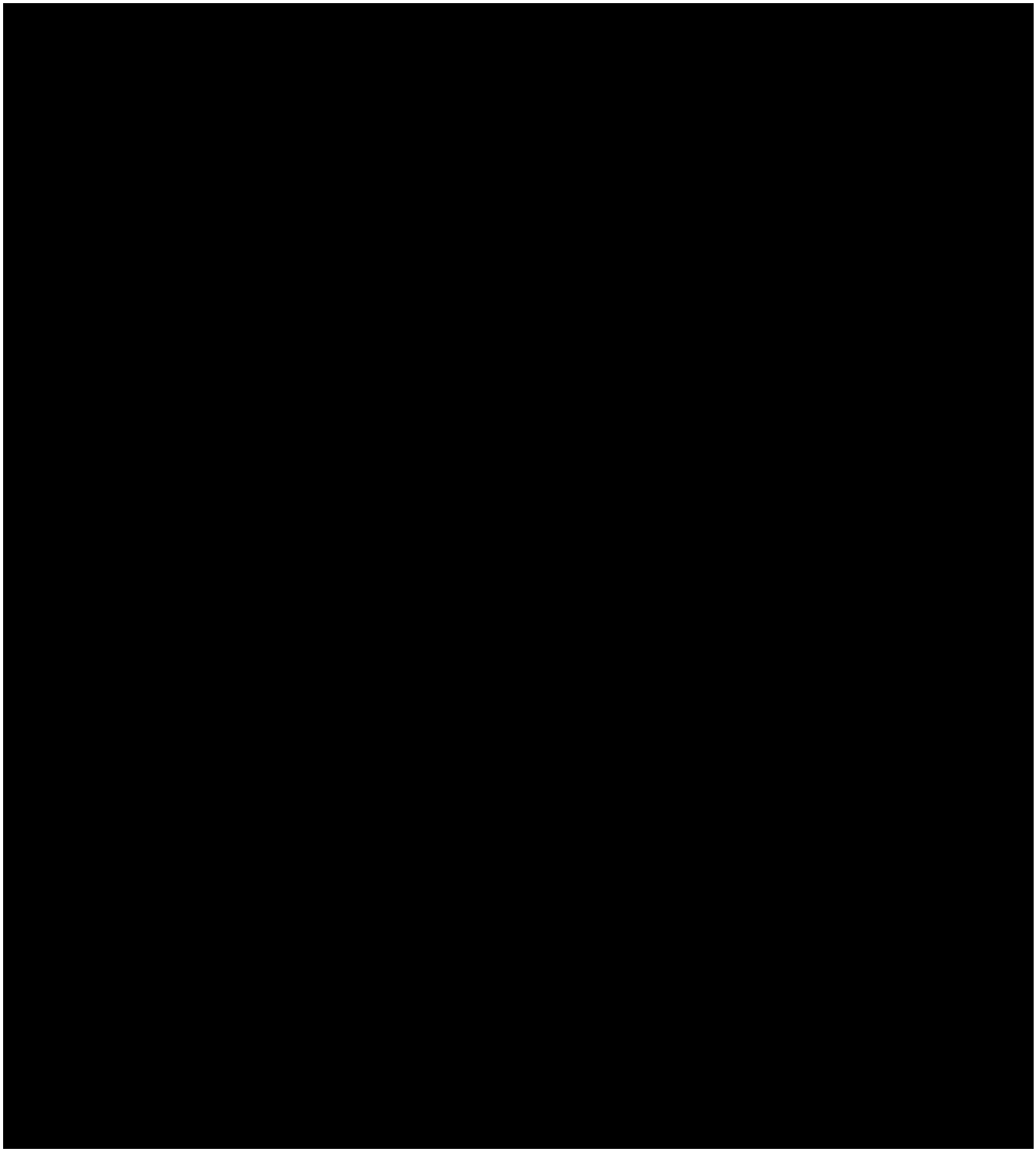




1. Abbreviations and Terms

Term/Abbreviation	Definition
2D	2-dimensional
3D	3-dimensional
ACRS	Allergan Chin Retrusion Scale
ADE	adverse device effect
AE	adverse event
CFR	Code of Federal Regulations
CI	confidence interval
eCRF	electronic case report form
EI	Evaluating Investigator
DFU	directions for use
FDA	Food and Drug Administration
[redacted]	[redacted]
GAIS	Global Aesthetic Improvement Scale
HA	hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
IC	informed consent
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	injection site response
ITT	Intent-to-treat
IWRS	interactive web response system
mITT	modified intent-to-treat
PP	per-protocol
PT	preferred term
SADE	serious adverse device effect
SOC	system organ class
TI	Treating Investigator
UADE	unanticipated adverse device effect
US	United States

2. Background, Risk and Benefit, and Clinical Rationale

2.1 Background

Hyaluronic acid (HA) injectable gels have become a primary treatment for facial rejuvenation, with an established record of safety and effectiveness (Jones and Flynn, 2010). A range of HA injectable gels is available for correction of wrinkles and folds. However, the paradigm for achieving a more youthful looking face has moved away from the approach of treating discrete wrinkles and folds to one focused on panfacial volumizing. One such product, JUVÉDERM VOLUMA® XC, was specifically designed for volumizing and has demonstrated effectiveness in restoring age-related volume deficit to the mid-face (Jones and Murphy, 2013). JUVÉDERM VOLUMA XC can better achieve balanced facial proportions because it has improved qualities of lift and projection compared with HA gels designed for correction of wrinkles and folds. Another area of the face where lift and projection are important aspects of volumizing includes the chin area.

The shape and projection of the chin contribute to the proportional balance of the face that underlies attractiveness. A chin lacking projection is commonly labeled a "weak chin" whereas prominent chins are labeled "strong chins" and imply strength of personality (Naini, 2011). Several studies have suggested that faces with average proportions are viewed as the most attractive and that juvenile features including a small chin are interpreted as attractive in females while a strong chin and jaw are interpreted as attractive in males (Jones and Hill, 1993; Schact, 2005). The appearance of the chin is a determinant of perceived attractiveness and can influence an individual's psychosocial well-being (Naini et al, 2012).

In a survey to understand the role of the nose, lips, and chin in achieving a balanced facial profile, 545 professionals viewed a series of silhouettes that varied in the size of the nose, lips, angle of facial convexity, and facial angle. Both males and females least favored retrusive chin profiles. Sagittal changes in the position of the chin formed by varying the soft tissue facial angle and resulting in a more pronounced chin were more favored, especially by males (Czarnecki et al, 1993).

As the mandible and chin are the framework of the lower face, augmentation methods to treat chin retrusion and contour changes of the chin area or to treat microgenia have been explored for decades. Where the approach in correcting chin retrusion is to add volume, treatment methods have included chin implants, genioplasty, and injection of silicone and semi-permanent fillers, such as polymethylmethacrylate microspheres, and calcium

hydroxyapatite. However, all of these treatment methods have drawbacks. For example, chin implants and genioplasty involve painful surgery that may not result in correction of chin retrusion and aesthetic blending of the area. This approach may exacerbate bone resorption and infection, resulting in the need for implant removal (Frodel, 2005; Rubin and Yaremchuk, 1997; Yaremchuk, 2003). Injection of semi-permanent fillers has trade-offs between volumizing capacity and adverse events (AEs). Temporary dermal fillers offer a better alternative.

JUVÉDERM VOLUMA XC is a temporary HA dermal filler that is a structural gel manufactured specifically to provide a safe, minimally invasive method to restore and create facial volume. JUVÉDERM VOLUMA XC is currently indicated in the United States (US) for injection into the subcutaneous and/or supraperiosteal space of the mid-face to add volume in the cheek area; and it is approved outside of the US for volumizing other areas of the face, including the chin and chin area. As JUVÉDERM VOLUMA XC is moldable after injection, it allows for sculpting, contouring, and shaping across the injected areas to achieve the optimal aesthetic outcome. As the chin and chin area is a high mobility areas where a structural filler is expected to be more effective, this area represents an excellent target for leveraging the volumizing and lifting capabilities of JUVÉDERM VOLUMA XC. The current study will investigate the safety and effectiveness of JUVÉDERM VOLUMA XC in subjects seeking to correct volume deficit in the chin and chin area.

2.2 Risk and Benefit

The injection procedure, anesthetic agents, or JUVÉDERM VOLUMA XC may cause some of the risks and/or discomforts listed below. Unforeseeable risks or results are also a possibility. The risk of developing a serious complication is small. If a complication occurs, subjects will be advised to contact the Treating Investigator (TI) who will use his/her medical judgment to do whatever is necessary to treat the subject.

For a more comprehensive review of the risk profile of JUVÉDERM VOLUMA XC, including Contraindications, Warnings, and Precautions, please refer to the VOLUMA-006 directions for use (DFU).

As with any skin injection, risks can be posed by the injection procedure itself, the anesthetic agent, and injection of JUVÉDERM VOLUMA XC Injectable Gel. Risks related to the injection procedure include redness, itching, pain, tenderness, swelling, bruising, and lumps and bumps, which are common to dermal filler injection procedures, in general. The use of a small gauge needle to deliver JUVEDERM VOLUMA XC in this study is intended to

minimize tissue trauma. Risks associated with the anesthetic agent include allergic reactions that may manifest as an anaphylactic reaction, skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient loss of skin color. The inclusion of 0.3% lidocaine in the formulation is meant to reduce pain during the injection and this should be taken into account when administering concomitant additional anesthetics.

Prior to administering any topical pretreatment anesthesia, the Investigator will thoroughly review the subject's history to confirm the suitability of the planned anesthetic agent and route of administration. Additionally, the VOLUMA-006 DFU must be carefully reviewed, and each individual subject's medical history should be carefully considered, when evaluating a potential subject's candidacy for study enrollment.

The safety and effectiveness of JUVÉDERM VOLUMA XC has been established for increasing facial volume in the cheeks (Jones, 2013). Since the injections will be in the same tissue planes, and the neurovascular structures of the cheeks and chin are similar, the safety and effectiveness profiles of JUVÉDERM VOLUMA XC in the chin are expected to be similar to the safety and effectiveness profiles of JUVÉDERM VOLUMA XC demonstrated in the cheeks.

In a multicenter study of JUVÉDERM VOLUMA XC in the cheeks, safety and effectiveness information was collected for 270 subjects who received treatment. The volume of treatment injected varied depending on the subject's volume deficit and treatment goal, and ranged from 1.2 mL to 13.9 mL (median 4.8 mL). After initial treatment with JUVEDERM VOLUMA XC, 98% of subjects reported experiencing a local treatment site response, predominantly mild or moderate in severity (80.7%), lasting 2 to 4 weeks. The most frequent treatment site responses were tenderness (92.1%), swelling (85.7%), and firmness (82.3%). AEs were experienced less frequently (32.6%) than treatment site responses, and were also generally mild to moderate in severity. Almost all (99%) of the reported AEs were at a treatment site, with the most frequently reported device- and injection-related AEs being treatment site mass (18.9%), treatment site induration (14.1%), and treatment site swelling (7.0%).

A treatment responder was identified as having an improvement of ≥ 1-grade change on the validated 6-point photometric mid-face volume deficit scale (MFVDS) at 6 months after the initial treatment compared to baseline. The responder rate of the treatment group was 85.6%, which was significantly greater ($p < 0.0001$) than the responder rate for the control group (38.9%), demonstrating that the vast majority of treatment group subjects experienced

improvement in their facial appearance at the primary timepoint of 6 months after treatment. When followed through 24 months after treatment, the responder rate was 67.1%.

The benefits of the study treatment are expected to include greater lift capacity with a favorable tolerability profile compared with alternative available treatments. Although there are risks associated with the injection procedure and with the product formulation (including HA, lidocaine, and crosslinker), the enhanced product characteristics of a viscous and cohesive gel are expected to result in significant advantages to the subject as they allow the investigator to treat a discrete area using a minimally invasive procedure with the ability to sculpt for optimal aesthetic augmentation of the chin and chin area.

The safety and effectiveness after injection of study treatment to the chin area are expected to be similar to the profiles described for JUVÉDERM VOLUMA XC when injected in the cheeks.

2.3 Clinical Rationale

JUVÉDERM VOLUMA XC was designed specifically for volumizing and has demonstrated effectiveness in restoring age-related mid-face volume deficit (Jones, 2013). The protocol is designed as a pivotal study to collect safety and effectiveness data associated with the implantation of JUVÉDERM VOLUMA XC for the augmentation of chin retrusion in adult subjects seeking improvement in chin volume deficit.

3. Study Objectives and Clinical Hypotheses

3.1 Study Objectives

The objectives of this study are to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC injectable gel in augmentation of chin retrusion in adult subjects seeking improvement in chin volume deficit.

3.2 Clinical Hypothesis

The clinical hypothesis is that the percentage of subjects with a clinically significant change (defined as at least a 1-point improvement in the Allergan Chin Retrusion Scale [ACRS] score as assessed by the Evaluating Investigator [EI] based on assessment of 2-dimensional [2D] renderings of 3-dimensional [3D] digital facial images) in chin retrusion from baseline to month 6 will be significantly greater in the JUVÉDERM VOLUMA XC treatment group

than in the untreated control group and the percentage of the treatment group with a clinically significant change in chin retrusion from baseline to month 6 will be greater than 50%.

4. Study Design

4.1 Structure

This is a prospective, multicenter, evaluator-blinded, randomized, controlled study. Up to 15 investigational sites will enroll and follow subjects who meet the study criteria.

4.2 Duration

The study will span a total of approximately 23 months: an estimated 9 months for recruitment, 1 month for treatment, and up to 13 months for follow-up. Participation for each subject randomized to the treatment group will encompass up to 1 month for screening, up to 1 month for treatment, 12 months of follow-up after the last treatment (initial or touch-up), and 1 month of follow-up after optional repeat treatment. Participation for each subject in the control group will encompass up to 1 month for screening, 6 months for the no-treatment control period, up to 1 month for optional treatment, and 6 months of follow-up after the last treatment (initial or touch-up).

4.3 Treatment Groups and Treatment Regimen

4.3.1 Study Treatment

JUVÉDERM VOLUMA XC injectable gel

4.3.2 Control Treatment

No treatment

4.3.3 Methods for Blinding

The EI and the Canfield image analysis technician will be blinded to treatment until after the month 6 visit when the control group subjects complete the control period. The EI will not be present during the injection procedures. The 2D images used for ACRS assessments will be cropped by the Canfield image technician to include only the lower face. The EI will not be blinded to the timepoint at which photos were taken. As the image files will be accessed by the blinded image analysis technician, the image files will not reveal subject treatment

randomization or the timepoint at which the image was captured. The EI will access images through a web-based portal that can have additional information.

The Treating Investigators (TIs), study coordinators, and subjects will not be blinded to treatment, but they will secure the randomization and other records (eg, records of study treatments and records of all prior study assessments, including scores and whether an assessment was performed) from potential discovery by the blinded EI. The TI will not discuss the randomized treatment assignments with or in the presence of the EI.

4.3.4 Retreatment Criteria

The subject may undergo a touch-up treatment 30 days after the initial treatment (ie, at the month 1 follow-up visit) if both the subject and TI determine that optimal correction has not been achieved and total treatment has been less than 4.0 mL. The total injection volume for an individual subject for the initial and touch-up treatments combined cannot exceed 4.0 mL.

Subjects in the treatment group may undergo repeat treatment 12 months after the last treatment (ie, at the month 12 follow-up visit after all procedures are completed). The total injection volume for repeat treatment cannot exceed 4.0 mL.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

Topical anesthesia may be used during treatment according to routine practice, but it must be limited to the treatment areas only. Examples of permitted topical anesthesia include: ice, lidocaine cream, or both.

If a subject is on a regimen of over-the-counter or prescription, oral or topical, anti-wrinkle products below the subnasale, the regimen must have been stable for at least 30 days prior to study enrollment and the subject must continue with the regimen throughout the study.

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the subject's electronic case report form (eCRF) at each visit along with the reason the medication is taken.

Therapy considered necessary for the subject's welfare may be given at the discretion of the TI. If the permissibility of a specific medication/treatment is in question, please contact Allergan.

4.4.2 Prohibited Medications/Treatments

Subjects must not initiate or be on an existing regimen of anti-coagulant medications (eg, warfarin, clopidogrel) or other medications or substances known to increase coagulation time (eg, aspirin, ibuprofen, or herbal supplements) in the 10 days prior to undergoing study device injection and for 3 days afterward.

During the course of the study, subjects must not:

- be on an ongoing regimen of lidocaine or structurally-related local anesthetics
- be on an ongoing regimen of drugs that reduce or inhibit hepatic metabolism (eg, cimetidine, beta-blockers)
- be enrolled in another study and may not receive another investigational product in the 30 days prior to study enrollment
- receive permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck
- receive facial tissue augmentation with fat injections below the subnasale; semi-permanent dermal fillers (eg, calcium hydroxyapatite, poly-L-lactic acid) in the chin or jaw; or dermal filler injections in the glabellar area, nose, lips, or perioral area
- receive botulinum toxin injections below the subnasale (including the masseter muscles)
- undergo mesotherapy or receive cosmetic facial procedures (eg, face-lift, brow lift, facial reconstructive surgery, laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) anywhere in the face or neck
- undergo allergen desensitization therapy
- undergo any piercing or tattooing procedures below the subnasale
- undergo any dental procedure (other than prophylaxis or dental fillings)

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan is to be notified before the prohibited medication/treatment is administered.

4.4.3 Escape Medications

Although several authors have reported that hyaluronidase (Vitrase™ or Amphadase®) is effective in reversing the effects of misplaced or excess HA-based dermal fillers, no hyaluronidase product has been approved for this indication. Therefore, administration of hyaluronidase for this use should not be performed during this study.

4.4.4 Special Diet or Activities

Within the first 24 hours after treatment, subjects should avoid strenuous exercise, extensive sun or heat exposure, and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection sites.

For 2 days after treatment, subjects should avoid unnecessary external compression of the treatment site that could cause displacement or indentation where the product has been placed. Subjects will be advised not to have a massage, enter a hot spring or sauna, receive excessive sun exposure, or go swimming during the week following study treatment (initial, touch-up, or repeat).

4.5 Treatment Allocation Ratio

Subjects are randomized at an allocation ratio of 3 treatment with JUVÉDERM VOLUMA XC to 1 control group.

5. Study Population

5.1 Number of Subjects

Up to 224 subjects will be enrolled at up to 15 sites.

5.2 Study Population Characteristics

Adult subjects with chin retrusion who are seeking to increase facial volume in the chin area will be recruited.

5.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Age 22 or over and in good general health

[redacted]

3. Treating Investigator considers the subject's chin retrusion to be amenable to temporary correction

[redacted]

5.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. Has ever received permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
2. Has ever undergone fat injections below the subnasale or is planning to undergo this procedure during the study
3. Has tattoos, piercings, facial hair (ie, beard, mustache), or scars below and including the subnasale that would interfere with visual assessment of the chin, jowls, or jawline
4. Has undergone semipermanent dermal filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) in the chin or jaw within 36 months before enrollment or is planning to undergo such treatment during the study
5. Has undergone dermal filler injections, or has undergone any surgery in the chin or jaw area (including marionette lines, pre-jowl sulci, mandibular body, or masseter muscles) within 24 months before enrollment or is planning to undergo any of these procedures during the study
6. Has undergone dermal filler injection in the lips or perioral area within 12 months before enrollment or is planning to undergo such treatment during the study

[redacted]

10. Has undergone mesotherapy or cosmetic treatment (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, liposuction, lipolysis, or other ablative procedures) anywhere in the face or neck, or botulinum toxin treatment below the subnasale (including injections to the masseter muscles) within 6 months before enrollment or is planning to undergo any of these procedures during the study

[redacted]

[redacted]

6. Procedures

6.1 Washout or Run-In Intervals

[redacted]

6.1.2 Run-in Intervals

Run-in Intervals	Medication or Procedure
2 days before treatment 30 days before enrollment	• Prophylactic herpes treatment for subjects with a history of recurrent oral herpes lesions • Over-the-counter or prescription, oral or topical, anti-wrinkle products below the subnasale for subjects who will use such products during the study

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3 Instructions for the Subjects

At the screening visit, the TI (or designee) will discuss alternative treatments that may be available with any subject who is interested in participating in the study; he/she will counsel the subject regarding his/her treatment goals and the potential benefits and limitations of study treatment. After counseling, if the subject's expectations are achievable within the parameters of the study, the TI (or designee) will proceed with obtaining the subject's signature on the ICF and will continue the subject in the study.

During each study visit, subjects will be required to remove all jewelry, make-up, and lipstick, and male subjects must be clean-shaven below the subnasale to avoid interference with digital imaging and evaluations of the chin and chin area.

To reduce the risk of posttreatment bleeding or bruising, subjects on a regimen of medications (eg, aspirin or ibuprofen) or other substances known to increase coagulation time (eg, herbal supplements with garlic or gingko biloba) must suspend the regimen for at least 10 days before and 3 days after study treatment (initial, touch-up, and repeat).

For at least 24 hours after treatment, subjects should avoid strenuous exercise, consumption of alcoholic beverages, and extended exposure to sun or heat to reduce the risk of posttreatment redness, swelling, and/or itching.

For 2 days after treatment, subjects should avoid unnecessary external compression to the treatment site that could cause displacement or indentation where the product has been placed. Subjects should also avoid having a massage, entering a hot spring or sauna, receiving excessive sun exposure, or going swimming during the week following study treatment (initial, touch-up, and repeat).

Subjects will also be instructed to contact the TI or his/her research staff to report any unexpected symptoms or to ask questions about the study.

6.4 Unscheduled Visits

An unscheduled visit may occur for safety purposes (eg, evaluation of AEs or ISRs as requested by the subject and/or TI). Applicable procedures will be performed and recorded on the eCRF.

An unscheduled visit may also occur to repeat facial digital images if those obtained at the scheduled visit are poor quality images.

6.5 Early Discontinuation of Subjects

Each subject reserves the right to withdraw from the study at any time without jeopardy to his/her future medical care. The month 12/early exit procedures are to be performed at the final study visit. Subjects may also be administratively withdrawn if they do not return for follow-up visits. For any subject who withdraws from the study, the date and reason for withdrawal will be recorded on the eCRF. If an AE is ongoing at the time of withdrawal and is related to the study treatment, the TI will attempt to follow the subject until the AE has

been resolved or follow-up is no longer possible. The TI shall ask for the subject's permission to follow his/her status/ condition outside the study.

If a subject fails to return for 1 or more scheduled study visits, the TI (or designee) will attempt to contact the subject to determine and document the reason the subject has failed to return, and to encourage compliance with the study visit schedule.

6.6 Withdrawal Criteria

If a subject has a positive urine pregnancy test at the time of the initial, touch-up, or repeat treatment visit, the subject will not be eligible for treatment and will be withdrawn from the study. The pregnancy will be followed as described in Section 10.3.

In addition, a subject must be withdrawn from the study if he or she:

- receives any dermal filler or fat injection to the chin area
- undergoes facelift or facial reconstructive surgery
- receives treatment with hyaluronidase in the chin area

7. Response Measures and Summary of Data Collection Methods

7.1 Effectiveness Measures

7.1.1 Primary Effectiveness Measure

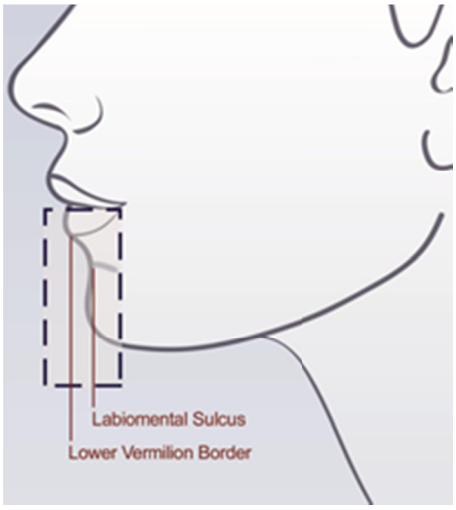
The primary effectiveness measure is the EI's photo assessment of chin retrusion using the ACRS described in Table 6 and Figure 1. The EI will assess 2D profile images of the left side of the chin rendered by the Canfield image analysis technician from the 3D images.

Table 6 Allergan Chin Retrusion Scale

Score	Grade	Description
0	None	No chin retrusion; Chin midpoint* at or in front of the lower vermilion border vertical line
1	Minimal	Minimal chin retrusion; Chin midpoint* is between the labiomental sulcus vertical line and lower vermilion border vertical line
2	Moderate	Moderate chin retrusion; Chin midpoint* at labiomental sulcus vertical line
3	Severe	Severe chin retrusion; Chin midpoint* slightly behind labiomental sulcus vertical line
4	Extreme	Extreme chin retrusion; Chin midpoint* significantly behind labiomental sulcus vertical line

* Chin midpoint: the midpoint between the labiomental sulcus and the inferior point of the chin

Figure 1 Lines Used in the ACRS Descriptors



The ACRS is a 5-point ordinal scale developed by Allergan to grade the severity of chin retrusion. The ACRS contains photographic images of subjects representing different Fitzpatrick skin types, race categories, and severities of chin retrusion (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Extreme). A scale validation study was conducted to assess the inter- and intra-rater reliability of the ACRS. The results confirmed that the ACRS is validated and appropriate to be used as a primary effectiveness measure for this study.

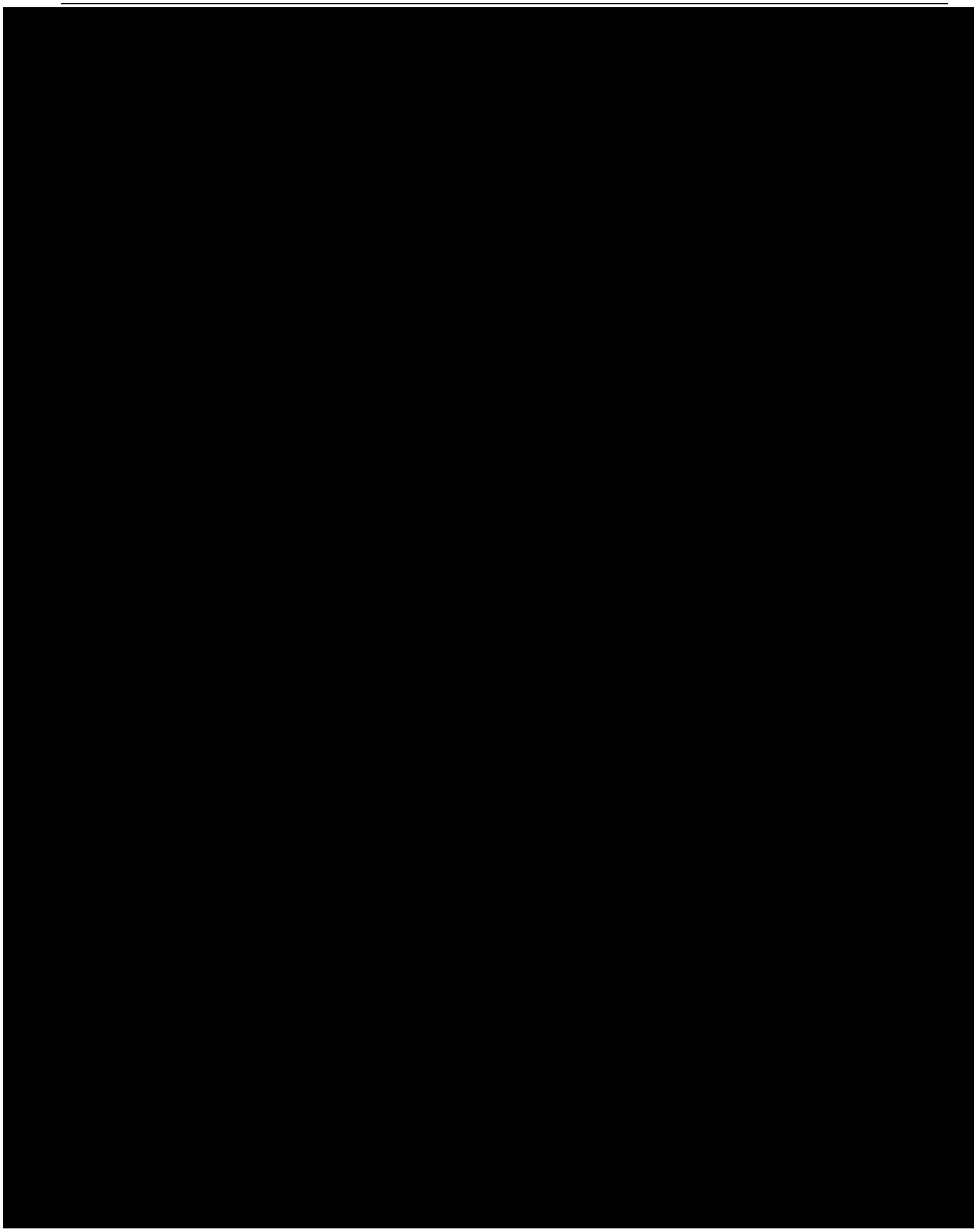
7.1.2 Secondary Effectiveness Measures

The secondary effectiveness measures include independent, noncollaborative assessments by both the EI and the subject of global aesthetic improvement in the chin area using the 5-point GAIS (Table 7), and subject responses on the Satisfaction with Chin module of the validated FACE-Q questionnaire.

Table 7 Global Aesthetic Improvement Scale

Score	Grade	Description
2	Much Improved	Marked improvement in appearance
1	Improved	Improvement in appearance, but a touch-up or retreatment is indicated
0	No Change	The appearance is essentially the same as the original condition
-1	Worse	The appearance is worse than the original condition
-2	Much Worse	The appearance is much worse than the original condition

[redacted]



[redacted]

7.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics to be collected include sex, age, race, height, weight, Fitzpatrick skin phototype and sun exposure, smoking history, medical/surgical/cosmetic/dental procedure history, and prior medications.

7.4 Treatment Characteristics

Treatment characteristics will be evaluated by collecting information on topical anesthesia usage, injection ease, product moldability, volume injected, needle/cannula usage, plane of injection, and treatment area.

7.5 Summary of Methods of Data Collection

Electronic data capture will be used to collect study-specific information, such as subject and Investigator assessments. Completed eCRFs will be reviewed by the TI or EI as applicable (or designee), and the designated monitor will verify the data. Investigators will provide access to hospital files, medical records, and other source documents containing subject clinical/medical information. Source document verification will be performed.

Subjects will complete the ISR diaries. FACE-Q questionnaires will be completed on paper and the data will be entered into the clinical database by a third party vendor. Sites will save facial digital imaging onto supplied electronic media and send the storage device to Canfield Scientific. Alternatively, files containing the facial digital imaging may be uploaded directly to Canfield Scientific from the Canfield Scientific equipment.

The clinical database or a subset of the clinical database will be locked prior to initiation of statistical analysis. All data review and verification procedures and resolution of queries must be completed prior to database lock.

Allergan will permit trial-related monitoring, audits, Institutional Review Board (IRB) review, and regulatory inspections, and will provide direct access to source documents, which will be retained for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an International Conference on Harmonisation (ICH) region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

8. Statistical Procedures

A statistical analysis plan will be prepared to provide specifications for all analyses. The plan will be finalized and approved prior to clinical database lock once all data are collected through the end of the study.

In general, descriptive statistics will be presented. Categorical variables will be summarized with frequency and percentage. Continuous variables will be summarized by number of subjects, mean, median, standard deviation, minimum, and maximum. Where appropriate, 2-sided 95% confidence intervals (CIs) for mean or proportion will be provided as part of the descriptive summary.

Unless otherwise noted, baseline refers to the EI assessment of the 2D renderings from the 3D image taken at randomization (or screening if the randomization image is not usable).

Every attempt will be made to collect complete data and limit the occurrence of missing data. No imputation of missing data will be performed. Deviations from the analyses planned in the statistical plan will be documented in the clinical study report.

8.1 Analysis Populations

The following analysis populations will be used in the analyses for this study:

- intent-to-treat (ITT) population: all randomized subjects
- modified intent-to-treat (mITT) population: subjects who are randomized to study treatment (treatment group) and receive at least 1 study device treatment or are randomized to the control group
- per-protocol (PP) population: all mITT subjects who do not have any significant protocol deviations affecting the primary effectiveness endpoint
- safety population: all subjects randomized to treatment (treatment group) who receive at least 1 study device treatment and all subjects randomized to control group

Unless specified otherwise, all effectiveness analyses will be performed on the mITT population using the "as-randomized" assignment for each subject (ie, if a subject randomized to the control group is treated inadvertently at the start of the study, the assessments for that subject will nonetheless be included in the control group analysis). The ITT and PP populations as well as missing data imputation will be used to perform sensitivity

analyses for the primary effectiveness variable. Additionally, sensitivity analysis will be performed on mITT subjects with a baseline ACRS photo score of 2 or 3. All safety analyses will be conducted using the safety population.

8.2 Collection/Derivation of Primary and Secondary Effectiveness Assessments

8.2.1 Primary Effectiveness Variable

The primary effectiveness variable is defined as the change in the EI's assessment of chin retrusion using the ACRS based on 2D renderings of 3D images. A subject showing ≥ 1-point improvement (decrease in retrusion) in ACRS score compared with baseline will be considered to be a responder. The primary evaluation timepoint is month 6 after last treatment for subjects in the treatment group and month 6 after randomization for subjects in the control group.

The primary effectiveness endpoint is the difference in mean scores on the ACRS between the treatment group and the control group at month 6.

8.2.2 Secondary Effectiveness Variables

The 3 secondary effectiveness variables are:

- Subject responses on the Satisfaction with Chin module of the FACE-Q questionnaire
    - Change from baseline in subjects' score on the Satisfaction with Chin module of the FACE-Q questionnaire will be calculated for the subjects in the treatment group in 2 steps: 1) an overall score for this module on a 100-point scale will be calculated by the conversion table created by the scale developers, and 2) the change from baseline will be calculated as month 6 score (since last treatment) minus the baseline score
- GAIS responder based on EI assessment of global aesthetic improvement in the chin area using the GAIS where a responder is defined as "improved" or "much improved" on the GAIS
- GAIS responder based on subject assessments of global aesthetic improvement in the chin area using the GAIS where a responder is defined as "improved" or "much improved" on the GAIS

8.3 Hypothesis and Methods of Analysis

8.3.1 Primary Effectiveness Analyses

The study device will be determined to be clinically effective if at least 50% (a point estimate of 50% or greater) of subjects treated with JUVÉDERM VOLUMA XC are observed to be responders (subjects who show clinically significant improvement [≥ 1-point decrease] on the ACRS compared with pretreatment) at month 6 and if the responder rate for treatment group is statistically superior to the responder rate for the control group at month 6. The following hypothesis will be tested:

H_o: $P_v = P_c$

H_a: $P_v \neq P_c$

where P_v and P_c denote the responder rates for the treatment group at month 6 after last treatment and control group at month 6 after randomization, respectively. Two-sided Fisher´s exact test with 5% significance level will be used to compare responder rates between the treatment and control groups. If the 2-sided p-value is < 0.05, the responder rate is greater for treatment than for the control group, and the point estimate of the responder rater for the treatment group is greater than 50%, then treatment will be considered superior to the control group.

The primary effectiveness analysis will be performed on the mITT population.

8.3.2 Secondary Effectiveness Analyses

The following analyses will be performed for each of the secondary effectiveness endpoints:

- responder rates with 95% exact CIs for the treatment group based on EI and subject assessments of GAIS, where a “responder” is a subject who shows improvement in the overall aesthetic assessment in the chin area (Improved or Much Improved on GAIS) at the month 6 visit
- descriptive summary of the change from baseline to month 6 (since last treatment) in overall scores of the Satisfaction with Chin module of the FACE-Q questionnaire and a 2-sided paired t-test at the 5% level to demonstrate that the mean overall satisfaction score at month 6 visit is statistically greater than that at the baseline for the treatment group.

No multiplicity adjustment will be made for the 2 GAIS responder rates, since these endpoints are descriptive in nature. The secondary effectiveness analysis for Satisfaction with Chin module of the FACE-Q questionnaire will be conducted only if the primary endpoint is met.

[redacted]

8.4 Subgroup Analyses

The primary effectiveness endpoint will be summarized by baseline photo ACRS score, volume injected, and investigational site. Subgroup analyses by injection with cannula versus without cannula will be conducted on the primary endpoint, ISRs collected via the 30-day subject diaries, and treatment-related AEs. The analyses will include count and percent along with exact binomial 95% CI. Details will be provided in the statistical analysis plan.

8.5 Sample Size Calculation

A sample size of 120 subjects in the treatment group and 40 subjects in the control group will provide > 99% power to detect a difference of at least 40% in the responder rates between the groups. This calculation is based on a 2-sided Fisher's exact test at the 5% level. The treatment group is assumed to have at least 80% responder rate and the control group will have at most 40% responder rate. Assuming a screen fail rate of 15% and a drop-out rate of 15% between randomization and the month 6 visit, up to 224 subjects will be enrolled, resulting in up to 168 subjects randomized to the treatment group and up to 56 subjects to the control group (3:1 ratio). Assuming a screen fail rate of 15% and an overall drop-out rate of 20% between randomization and study completion, an estimated 152 subjects will complete the study.

With up to 168 subjects randomized to the treatment group and an estimated screen fail rate of 15%, it is estimated that at least 143 subjects will be treated in the study. With 143 treated subjects, there is at least an 88% power to detect an AE related to treatment with an incidence rate of 1.5% in the population using a 1-sided exact binomial test at the 2.5% level.

Due to an estimated 15% of subjects having a baseline photo assessment of 1 or 4, up to 36 additional subjects may be randomized to ensure sufficient power for sensitivity analyses, resulting in a total of up to 260 subjects enrolled.

The commercial software, PASS (2008, Version 8.0.13), was used for the power calculation. The sample size calculation used an inequality test for 2 proportions to demonstrate that the treatment group is superior to the control group. The safety calculation used an inequality test for 1 proportion.

8.6 Interim Analyses

No interim analysis is planned for this study.

9. Materials

9.1 Study Treatment

9.1.1 Product Description

JUVÉDERM VOLUMA XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized, HA gel implant (dermal filler). JUVÉDERM VOLUMA XC

[redacted]

9.1.2 Instructions for Use and Administration

[redacted]

The TIs must be experienced in the use and administration of HA implants and be practicing in the field(s) of aesthetic medicine, plastic/cosmetic/reconstructive surgery, or dermatology. Before the study begins, the TIs will receive training in the administration of JUVÉDERM VOLUMA XC according to the technique specified for this study.

[redacted]. The detailed recommended injection technique is provided in the VOLUMA-006 DFU included in the Site Study Binder.

9.1.3 Treatment Regimen Adjustments

Up to 2 treatment sessions 30 days apart are allowed; repeat treatment is allowed 12 months after initial treatment. The TI will determine the appropriate volume of JUVÉDERM VOLUMA XC to inject at the initial and touch-up treatments based on his/her clinical experience and the randomization assignment, but the maximum volume is not to exceed 4.0 mL for initial and touch-up treatments combined. The maximum volume for repeat treatment is not to exceed 4.0 mL.

9.2 Other Study Supplies

Allergan will provide urine pregnancy test kits, digital imaging equipment, and other supplies specific to this study [redacted] The investigational site is responsible for routine supplies related to device storage, administration, and follow-up visits (eg, antiseptics, drapes, gloves, gauze, topical anesthesia, ice packs, blood pressure cuff), and internet connection for eCRF completion and IWRS.

10. Study Administration Procedures

The clinical study shall not begin until the required approvals from the appropriate regulatory authorities and IRBs have been obtained.

10.1 Subject Entry Procedures

10.1.1 Overview of Entry Procedures

Prospective subjects as defined by the criteria in Sections 5.3 and 5.4 (inclusion/exclusion criteria) will be considered for entry into this study. A subject is considered to have entered the study upon signing the ICF, which will occur prior to any screening procedures. Screening procedures include:

- collection of demographic information
- collection of height, weight, and vital signs
- evaluation of Fitzpatrick skin phototype and history of sun exposure
- collection of smoking history
- collection of medical/surgical/cosmetic/dental procedures history
- administration of urine pregnancy test to female subjects of childbearing potential (women who are not of childbearing potential are considered as postmenopausal for at least 1 year or have no uterus)
- capture of 3D facial digital images
- evaluation by both the EI and the TI of the subject's chin retrusion using the ACRS

- evaluation of inclusion/exclusion criteria
- administration of FACE-Q questionnaire modules for Satisfaction with Chin and Psychological Well-Being
- EI assessments of subject's facial sensation and facial function
- collection of AEs, concomitant medications, and concurrent procedures

Subjects choosing not to participate in facial digital imaging through checkbox selection on the ICF will be excluded from the study. Allergan shall have full ownership rights to any facial digital imaging derived from the study.

10.1.2 Informed Consent and Subject Privacy

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject. The subject must also give Authorization for Use and Release of Health and Research Study Information, including digital images and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

The TI or his/her authorized designee conducts the informed consent (IC) discussion and will document in the subject's medical records the acquisition of IC and the subject's agreement or refusal to notify his/her primary care physician about the study. The IC shall include all aspects of the study that are relevant to the subject's decision to participate throughout the study. The IC process is to avoid any coercion or undue influence on, or inducement of, the subject to participate. The subject is to personally sign and date the ICF. The TI will retain the original copy of the signed form, and the subject will receive a copy. Upon signing the ICF, the subject is considered to be enrolled in the study and receives a subject number that will be used on all documentation for the subject throughout the study. Subject numbers will be assigned in ascending order, and numbers will not be omitted or reused. The subject number is coupled with the site identification number for unique identification of each subject. The TI is to ensure important new information is provided to new or existing subjects throughout the study. For studies involving emergency treatments, when prior IC of the subject is not possible because of the subject's medical condition, the IC of the subject's legally authorized representative shall be requested. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's

inclusion in the study and about all aspects of the study. The subject shall be asked to provide IC for continued participation as soon as his/her medical condition allows.

10.1.3 Method for Assignment to Treatment Groups

At the time of randomization (ie, at or within 30 days after screening/signing of the ICF), eligible subjects will be assigned to 1 of 2 treatment groups (treatment and control) in a 3:1 ratio to receive JUVÉDERM VOLUMA XC or to the control group based on a central randomization schedule. An automated IWRS will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan. Study treatments will be labeled with kit numbers. The IWRS will provide the site with the specific kit number(s) for each randomized subject at the time of randomization and at each subsequent treatment visit. Sites will dispense treatment according to the IWRS instructions provided by the system.

10.2 Compliance with Protocol

The TI is responsible for compliance with the protocol at the investigational site. A representative of Allergan will make frequent contact with the TI and his/her research staff and will conduct regular monitoring visits at the site to review subject and device accountability records for compliance with the protocol. Any protocol deviations will be discussed with the TI upon identification. The use of the data collected for the subject will be discussed to determine if the data is to be included in the analysis. All protocol deviations will be reported to the IRB according to the IRBs reporting requirements.

10.3 Pregnancy

If a female becomes pregnant after treatment, the TI will notify Allergan immediately after the pregnancy is confirmed. The TI shall (1) instruct the subject to notify her physician of the presence of the investigational device and (2) follow the pregnancy to term. Best practices are to be followed in order to ensure the welfare of the subject and the fetus. The Medical Safety Physician will contact the TI to obtain information about the pregnancy outcome. The subject will continue to be followed as part of the mITT Population, but the pregnancy will be documented as a protocol deviation, and the subject will not be evaluated as part of the PP Population for timepoints after the pregnancy is confirmed.

Pregnancy by itself will not be considered an AE or serious adverse event (SAE). Hospitalization for a normal delivery or elective abortion of a normal fetus does not

constitute a SAE. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an AE or SAE, and these are to be reported as described in Sections 11.1.3 and 11.1.4.

10.4 Study Termination

If conditions arise during the study that indicate that the study or an investigational site needs to be terminated, Allergan, TI, Monitor, IRB, and/or regulatory agencies will discuss the situation and take appropriate action after consultation. Conditions that may warrant termination of the study or site include, but are not limited to:

- the discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- the decision on the part of Allergan to suspend or discontinue testing, evaluation, or development of the study device
- failure of the TI to comply with pertinent national or state regulations, IRB-imposed conditions, or protocol requirements
- TI submission of knowingly false information to Allergan, a study monitor, the IRB, or any regulatory agency

Per International Organization for Standardization (ISO) 14155, if a study is prematurely terminated or suspended due to safety issues, Allergan shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB is also to be informed promptly and provided the reason(s) for the termination or suspension by Allergan or by the Investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, Allergan shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of subjects enrolled in the study, and each Investigator or authorized designee shall promptly inform enrolled subjects, if applicable.

11. Adverse Events

Throughout the course of the study, all AEs will be monitored and reported on an AE eCRF, including seriousness, severity, action taken, and relationship to study treatment. If AEs occur, the first concern will be the safety of the study participants.

The TI and the research staff will monitor each subject closely, and, if a complication occurs, they will use their medical judgment to do whatever is necessary to treat the subject. Additional information is available in the VOLUMA-006 DFU. If subjects have any ongoing treatment-related SAEs at the time of the final visit, they should continue to be followed up until resolution of these events or the subject condition is considered stable by the TI. After the final visit, the subject will resume receiving the standard medical care according to the standard care of the clinic.

For a description of potential AEs, see Section 2.2 and the VOLUMA-006 DFU.

11.1 Definitions

11.1.1 Adverse Event

An AE is defined in accordance with ISO 14155 as "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device." This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational medical devices.

Disease signs and symptoms that existed prior to the study treatment are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

AEs will be monitored throughout the study beginning with signing of the ICF. At each postscreening visit, the TI (or designee) will begin querying for AEs by asking each subject a general, non-directed question such as "Have you had any changes to your condition since your last visit?" Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate eCRF.

11.1.2 Serious Adverse Event

A SAE is defined in accordance with ISO 14155 as an AE that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient or prolonged hospitalization, or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Allergan considers all cancer AEs as SAEs. Abortion is also considered an SAE except for elective abortion of a normal fetus.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

See Section 11.4 for procedures for reporting a SAE/serious adverse device effect (SADE).

11.1.3 Adverse Device Effect

An adverse device effect (ADE) is defined in accordance with ISO 14155 as "an adverse event related to the use of an investigational medical device." This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.

See Section 11.3 for procedures for reporting an ADE.

11.1.4 Serious Adverse Device Effect

A SADE is defined in accordance with ISO 14155 as "an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event."

See Section 11.4 for procedures for reporting a SADE.

11.1.5 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is defined in accordance with 21 Code of Federal Regulations (CFR) 812.3 as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

11.1.6 Device Deficiency

A device deficiency is defined in accordance with ISO 14155 as "inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance." Device deficiencies include malfunctions, use errors, and inadequate labeling.

If a device deficiency occurs, the TI will notify Allergan using the fax number or email on the front page of the protocol. Device deficiencies shall be documented throughout the study and appropriately managed by Allergan. Allergan shall review all device deficiencies and determine and document in writing whether they could have led to a SADE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

11.1.7 Severity

Severity is a clinical determination of the intensity of an AE. The severity assessment for a clinical AE is to be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort affecting daily activity
Severe	Disabling with inability to do daily activities

11.1.8 Relationship to Treatment

Relationship to a treatment refers to a determination of the relationship (if any) between an AE and the device or treatment procedure. A causal relationship is present if the TI determines that there is a reasonable possibility that the AE may have been caused by the device or is associated with the procedure, such as an event that can be attributed to other products, surgical techniques, or medications required specifically for the procedure.

Relationship to the treatment must be determined by the TI and cannot be delegated to other study staff.

11.2 Timelines for Reporting

The TI (or designee) is to adhere to the following schedule in reporting different types of AEs.

Adverse Event Type	Reporting to Allergan	Start of Collection	End of Collection
AEs, ADEs	Record on AE eCRF upon awareness for review by the Clinical Monitor	Signing ICF	Last subject visit
SAEs, SADEs	Record on SAE Form and fax/e-mail to Allergan within 24 hours of awareness	Signing ICF	Last subject visit

11.3 Procedures for Reporting an AE or ADE

All AEs or ADEs occurring during the study period (beginning with signing ICF) are to be recorded on the appropriate eCRF. Any AE that is ongoing at the exit visit must be followed up as appropriate.

11.4 Procedures for Reporting an SAE or SADE

All SAEs and SADEs occurring during the study period (from signing ICF) through the last subject visit are to be immediately reported to an Allergan representative at a fax number/e-mail address listed on the cover page and recorded on the appropriate eCRFs. All subjects with an SAE/SADE must be followed up and the outcomes reported. The TI is to supply Allergan and the IRB with any additional requested information (eg, hospital discharge summary, autopsy reports and terminal medical reports). Allergan shall evaluate all SADEs and determine and document in writing whether they meet the definition of a UADE. These shall be reported to all participating TIs, the regulatory authorities, and IRBs/ECs as required by national regulations.

In the event of an SAE/SADE, the TI must:

1. Notify Allergan immediately by fax/e-mail using the SAE/SADE reporting forms. For the SAE/SADE fax number/e-mail address, see the front page of the protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.

3. Provide Allergan with a complete, written case history which includes a statement as to whether the event was or was not related to the use of the investigational device.

4. Promptly inform the governing IRB of the event, if it is treatment-related. For other SAEs, notify the governing IRB as required by the IRB, local regulations, and the governing health authorities.

12. Administrative Issues

12.1 Protection of Human Subjects

12.1.1 Compliance with Informed Consent Regulations

Written IC is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative according to 21 CFR 50.

12.1.2 Compliance with IRB Regulations

This study is to be conducted in accordance with IRB regulations (21 CFR 56). The TI must obtain approval from a properly constituted IRB prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB correspondence with the TI are to be provided to Allergan.

12.1.3 Compliance with Good Clinical Practice

This protocol is to be conducted in compliance with Good Clinical Practice (GCP) guidelines and with ethical principles for clinical research.

12.1.4 Financial Disclosure/Certification Form

In accordance with 21 CFR 54.4, the TI and any Sub-Investigators who are directly involved in the treatment or evaluation of subjects must complete the Financial Disclosure Form disclosing completely and accurately any financial interests or arrangements that apply to themselves, their spouse, or their dependent children.

- Any financial arrangement entered into between Allergan and the Investigator involved in the conduct of a covered clinical trial, whereby the value of the compensation to the Investigator for conducting the study could be influenced by the outcome of the study

- Any significant payments of other sorts from Allergan, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria

- Any proprietary interest in the tested product held by any Investigator involved in a study

- Any significant equity interest in Allergan held by any Investigator involved in any clinical study

- Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

The Investigator shall provide to Allergan accurate financial information on an annual basis, with prompt updates if any relevant changes occur over the course of the investigation, and at 1 year following completion of this study.

12.1.5 Compliance with Electronic Records and Signature Regulations

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

12.2 Changes to the Protocol

The TI is not to implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers). Allergan may amend the protocol during the course of the study. The amended protocol shall be distributed to the TIs and IRBs upon approval by regulatory authorities.

12.3 Subject Confidentiality and Privacy

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study device may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to Allergan, the governing health authorities, or the FDA, if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (eg, Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information [HIPAA]).

In accordance with HIPAA requirements, additional purposes of this study include the following: to publish anonymous subject data from the study and to create and maintain a data repository.

12.4 Documentation

12.4.1 Source Documents

Source documents may include a subject's medical records, hospital charts, laboratory notes, device accountability records, TI and EI assessments of chin retrusion, [redacted] subject FACE-Q questionnaires, [redacted] diaries, EI and subject assessments of global aesthetic improvement in the chin area using the GAIS, photographic negatives, digital images, or renderings, clinic charts, the TI's subject study files, results of pregnancy tests, and any other diagnostic tests that may be performed, such as X-rays, laboratory tests, and magnetic resonance imaging. If the Serious Adverse Event Form and Pregnancy Surveillance Form are used in this study, they are also considered source documents. The TI's copies of the eCRFs serve as part of the TI's record of a subject's study-related data.

The following information is to be entered into the subject's medical record:

- Subject's name

- Subject's contact information
- Date that the subject entered the study, subject number, and subject randomization number
- Study title and/or the protocol number and study Sponsor
- A statement that IC was obtained, including the date and a statement that HIPAA Authorization or other country and local subject privacy required documentation for this study has been obtained, including the date
- Details of the injection procedure including anesthetic used, treatment areas injected, volume injected in each treatment area, ease of injection, details regarding molding and massage, kit and lot numbers of study device injected, subject's assessment of procedural pain
- Dates of all subject visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications are to be recorded.)
- Occurrence and status of any AEs
- Date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation
- Results of laboratory tests performed by the site (eg, results of urine pregnancy tests)

12.4.2 Case Report Form Completion

The TI is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. The TI who has signed the protocol signature page or his/her authorized designee is to personally sign the eCRFs (as indicated on the eCRF) to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on an eCRF shall be dated, initialed and explained, if necessary, and shall not obscure the original entry (ie, an audit trail shall be maintained); this applies to both written and electronic changes or corrections.

12.4.3 Investigator Reports

In accordance with 21 CFR 812.150, the TI shall prepare and submit complete, accurate, and timely reports as follows: report to Allergan within 5 working days a withdrawal of IRB approval, study progress reports to Allergan and IRB at least annually, and a final report to Allergan and IRB within 3 months after study termination or completion.

12.4.4 Retention of Documentation

All study related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs are to be maintained on file.

Allergan-specific essential documents are to be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents are to be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by Allergan.

Allergan requires notification in writing if the TI wishes to store study documents off-site or to relinquish the study data records so that mutually agreed-upon arrangements can be made for transfer of the data records to a suitably qualified, responsible person. Notification is to go to Allergan, Attn: Clinical Research Dept., 2525 Dupont Drive, Irvine, CA 92612.

12.5 Labeling, Packaging, Storage, and Return of Study Devices

[redacted]

[redacted]

12.5.2 Storage of Study Devices

The study device must be stored in a secure area accessible to delegated study personnel only and administered only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in this protocol.

[redacted]. The temperature monitoring device has been pre-programmed by Allergan with temperature storage-range limits required to ensure study product stability during the study. Use of the device is required to ensure that the study product is being maintained within the acceptable storage-range conditions. If the storage temperature varies from the programmed limits, the device alarm will trigger indicating an excursion that may impact the stability of the study product. Sites must report any alarmed temperature excursion to Allergan, and avoid administering the impacted study product, by isolating the product, until receiving further instructions from Allergan. Do not freeze or expose to extreme heat. Do not use if the package is open or damaged or if the product is not clear.

12.5.3 Study Device Accountability

The TI (or designee) must keep an accurate accounting of the number of study devices received from Allergan, dispensed to subjects, and returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study devices including subject initials, device serial/lot number, date of implantation, and date of explantation if applicable. The study product must be dispensed to study subjects by an appropriately qualified person and is to be used in accordance with the protocol under the direct supervision of a study TI.

12.5.4 Return of Study Devices

Upon completion of the treatment period, the quantities of all used and unused study devices will be reconciled. Used syringes will be disposed of onsite. Unused syringes will be returned to Allergan unless other disposition arrangements are agreed upon in writing with Allergan.

Devices that are damaged during shipment or at the site or that malfunction during use (eg, faulty syringe or plunger) must be accounted for and returned. The TI will promptly notify Allergan's Clinical Research department of any device malfunction. The Clinical Research or Product Support representative will provide instruction for the return of any faulty syringe for evaluation.

12.6 Monitoring by Allergan

Appropriately trained representatives of Allergan will monitor the conduct of the trial at each investigational site, including visits to the site to review, audit, and retrieve copies of study-related documents. It is the responsibility of the Principal Investigator to be present or available for consultation and to assure that Allergan has access to all study-related records during scheduled monitoring visits.

Allergan will review device accountability records and completed eCRFs to ensure completeness and consistency with the source records and compliance with the protocol requirements.

Allergan representatives will meet with the TI(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

12.7 Testing of Biological Specimens

At screening and before each study treatment (initial and touch-up), a trained research staff member will perform pregnancy testing on urine samples of women of childbearing potential. The test employed should have a sensitivity of at least 50 mIU/mL for human chorionic gonadotropin.

12.8 Publications

This study will be registered and results posted on www.clinicaltrials.gov. Allergan, as the Sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study Investigators 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.

13. References

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14. Protocol Amendment Summary

Version Date/ Amend. No.	Changes to Protocol
28 Mar 2016/1	• Synopsis, Tables 1, 3, and 5, and Section 12.4.1 - Changed e-diary to diary (paper diaries will be used) • Synopsis (Study design) - clarified timing of EI assessment as after the visits when the 3D images are made available. • Synopsis (Inclusion criteria) - Criterion #1 clarified subject age from "Over age 21" to "Age 22 or over"; Criterion #6 clarified from ..."within the first 3 months after study treatment" to "during the study" • Synopsis (Response Measures) - added ..."2D profile images of the left side of the chin rendered by the Canfield image analysis technician from the 3D images." • Synopsis (Statistical Methods) - clarified that 1) the responder rate is based on EI assessment of 2D images of the chin profile, and 2) baseline is defined as the EI assessment of the 2D image at randomization (or screening if no usable randomization photo is available). [redacted] • Section 1 - added abbreviation for 2-dimensional • Section 3.2 - clarified that the ACRS score as assessed by the EI is based on assessment of 2D renderings of 3D facial images • Section 4.3.3 - added that the 2D images used for ACRS assessments will be cropped by Canfield to include only the lower face, that the EI will not be blinded to the timepoint at which photos were taken, and that the EI will access images through a web-based portal that can have additional information. • Section 5.3 - Criterion #1 clarified subject age from "Over age 21" to "Age 22 or over"; • Section 5.4 - Criterion #6 clarified from ..."within the first 3 months after study treatment" to "during the study" [redacted]

	[redacted]. • [redacted] • Section 7.1.1 - clarified primary effectiveness measure as the EI assessment of 2D profile images of the left side of the chin rendered from the 3D images by the Canfield image analysis technician • Section 8 - clarified baseline as EI assessment of the photo taken at randomization (or screening if the randomization image is not usable) • Section 8.2.1 - clarified the primary effectiveness variable as EI's assessment of chin retrusion using the ACRS based on ACRS based on 2D renderings of 3D images • Section 8.3.2 (second bullet) - the timepoint for secondary effectiveness analysis was corrected from "month 3" to "month 6" • Section 8.5.1 - corrected to Section 4.4.2 • [redacted] • Section 13.1 - removed study report reference • Section 13.2 - subheading deleted
24 May 2016/2	[redacted]. • Synopsis (Sample Size Calculation) - added "Assuming a drop-out rate of 20% between randomization and study completion, an estimated 170 subjects will complete the study." • Section 8.5 - added "Assuming a drop out-rate of 20% between randomization and study completion, an estimated 170 subjects will complete the study." [redacted]
11 Jan 2017/3	• Synopsis (Number of Subjects) - Changed "212" to "224" • Synopsis (Study Design) - Treatment Group: Added "At the month 6 visit, the EI will conduct a live ACRS assessment." • Synopsis (Study Design) - Control Group: Added "At the month 6 visit, the EI will conduct a live ACRS assessment." • Synopsis (Inclusion criteria) - Criterion #2: Added the category "Extreme" to chin retrusion and grade "4" on the ACRS • Synopsis (Response Measures) - Effectiveness: Primary effectiveness measure added "photo" in front of "assessment of chin retrusion" [redacted] • Synopsis (Statistical Methods) - Sample Size Calculation: Changed screen fail rate from "10%" to "15%", number of subjects from "212" to "224", number of subjects per treatment group from "159" to "168", number of subjects in the control group from "53" to "56", changed the number of

	subjects who complete the study from "170" to "152" based on both the screen fail rate and the overall dropout rate. • Synopsis (Statistical Methods) - Sample Size Calculation: Deleted "and an inequality test for 1 proportion to demonstrate that the responder rate of the treatment group is > 50%" • Synopsis (Statistical Methods) - Effectiveness: Modified the definition of the mITT population to read "which includes subjects with a baseline photo assessment of 2, 3, or 4 who are randomized to study treatment (treatment group) and receive at least 1 study device treatment or are randomized to the control group." • Synopsis (Statistical Methods) - Effectiveness: Added "A sensitivity analysis will be performed on the intent-to-treat (ITT) population, which includes all randomized subjects." • Synopsis (Statistical Methods) - Effectiveness: Deleted "and" before "subject assessments" and added "and the EI's live ACRS assessment" [redacted] • Section 5.1 (Number of Subjects) - Changed "212" to "224" • Section 5.3 - Criterion #2 added the category "Extreme" to chin retrusion and grade "4" on the ACRS [redacted] • Section 7.1.1 - Added "photo" in front of "assessment of chin retrusion" [redacted] • Section 8.1 - Modified the definition of the mITT population to read "subjects with a baseline photo assessment of 2, 3, or 4 who are randomized to study treatment (treatment group) and receive at least 1 study device treatment or are randomized to the control group." • Section 8.1 - Modified the definition of the safety population to read "all subjects randomized to treatment (treatment group) who receive at least 1 study device treatment and all subjects randomized to the control group." • Section 8.1 - Added "all" in front of "effectiveness analyses will be performed on the mITT population" • Section 8.1 - Added "ITT and" in front of "PP population will be used to perform sensitivity analyses". Changed "population" to "populations". • Section 8.1 - Deleted "Additionally, the ITT population will be used to assess the impact of missing data on the primary effectiveness endpoint."

	• Section 8.3.1 - Added "The primary effectiveness analysis will be performed on the mITT population." [redacted] • Section 8.4 - Primary effectiveness endpoint added "photo" in front of ACRS • Section 8.5 (Sample Size Calculation) - Changed screen fail rate from "10%" to "15%", number of subjects from "212" to "224", number of subjects per treatment group from "159" to "168", number of subjects in the control group from "53" to "56", changed the number of subjects who complete the study from "170" to "152" based on both the screen fail rate and the overall dropout rate. • Section 8.5 (Sample Size Calculation) - Deleted "and an inequality test for 1 proportion to demonstrate that the responder rate of the treatment group is > 50%"
01 Mar 2017/4	• Synopsis (Inclusion Criterion #2) - Deleted "extreme" and grade "4" • Synopsis (Statistical Methods, Sample Size Calculation) - Added "Due to an estimated 15% of subjects having a baseline photo assessment of 1 or 4, up to 36 additional subjects may be randomized to ensure sufficient power for sensitivity analyses, resulting in a total of up to 260 subjects enrolled". • Synopsis (Statistical Methods, Effectiveness) - Deleted "with a baseline photo assessment of 2, 3, or 4" • Section 5.3 (Inclusion Criterion #2) - Deleted "extreme" and grade "4" [redacted] • Section 8.1 (Analysis Populations, mITT) - Deleted "with a baseline photo assessment of 2, 3, or 4" • Section 8.1 (Analysis Populations) - Added "as well as missing data imputation" and "Additionally, sensitivity analysis will be performed on mITT subjects with a baseline ACRS photo score of 2 or 3." • Section 8.5 (Sample Size Calculation) - Added "Due to an estimated 15% of subjects having a baseline photo assessment of 1 or 4, up to 36 additional subjects may be randomized to ensure sufficient power for sensitivity analyses, resulting in a total of up to 260 subjects enrolled". • Section 11.1.2 (Serious Adverse Event) - Added "NOTE: Allergan considers all cancer AEs as SAEs. Abortion is also considered an SAE except for elective abortion of a normal fetus."

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Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
[redacted]	[redacted]	[redacted]