NCT03438266

Study ID: 1650-801-008

Title: A Multicenter, Single-blind, Randomized, Controlled Study of the Safety and Effectiveness of JUVÉDERM VOLUMA® XC Injectable Gel for Cheek Augmentation Using Cannula

Protocol Date: 19 October 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 cheek augmentation using cannula
Protocol Number:	1650-801-008
Product Name:	JUVÉDERM VOLUMA® XC injectable gel
Development Phase:	Post-market
Sponsor:	Allergan 2525 Dupont Drive Irvine, CA 92612
Manufacturer:	Allergan
Safety reporting:	[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 cheek augmentation using cannula
Protocol Number:	1650-801-008
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

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Synopsis

NUMBER AND TITLE OF STUDY:
1650-801-008: A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for cheek augmentation using cannula

DEVELOPMENT PHASE: Postmarket

STUDY CENTERS: Up to 7 United States sites

NUMBER OF SUBJECTS: Up to 75 subjects will be enrolled in order to have 60 subjects treated

OBJECTIVES: The objective of this study is to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC (hereafter VOLUMA XC) injectable gel using cannula in subjects seeking correction of age-related volume deficit in the mid-face.

STUDY DESIGN:

This is a multicenter, evaluator-blind, randomized, within-subject controlled, paired-comparison study of the safety and effectiveness of VOLUMA XC injectable gel using a cannula and needle for cheek augmentation to correct age-related volume deficit in the mid-face.

At screening, after written informed consent has been obtained, the Treating Investigator (TI) will document the subject's demographics, Fitzpatrick skin phototype, height, weight, vital signs, and medical, surgical, cosmetic, and dental procedures history. Female subjects of childbearing potential will undergo urine pregnancy testing. All subjects will complete the validated 5-item Satisfaction with Cheeks module of the FACE-Q questionnaire. The blinded Evaluating Investigator (EI) will rate the subject's mid-face deficit for the overall mid-face area, [redacted] on the validated 6-point photonumeric Mid-Face Volume Deficit Scale (MFVDS) (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = significant, 5 = severe) to determine eligibility for the study.

On the randomization/treatment day, subjects will have 1 cheek treated with VOLUMA XC injectable gel using a [redacted] cannula and the contralateral cheek treated using a [redacted] with a goal to achieve at least a 1-grade improvement. In the cheek randomized for cannula use, a maximum treatment with cannula should be attempted. [redacted] The side of treatment (ie, side of face for needle or cannula) will be randomized. The left side of face will be treated first for all subjects. For the cheek treated with cannula, an anesthetic agent must be used on the treatment area prior to making the entry point with the introductory needle; use of anesthesia is optional for the cheek treated with needle only. The TI will inject VOLUMA XC in the mid-face to correct mid-face volume deficit. [redacted]

At 1 and 3 months after treatment, subjects will return for a visit during which the EI will rate subjects on the MFVDS for the overall mid-face area, [redacted] the TI will record any adverse events (AEs), and subjects will complete the Satisfaction with Cheeks module of the FACE-Q questionnaire. Subjects will be exited from the study at the end of the Month 3 visit.

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION:

Adults with age-related volume deficit in the mid-face who are seeking to increase facial volume in the mid-face.

INCLUSION:

1. 35 to 65 (inclusive) years of age and in good general health
2. Has overall mid-face severity of Moderate (3) for both cheeks, Significant (4) for both cheeks, or Severe (5) for both cheeks on the 6-point photonumeric MFVDS as assessed by the EI [redacted]

[redacted]

EXCLUSION:

[redacted]

8. Has experienced trauma to the mid-face area within 6 months before enrollment or has residual deficiencies, deformities, or scarring

[redacted]

10. Has a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), HA products, or Streptococcal protein, or is planning to undergo allergen desensitization therapy during the term of the study
11. Has active autoimmune disease
12. Has current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, above the subnasale

[redacted]

TEST PRODUCT, DEVICE VOLUME, AND MODE OF ADMINISTRATION:
VOLUMA® XC (a hyaluronic acid injectable gel with lidocaine) will be administered via [redacted] cannula and [redacted] needle to the mid-face to correct mid-face volume deficit. Appropriate injection volume for the mid-face will be determined by the TI[redacted]

DURATION OF STUDY: Treatment period: 1 day. Follow-up period: 3 months

RESPONSE MEASURES:

Effectiveness: The primary effectiveness measure is the blinded EI's assessment of the subject's overall mid-face volume deficit for each cheek on the MFVDS. The timepoint for the primary effectiveness endpoint is Month 1. The secondary effectiveness measure is the FACE-Q Satisfaction with Cheeks questionnaire evaluated by the subject.

Safety: Safety measures include the presence and severity of injection site responses (ISRs), which will be recorded by the subject in the subject diary for 30 days after treatment, procedural pain assessments, and any adverse events (AEs). Location of these assessments will be noted as being on the right and/or left cheek or not applicable.

STATISTICAL METHODS:

[redacted]

Effectiveness analyses: For the primary effectiveness analysis of change from baseline (screening) to Month 1 in overall mid-face MFVDS, the mean paired difference between treatment with cannula and treatment with needle and its 95% CI based on paired t-test will be calculated. If the upper confidence limit is < 0.5, statistical non-inferiority will be concluded.

[redacted]

Safety analyses: ISRs, procedural pain assessment, and AEs will be summarized using descriptive statistics. ISRs and, separately, AEs will be summarized by the percentage (and 95% CI) of subjects who have the ISR (or AE) on both sides, by the percentage (and 95% CI) of subjects who have the ISR (or AE) on the cannula side and not on the needle side, and by the percentage (and 95% CI) of subjects who have the ISR (or AE) on the needle side and not on the cannula side. Also, the within-treatment percentage (and 95% CI) of subjects who have the ISR (or AE) will be summarized for the cannula side and, separately, for the needle side.

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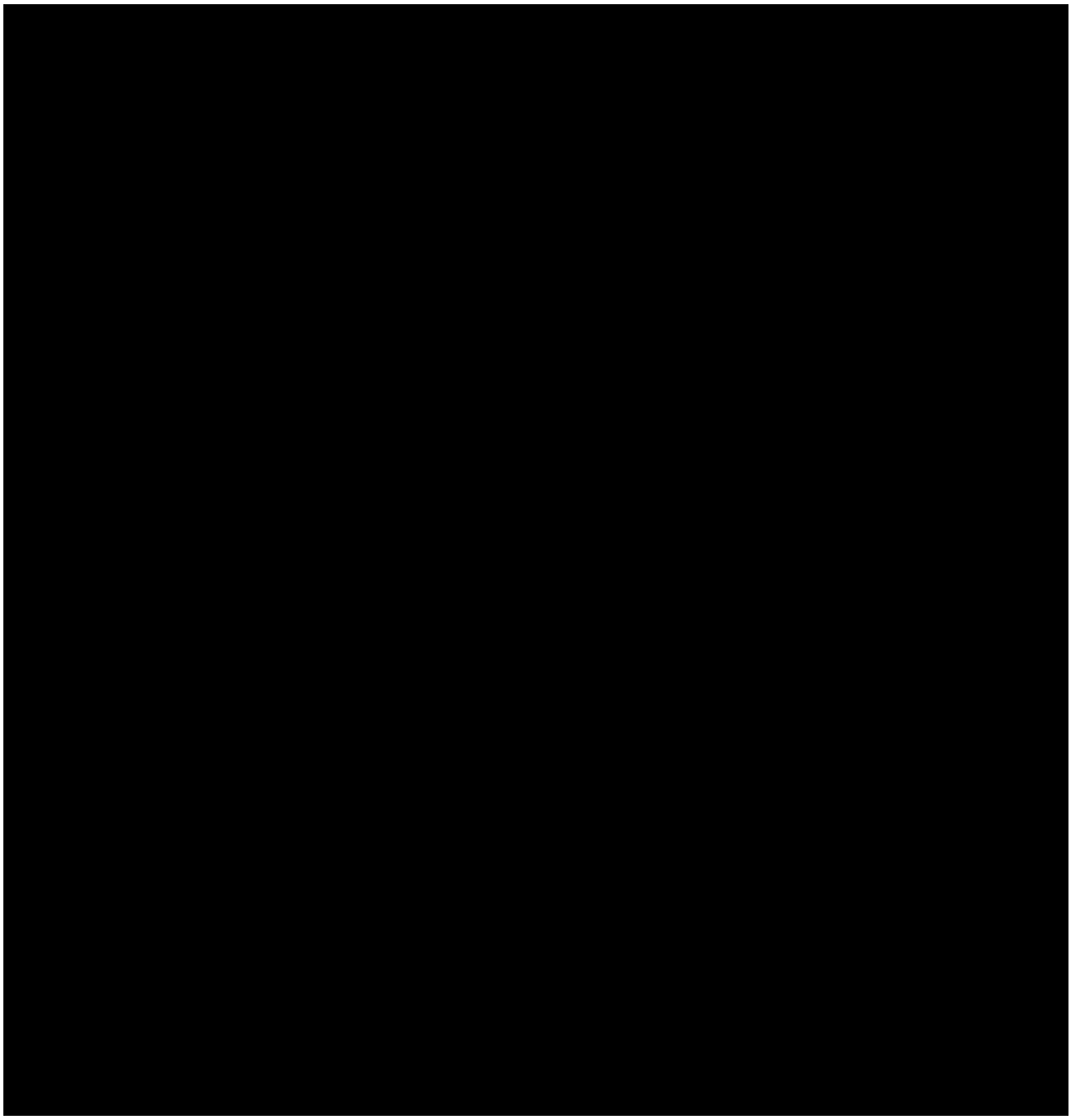


1. Abbreviations and Terms

Term/Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
BMI	Body mass index
BOCF	Baseline observation carried forward
CFR	US Code of Federal Regulations
eCRF	Electronic case report form
EI	Evaluating Investigator
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
IC(F)	Informed consent (Form)
ICH	International Council on Harmonisation
IDFU	Investigational directions for use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISRs	injection site responses
IWRS	Interactive web response system
MFVDS	Mid-Face Volume Deficit Scale
MI	Multiple imputation
mITT	Modified intent-to-treat
PP	Per-protocol
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard deviation
TI	Treating Investigator
UADE	Unanticipated Adverse Device Effect

2. Background, Risk and Benefit, and Clinical Rationale

[redacted]

2.3 Clinical Rationale

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 to collect safety and effectiveness data of VOLUMA XC injectable gel using cannula in subjects seeking correction of age-related volume deficit in the mid-face.

3. Study Objectives and Clinical Hypotheses

3.1 Study Objectives

The objective of this study is to evaluate the safety and effectiveness of VOLUMA XC injectable gel using cannula in subjects seeking correction of age-related volume deficit in the mid-face.

3.2 Clinical Hypotheses

The response to treatment in terms of the Mid-Face Volume Deficit Scale (MFVDS) change from baseline (screening) to Month 1 with cannula will be non-inferior to response to treatment with needle.

4. Study Design

4.1 Structure

This is a multicenter, evaluator-blind, randomized, within-subject controlled, paired-comparison study. Up to 7 investigational sites in the United States will enroll and follow subjects who meet the study criteria.

4.2 Duration

Each subject's participation will encompass 1 day of treatment and 3 months of follow-up.

4.3 Treatment Groups and Treatment Regimen

4.3.1 Study Treatment

VOLUMA XC injectable gel injected with a [redacted] cannula and an optional [redacted]

4.3.2 Control Treatment

VOLUMA XC injectable gel injected with a [redacted] needle

4.3.3 Methods for Blinding

The Evaluating Investigator (EI) will be blinded to treatment. The EI will not be present during the injection procedures. The Treating Investigator (TI), study coordinator, and subject will not be blinded to treatment, but they will secure the randomization and other records (eg, records of study treatments and prior study assessments) from potential discovery by the blinded EI. The TI will not discuss the randomized treatment assignments with or in the presence of the EI.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

For the cheek treated with cannula, an anesthetic agent must be used on the treatment area prior to making the entry point with the introductory needle. For the cheek treated with needle, use of anesthesia is optional, according to routine practice, but it must be limited to the treatment area only. Acceptable topical and injectable anesthetic agents are listed in the investigational directions for use (IDFU).

[redacted]

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) [redacted]

During the course of the study, subjects must not:

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

[redacted]

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 Special Diet or Activities

Within the first 24 hours after treatment, it is recommended that subjects 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, it is recommended that subjects avoid unnecessary external compression of the treatment site that could cause displacement or indentation where the product has been placed.

For 1 week after treatment, subjects will be advised not to have a massage, enter a hot spring or sauna, or go swimming.

4.5 Treatment Allocation Ratio and Stratification

Subjects will be randomized in a 1:1 ratio to receive treatment on the first side with the cannula or needle.

5. Study Population

5.1 Number of Subjects

Up to 75 subjects will be enrolled at up to 7 sites in order to have 60 subjects treated.

5.2 Study Population Characteristics

Adult subjects who are seeking correction of age-related volume deficit in the mid-face will be recruited.

5.3 Inclusion Criteria

The following are requirements for entry into the study:

1. 35 to 65 (inclusive) years of age and in good general health
2. Has overall mid-face severity of Moderate (3) for both cheeks, Significant (4) for both cheeks, or Severe (5) for both cheeks on the 6-point photonumeric MFVDS as assessed by the EI
3. [redacted]

5.4 Exclusion Criteria

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

[redacted]

[redacted]

8. Has experienced trauma to the mid-face area within 6 months before enrollment or has residual deficiencies, deformities, or scarring

[redacted]

10. Has a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), HA products, or *Streptococcal* protein, or is planning to undergo allergen desensitization therapy during the term of the study

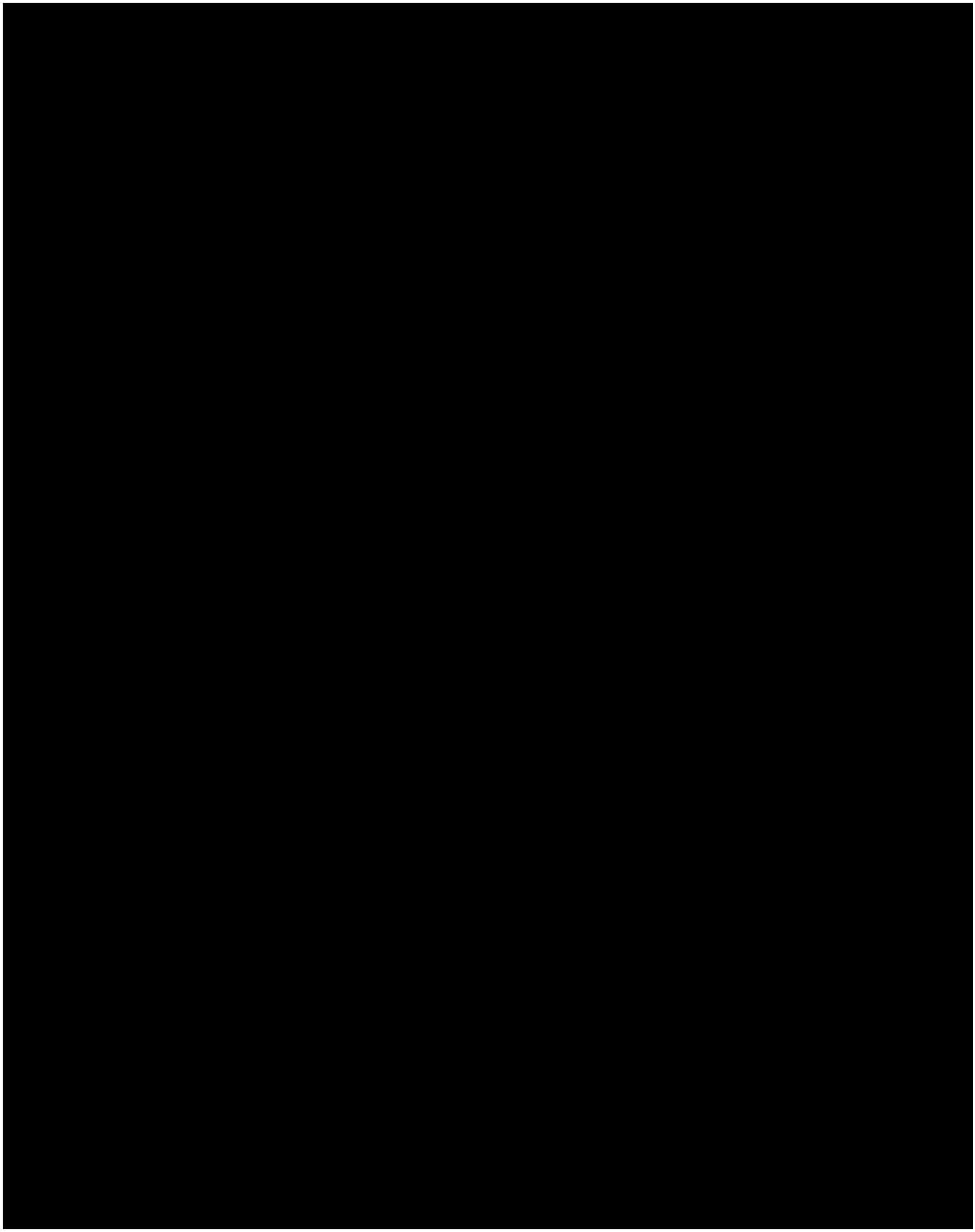
11. Has active autoimmune disease

12. Has current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, above the subnasale

[redacted]

[redacted]

[redacted]



[redacted]

6.3 Instructions for the Subjects

During each study visit, subjects will be required to remove all makeup to avoid interference with the assessments.

[redacted]

[redacted]

For at least 24 hours after treatment, it is recommended that subjects avoid strenuous exercise, extensive sun or heat exposure, and alcoholic beverages to reduce the risk of posttreatment redness, swelling, and/or itching.

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 injection site responses [ISRs] as requested by the subject and/or TI). Applicable procedures will be performed and recorded on the eCRF.

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. It is recommended that all follow-up procedures scheduled to be performed at the final site visit be performed at the subject's last site 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 a treatment-related AE is ongoing at the time of withdrawal, 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.

Randomized subjects who withdraw before treatment will not be replaced by another subject. The subject number and associated randomization number of the withdrawn subject must not be reassigned to a different subject.

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.

At regular intervals, the TI (or designee) will record on the eCRF the reasons for which any subjects are discontinued from the study, including subjects who signed the ICF but do not proceed to randomization.

6.6 Withdrawal Criteria

The subject may withdraw at will at any time for any reason.

If a subject has a positive urine pregnancy test prior to treatment, the subject will not be eligible for treatment and will be withdrawn from the study. If a subject has a positive urine pregnancy test after treatment, she will continue all scheduled visit procedures. The pregnancy will be followed as described in Section 10.3.

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 blinded EI's assessment at Month 1 of the subject's overall mid-face volume deficit for each cheek on the validated 6-point photonumeric MFVDS described in Table 2.

Table 2 Midface Volume Deficit Scale

Score	Grade	Description
5	Severe	• Wasting • Severe concavity in the zygomaticomalar region, anteromedial region, and/or submalar region • Severe tear troughs and/or nasolabial folds • Significant nasojugal folds and/or prejowl sulcus • Significant prominence of bony landmarks • Significant visibility of underlying musculature
4	Significant	• Significant concavity in the zygomaticomalar region, anteromedial region, and/or submalar region • Significant tear troughs and/or nasolabial folds • Moderate nasojugal folds and/or prejowl sulcus • Moderate prominence of bony landmarks • Moderate visibility of musculature
3	Moderate	• Moderate concavity in the zygomaticomalar region, anteromedial region, and/or submalar region • Moderate tear troughs and/or nasolabial folds • Mild nasojugal folds and/or prejowl sulcus • Mild prominence of bony landmarks • Mild visibility of musculature
2	Mild	• Mild concavity in the zygomaticomalar region, anteromedial region, and/or submalar region • Mild tear troughs and/or nasolabial folds

Score	Grade	Description
1	Minimal	• Flattening in the zygomaticomalar region, anteromedial region, and/or submalar region
0	None	• Moon face • Fullness (convexity) in the zygomaticomalar region, anteromedial region, and/or submalar region

7.1.2 Secondary Effectiveness Measure

The secondary effectiveness measure is the validated 5-item Satisfaction with Cheeks module of the FACE-Q questionnaire evaluated by the subject (very dissatisfied, somewhat dissatisfied, somewhat satisfied, very satisfied).

7.2 Safety Measures

Safety measures will include:

- subject assessment of procedural pain during treatment on an 11-point scale [redacted]
- presence and severity (mild, moderate, or severe) of ISRs recorded by subjects in daily safety diaries for 30 days after treatment
- AEs observed by the TI or reported to the TI by the subject

The subject's daily safety diary will list the following ISRs that have been reported previously with HA dermal filler injections:

- redness
- pain after injection
- tenderness to touch
- firmness
- swelling
- lumps/bumps
- bruising
- itching
- discoloration

AEs will be monitored continuously throughout the study and documented on an AE eCRF.

7.3 Demographics and Baseline Characteristics

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

7.4 Treatment Characteristics

Treatment characteristics will be evaluated by collecting information on anesthesia usage injection volume, and injection ease [redacted]

7.5 Summary of Methods of Data Collection

Electronic data capture and questionnaires will be used to collect study-specific information, such as subject and Investigator assessments. Completed eCRFs will be reviewed by the Investigator, 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.

8. Statistical Procedures

A separate statistical analysis plan will be prepared to provide specifications for all analyses. The plan will be finalized and approved prior to clinical database lock.

Descriptive statistics will be presented for key outcome measures. Categorical variables will be summarized with response frequencies and percentages. Continuous variables will be summarized by number of subjects, mean, median, standard deviation, minimum, and maximum. Where appropriate, 2-sided 95% CIs for population mean, or population proportion, will be provided as part of the summary.

Every attempt will be made to collect complete data and limit the occurrence of missing data. No imputation of missing data is planned, except for sensitivity analyses described in Section 8.3.1 and to account for days with missing reports during the ISR duration discussed in Section 8.3.4.

8.1 Analysis Populations

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

- modified intent-to-treat (mITT) population: all randomized subjects who received treatment with cannula on 1 cheek and treatment with needle on the contralateral cheek
- safety population: all randomized subjects who received at least 1 study treatment
- per-protocol (PP) population: all mITT population subjects who did not have any significant protocol deviations that could affect the primary endpoint; a significant deviation that occurred after the primary endpoint would not lead to exclusion from the PP analysis

Analyses of safety variables will be performed on the safety population. Unless specified otherwise, all other analyses will be performed on the mITT population. The PP population will be used to perform PP sensitivity analyses for the primary and secondary effectiveness variables.

Analyses will be based on treatment received, regardless of randomization assignment (ie, "as treated" rather than "as randomized"), in order to prevent bias towards study success (non-inferiority) that would be due to randomization errors that reverse the direction of the paired comparison. In addition, the mITT population will be used to do an "as randomized" sensitivity analysis for the primary effectiveness variable. That will not be necessary for the PP population, since it will exclude subjects who were not treated as randomized.

8.2 Collection/Derivation of Primary and Secondary Effectiveness Assessments

8.2.1 Primary Effectiveness Variable

The primary effectiveness variable is the change from baseline (screening) to Month 1 in overall MFVDS based on EI assessment at each timepoint.

8.2.2 Secondary Effectiveness Variables

The secondary effectiveness variables include EI-assessed overall MFVDS responder rates and subject satisfaction score on the FACE-Q Satisfaction with Cheeks module at Month 1. An overall MFVDS responder is defined as a subject who improves at least 1 grade from baseline on the primary measure of overall MFVDS.

8.3 Hypothesis and Methods of Analysis

8.3.1 Primary Effectiveness Analyses

For the primary effectiveness analysis of change from baseline at Month 1 in EI-assessed overall MFVDS, the mean paired difference between treatment with cannula and treatment with needle, and its 95% CI based on the paired t-test will be calculated. If the upper confidence limit is less than 0.5, statistical non-inferiority will be concluded.

If there are any mITT subjects with missing scores for the primary effectiveness endpoint, the following 2 missing-data handling methods are pre-specified to use for missing-data sensitivity analysis of the primary effectiveness endpoint.

1) Multiple imputation [redacted]
2) Baseline observation carried forward (BOCF) to replace missing Month 1 scores

8.3.2 Secondary Effectiveness Analyses

The following analyses will be performed for secondary effectiveness variables:

- Within-treatment overall MFVDS responder rates at Month 1 (and 95% CI) for the cannula side and, separately, for the needle side will be displayed, with support from paired-comparison response categories [redacted]

- FACE-Q Satisfaction with Cheeks module (subject self-assessment) change from baseline at Month 1 Visit will be summarized with descriptive statistics.

[redacted]

[redacted]

[redacted]

8.3.4 Safety Analyses

ISRs, procedural pain assessment, and AEs will be summarized using descriptive statistics. The primary safety analysis of ISRs and AEs will be summarized by the percentage (and 95% CI) of subjects who have the ISR (or AE) on both sides, by the percentage (and 95% CI) of subjects who have the ISR (or AE) on the cannula side and not on the needle side, and by the percentage (and 95% CI) of subjects who have the ISR (or AE) on the needle side and not on the cannula side. Also, the within-treatment percentage (and 95% CI) of subjects who have the ISR (or AE) will be summarized for the cannula side and, separately, for the needle side.

ISRs reported by subjects will be summarized by symptom, maximum reported severity, maximum reported duration (ie, calendar days from first occurrence to last reported occurrence during the 30-day ISR period), and number of ISR days (ie, calendar days with non-zero severity, after accounting for days with missing reports during the ISR duration). Adverse events will be summarized by System Organ Class and Preferred Term, and will be tabulated by duration, severity, causality, action taken, relationship to treatment, and outcome. The summary will include incidence rate as well as total number of events. AEs that occur before treatment will be listed, but not summarized.

8.4 Subgroup Analyses

The primary effectiveness endpoint will be summarized by baseline overall MFVDS score and investigational site. Details will be provided in the statistical analysis plan.

[redacted]

[redacted]

[redacted]

8.6 Interim Analyses

No interim analysis is planned.

9. Materials

9.1 Study Treatment

[redacted]

[redacted]

9.1.2 Instructions for Use and Administration

For investigational use in this clinical study, VOLUMA XC dermal filler will be injected to the cheek area using the supplied [redacted] cannulas or needles [redacted] and aseptic injection technique. The TI will inject the treatment slowly using gentle, even pressure on the

syringe in accordance with the randomization scheme and the IDFU, which will be provided to the TI.

9.1.3 Treatment Regimen Adjustments

The TI will determine the appropriate volume of VOLUMA XC to inject based on his/her clinical experience, [redacted]

9.2 Other Study Supplies

The investigational site is responsible for urine pregnancy tests (sensitivity ≥ 50 mIU/mL for human chorionic gonadotropin), routine supplies related to device storage, administration, and follow-up visits (eg, antiseptics, drapes, gloves, gauze, 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:

[redacted]

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 or his/her authorized designee 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 study number and 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. 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

All subjects will have 1 cheek treated with VOLUMA XC injectable gel using a [redacted] cannula and the contralateral cheek treated using a [redacted] needle. The side of treatment (ie, side of face for needle or cannula) will be randomized based on a central randomization schedule. An automated IWRS will be used to manage the randomization 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. Sites will dispense treatment according to the IWRS instructions provided by the system. Kit numbers used for actual injection should be recorded on eCRFs in order to determine "as-treated" versus "as-randomized" treatment association.

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 IRB's reporting requirements.

10.3 Pregnancy

If a female subject becomes pregnant after treatment, the TI will notify Allergan immediately after the pregnancy is confirmed. The TI will (1) instruct the subject to notify her physician of the presence of the investigational device and (2) will 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 for safety, and the pregnancy will be documented as a protocol deviation.

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 an 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 Section 11.3 and 11.4.

10.4 Study Termination

If conditions arise during the study that indicate that the study or an investigational site needs to be terminated, Allergan, the 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 subjects.

Although the risk of developing a serious complication is small, 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 problem. If subjects have any ongoing treatment-related AE at the time of the final visit, they must 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.

Typical or expected AEs or risks include bruising, swelling, redness, tenderness, and/or itching at the treatment site. Additional information about the possible side effects is available in the IDFU for VOLUMA XC.

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 questions, "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.

The following is a list of known potential AEs:

- redness, swelling, or a rash, which may be associated with itching, pain on pressure, after the injection
- pain at injection site
- bruising
- nodules or "lumpiness" at the injection site
- discoloration of the injection site
- rare cases of allergy, severe sensitivity, localized inflammation and abscesses
- very occasionally, delayed side effects can occur many months after the treatment. These side effects may appear as red lumps showing up underneath the skin, or intermittent episodes of swelling.
- in rare circumstances, facial fillers have been injected into blood vessels causing blockage and embolization which can result in skin necrosis, ulceration, or vision changes. Risks to vision include complete blindness, partial blindness, blurred vision, double vision, loss of peripheral vision, loss of a portion of the visual field or anterior

segment ischemia (characterized by decreased vision and pain). These effects can be temporary or permanent but are rare.

- swelling or edema around the eye following an injection can result in a temporary decrease of vision.
- in rare circumstances, facial fillers have been associated with granulomas, which are small inflammatory nodules under the skin.

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 TI who will use his/her medical judgment to do whatever is necessary to treat the subject.

11.1.2 Serious Adverse Event

A serious adverse event (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: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Allergan considers all cancer AEs as SAEs. Abortion is also considered an SAE except for elective abortion of a normal fetus.

See Section 11.4 for procedures for reporting an SAE/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 adverse events 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 procedures for reporting an ADE.

11.1.4 Serious Adverse Device Effect

A serious adverse device effect (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 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 an SADE. These shall be reported to the regulatory authorities and IRBs as required by national regulations.

11.1.7 Severity

Severity is a clinical determination of the intensity of an adverse event. 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 usual 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/email 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 (after signing ICF) are to be recorded on the appropriate eCRF by the TI. 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 (after signing ICF) or through the last subject visit are to be immediately reported to an Allergan representative at the fax number/email address listed on the cover page and recorded on the appropriate eCRF. 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 will 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 as required by national regulations.

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

1. Notify Allergan immediately by fax/email using the SAE/SADE reporting forms. For the SAE/SADE fax number/email 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 GCP guidelines and with ethical principles for clinical research.

12.1.4 Financial Disclosure/Certification Form

In accordance with 21 CFR 54.4, the Investigator and any subinvestigators 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, the 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, investigator MFVDS assessments, subject questionnaires and diaries, clinic charts, the TI's subject study files, results of pregnancy tests, and results of any other diagnostic tests such as X-rays, laboratory tests, and magnetic resonance imaging. The SAE Form and Pregnancy Surveillance Form 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 and subject number assigned from IWRS
- Study title and/or the protocol number and study sponsor
- A statement that informed consent 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, volume injected, ease of injection, details regarding molding and massage, kit 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, 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. A 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

12.5.1 Labeling/Packaging

VOLUMA XC will be provided sterile in plastic syringes. An investigational caution label, such as the following, will appear on the individual syringe package and the outer box:

Study 1650-801-008 Kit# VVVVV
Lot# VVVVVV
Allergan
Irvine, CA 92612

CAUTION - Investigational Device.
Limited by Federal (or United States) law to Investigational Use

Use as directed by protocol

VOLUMA XC will be packaged into 2 kit types:

1. [redacted]

2. [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.

VOLUMA XC must be stored at room temperature [redacted]) with a continuous temperature monitoring device. Use of the temperature monitoring 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 identification number, device serial/lot number, date of implantation, and date of explantation if applicable. Study device accountability will be performed within IWRS according to the instructions provided by the system. 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, cannulas, and needles 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 or 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 TI 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 study treatment, a trained research staff member will perform pregnancy testing on urine samples of female subjects of childbearing potential. The test employed must 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 TIs 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.

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