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STUDY TITLE

A multicenter, single-blind, randomized, “no-treatment” control,
study of the safety and effectiveness of
JUVÉDERM® VOLUMA XC Injectable Gel
for cheek augmentation to correct age-related volume deficit in the mid-face

PROTOCOL NUMBER: VOLUMA-002

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GOVERNING IRB:

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INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices 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) 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.

Treating Investigator Printed Name	Signature	Date
Evaluating Investigator #1 Printed Name	Signature	Date
Evaluating Investigator #2 Printed Name	Signature	Date

Acknowledged By:

Signature of Sponsor’s Representative	Date
Printed Name and Title	

RETURN TO ALLERGAN WITH ATTACHED PROTOCOL

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Synopsis

A multicenter, single-blind, randomized, “no-treatment” control study of the safety and effectiveness of JUVÉDERM® VOLUMA XC Injectable Gel for cheek augmentation to correct age-related volume deficit in the mid-face

PROTOCOL NUMBER: VOLUMA-002

STUDY TREATMENT: JUVÉDERM® VOLUMA XC Injectable Gel (VOLUMA XC)

PHASE: Pivotal study under an Investigational Device Exemption (IDE) for a modified formulation of JUVÉDERM® Injectable Gel and a new indication for use

STUDY OBJECTIVE: To demonstrate the safety and effectiveness of VOLUMA XC for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face

CLINICAL HYPOTHESES: At least 70% of Subjects treated with VOLUMA XC will be responders, i.e., the average of 2 blinded, independent Evaluating Investigators’ assessments of the Subject’s overall volume deficit in the mid-face, using the validated Mid-Face Volume Deficit Scale (MFVDS), at 6 months following the last treatment will be improved (reduced) by ≥ 1 grade compared with the average of the pre-treatment MFVDS assessments. In addition, clinical effectiveness will be demonstrated if the responder rate for Subjects treated with VOLUMA XC is statistically superior to the responder rate for the “no-treatment” control group at 6 months.

OVERALL STUDY DESIGN:

Structure: Multicenter, single-blind, randomized, “no-treatment” control

Duration: Up to 40 months after enrollment for run-in Subjects and 40 months after randomization for Subjects randomized to VOLUMA XC treatment (1-month treatment period, 6-month primary safety and effectiveness period, 18-month extended follow-up period, 3-month repeat treatment period, and 12-month post repeat treatment follow-up) and up to 46 months after randomization for those randomized to the “no-treatment” control group

Controls: A “no-treatment” control design will be used, i.e., Subjects will be randomized either to have treatment with VOLUMA XC at the outset of the study or to have treatment delayed at least 6 months. At each site 2 independent Evaluating

Investigators will remain blinded to the Subjects' randomized assignments, and all Subjects will undergo all effectiveness assessments through the 6-month follow-up visit.

Dosage/Dose regimen: Up to 2 treatment visits (Day -30, and/or Day 0) will be allowed. The Treating Investigator will determine the appropriate volume of VOLUMA XC to be injected during initial and touch-up treatment(s) up to a maximum total of 12 syringes (12 mL). One repeat treatment with up to 12 syringes (12 mL) may be performed at the Subject's option after the extended follow-up period (at/after the 12-month visit but no later than 3 months after the end of the extended follow-up period).

Injectable anesthesia (nerve block and/or local infusion) as well as topical anesthesia is allowed. The type, dose, and time of anesthesia will be recorded. The study treatment sites are the Right and Left cheeks. Treatment details, e.g., plane of injection, injection technique, and injection volume will be recorded for each treatment site by mid-facial sub-unit, i.e., the zygomaticomalar region, anteromedial cheek, and submalar region. Treatment of the tear troughs, nasolabial folds and upper lip are not permitted; however, contour improvement may be indirectly achieved in these areas by increased volume in the treated areas. For (optional) later biopsy each subject will also receive a subdermal depot injection of ~0.05 mL of VOLUMA XC in the medial aspect of the inner upper arm or behind the ear.

Visit schedule: Pre-treatment wash-out and run-in periods range from 10 days to 6 months for substances that affect coagulation, birth control (for females of child-bearing potential), and other facial products and procedures. Subjects randomized to treatment with VOLUMA XC will attend up to 2 treatment visits (Day -30 and/or Day 0), will complete a diary for 30 days, and will have telephone/e-mail contact with the Treating Investigator at 3 days after each treatment. Post-treatment follow-up office visits will occur at 1, 3, and 6 months and at quarterly intervals up to 24 months after the last treatment through the end of the extended follow-up period [at or after the 12-month follow-up visit when the average of the independent Evaluating Investigators' assessments of the Subject's zygomaticomalar region, anteromedial cheek, and submalar region, and overall mid-face volume deficit on the photometric Mid-Face Volume Deficit Scale (MFVDS) return to or exceed the average respective baseline score]. Unscheduled visits or telephone/e-mail contact with the Treating Investigator may occur at any time during the study that the Subject has questions or concerns about his/her treatment. After the extended follow-up period, Subjects opting for repeat treatment will complete a diary for 30 days, will have telephone/e-mail contact with the Treating Investigator on Day 3, and will return for an office visit at 1 month after repeat treatment. The subject will

complete further follow-up either with an office visit or with a telephone contact with the Treating Investigator at 3, 6, 9, and 12 months after repeat treatment. Subjects who had traversed the Month 12 follow-up window before Amendment 12 may be reconsented for a single (Month 12+) follow-up office visit. The Treating Investigator will monitor Subjects for safety throughout the study. The Evaluating Investigators will complete effectiveness assessments at the screening visit, at each scheduled follow-up visit, at the optional repeat treatment (prior to treatment), and at scheduled follow-up office visits after repeat treatment.

Because Subjects randomized to the “no-treatment” control group will not undergo treatment at the outset of the study, they will not be required to undergo safety evaluation by the Treating Investigator. However, to assure that the independent Evaluating Investigators remain blinded to which Subjects were treated and which were not, the control group will follow a similar effectiveness evaluation schedule through month 6, i.e., Months 1, 3, and 6. All Subjects will be instructed not to divulge their randomization assignments to either Evaluating Investigator at any time through Month 6. After Month 6, the control group will restart the study, i.e., treatment at Day -30 and/or Day 0 with the same follow-up schedule and optional repeat treatment and follow-up as the Subjects who were randomized to treatment with VOLUMA XC at the study outset.

STUDY POPULATION CHARACTERISTICS:

Number of subjects: Up to 345 subjects including up to 30 run-in subjects (maximum 2 per site), up to 240 subjects in the treatment group and at least 45 subjects in the “no treatment” control group. Enrollment targets include at least 40 enrolled Subjects per subgroup for analysis by gender, ethnicity, geographic location, injection site, plane of injection, and injection technique and at least 48 by Fitzpatrick Skin Phototype subgroup.

Condition/Disease: Normal, healthy adults with moderate, significant, or severe mid-facial volume deficit related to aging

Inclusion criteria: To be eligible for enrollment, the Subject must:

1. Be male or female, 35-65 years of age
2. Sign the IRB-approved Informed Consent form and the Authorization for Use and Release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed

3. Have zygomaticomalar region, anteromedial cheek, submalar region, and/or overall mid-facial volume deficit assessed by the Treating Investigator as grade 3, 4, or 5 on the photometric Mid-Face Volume Deficit Scale (MFVDS)
4. Desire cheek augmentation to correct age-related volume deficit in the mid-face, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region, as recommended by the Treating Investigator
5. Accept the obligation not to receive any other facial procedures or treatments affecting facial volume deficit at any time during the study
6. Be able to follow study instructions and likely to complete all required visits, as assessed by the Treating Investigator
7. If the subject is a female of child-bearing potential (sexually active and not sterile nor postmenopausal for at least 1 year), have a urine pregnancy test evaluated as negative within 10 days prior to enrollment, have used contraception for at least 30 days prior to enrollment, and agree to use a reliable method of contraception for the duration of the study

Exclusion criteria: Subject must not:

8. Have received (or is planning to receive) anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (oral/injectable corticosteroids or NSAIDs, e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., Vitamin E, garlic, ginkgo), from 10 days pre- to 3 days post injection [Study device injections may be delayed as necessary to accommodate this 10-day wash-out period.]
9. Have undergone facial plastic surgery (with the exception of rhinoplasty more than 2 years prior to enrollment), tissue grafting, or tissue augmentation with silicone, fat, or other permanent, or semi-permanent dermal fillers or be planning to undergo any of these procedures at any time during the study
10. Have undergone temporary facial dermal filler injections with hyaluronic acid-based fillers within 12 months, porcine-based collagen fillers within 24 months, or neuromodulator injections, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) within 6 months prior to entry in the study or be planning to undergo any of these procedures at any time during the study
11. Have begun use of any new over-the-counter or prescription, oral or topical, anti-wrinkle products in the treatment area within 90 days prior to enrollment or be planning to begin use of such products at any time during the study. [NOTE: Use of sunscreens and continued therapy with some cosmeceuticals (e.g., alpha hydroxyl acids, glycolic acids, retinol, or retinoic acids) is allowed if the regimen was established ≥ 90 days prior to enrollment]

12. Have very thin skin in the mid-facial region, tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, i.e., significant convexity or projection from the infraorbital fat pads
13. Have mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or HIV-related disease
14. Have a history of anaphylaxis, multiple severe allergies, atopy, or allergy to lidocaine (or any amide-based anesthetic), hyaluronic acid products, or *Streptococcal* protein, or have plans to undergo desensitization therapy during the term of the study
15. Have noticeable acne scarring, an active inflammation, infection, cancerous or pre-cancerous lesion, or unhealed wound or have undergone radiation treatment in the area to be treated
16. Be pregnant, lactating, or planning to become pregnant at any time during the study
17. Have received any investigational product within 30 days prior to study enrollment or be planning to participate in another investigation during the course of this study
18. Be an employee (or a relative of an employee) of the Evaluating Investigators, Treating Investigator, Sponsor, or representative of the Sponsor
19. Have a condition or be in a situation that, in the Treating Investigator's opinion, may put the Subject at significant risk, may confound the study results, or may interfere significantly with the Subject's participation in the study

STUDY DEVICE: JUVÉDERM[®] VOLUMA Injectable Gel (VOLUMA without lidocaine) is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant (dermal filler) that is currently available in Europe, Canada, Australia, Russia, Israel, and Brazil. Clinical data in humans is limited to European experience,^{3,5,19,22,26} and the product is investigational, i.e., not approved by the U.S. Food and Drug Administration (FDA). It consists of crosslinked hyaluronic acid (HA) formulated to a concentration of 20 mg/mL, suspended in a physiological buffer. The HA in VOLUMA XC is produced by *Streptococcus equi* bacteria. The HA is mixed with phosphate buffer and 0.3% Lidocaine and crosslinked by adding a minimum amount of BDDE (1,4-butanediol diglycidyl ether) to form a 3-dimensional HA gel. For clinical testing in the U.S. VOLUMA XC has been formulated with 0.3% Lidocaine to enhance patient comfort.

JUVÉDERM[®] 30, JUVÉDERM[®] Ultra, and JUVÉDERM[®] Ultra Plus Injectable Gels were approved by the U.S. Food and Drug Administration (FDA) in June 2006 as Class III devices for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles

and folds (such as nasolabial folds). JUVÉDERM® VOLUMA XC is formulated from the same raw materials [hyaluronic acid, 1,4-butanediol diglycidyl ether (BDDE), and phosphate buffer] as the other members of the JUVÉDERM® family of products, i.e., 30, Ultra, and Ultra Plus), but VOLUMA XC includes an additional molecular weight raw material HA and 0.3% Lidocaine. It also differs in its HA concentration (20 mg/mL vs. 24 mg/mL) and degree of crosslinking. The result is a gel with increased gel strength (resistance to flow, “stiffness”). All JUVÉDERM® Injectable Gels are significant risk devices as defined in 21 CFR Part 812.3(m)(1).

VOLUMA XC is provided sterile in glass or COC (cyclic olefin copolymer) syringes filled to 1.0 mL. The Sponsor is supplying 25G x 1” UTW (ultra thin wall) and 27G x ½” UTW needles for the implantation procedure separately. VOLUMA XC is an investigational device and will bear a label similar to the following:

CAUTION: Investigational Device
Limited by U.S. (Federal) law to investigational use

RESPONSE MEASURES:

Primary Effectiveness Measure: The primary effectiveness measure is the blinded Evaluating Investigator’s assessment of the Subject’s overall mid-face volume deficit on the validated 6-point photometric Mid-Face Volume Deficit Scale (MFVDS). Two (2) blinded Evaluating Investigators will provide independent MFVDS assessments prior to treatment and at all follow-up visits.

6-Point Mid-Face Volume Deficit Scale (MFVDS)

Score	Grade	Description
5	Severe	<ul style="list-style-type: none"> • Wasting • Severe concavity in the zygomaticomalar region, anteromedial cheek, 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	<ul style="list-style-type: none"> • Significant concavity in the zygomaticomalar region, anteromedial cheek, 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	<ul style="list-style-type: none"> • Moderate concavity in the zygomaticomalar region, anteromedial cheek, 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	<ul style="list-style-type: none"> • Mild concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Mild tear troughs and/or nasolabial folds
1	Minimal	<ul style="list-style-type: none"> • Flattening in the zygomaticomalar region, anteromedial cheek, and/or submalar region
0	None	<ul style="list-style-type: none"> • Moon face • Fullness (convexity) in the zygomaticomalar region, anteromedial cheek, and/or submalar region

Criteria for Effectiveness: To be considered a “responder” to VOLUMA XC, the average of the blinded, independent Evaluating Investigators’ assessments of the Subject’s overall mid-face volume deficit at 6 months following the last VOLUMA XC treatment (initial or touch-up, if performed) will be improved (reduced) by ≥ 1 grade compared with the average of the pre-treatment assessments.

Secondary Effectiveness Measures: The blinded, independent Evaluating Investigators will independently assess the Subject’s level of improvement on the 5-point Global Aesthetic Improvement Scale (GAIS), comparing the live Subject with his/her pre-treatment digital image, at all follow-up visits.

5-Point Global Aesthetic Improvement Scale (GAIS)

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

Additionally, the blinded, independent Evaluating Investigators will use the MFVDS to independently assess the Subject’s mid-face volume deficit for each treatment area (zygomaticomalar region, anteromedial cheek, and/or submalar region).

Additional Effectiveness Measures: Prior to treatment the Treating Investigator will assess the Subject’s mid-face volume deficit using the MFVDS to determine eligibility as well as Other Aesthetic Features of the Mid-Face (OAFM) and the severity of the Subject’s nasolabial folds using the NLF Severity Scale (NLFS). In consultation with the Treating Investigator, the Subject will assess his/her level of mid-face volume deficit and treatment goal(s) using the MFVDS and will record his/her current level of satisfaction with 5 mid-facial areas (GOAL1).

At all study visits the Evaluating Investigators as well as the Subject will independently assess the severity of the Subject’s nasolabial folds using the NLFS.

5-Point NLF Severity Scale (NLFS)

Score	Severity Descriptions	
4	Extreme	Very deep wrinkle, redundant fold (overlapping skin)
3	Severe	Deep wrinkle, well-defined edges (but not overlapping)
2	Moderate	Moderately deep wrinkle
1	Mild	Shallow, just perceptible wrinkle
0	None	No wrinkle

At all follow-up visits the Subject will independently assess overall MFVDS, whether the goal(s) of treatment have been met, NLFS, level of satisfaction with the 5 mid-facial areas (GOAL2), and level of mid-face improvement (compared with his/her pre-treatment digital image) on the 5-point Global Aesthetic Improvement Scale (GAIS).

The Evaluating Investigators will independently examine the Subject's mid-face from multiple angles, in repose and in animation, for other aesthetic features such as symmetry, proportion, and shape (OAFM) at pre-treatment and at all follow-up visits. At 6 months after treatment the Evaluating Investigators will independently guess the Subject's randomization assignment, i.e., treated or not treated, and will give the reasons for their guesses.

Additional Subject outcome measures will include qualitative satisfaction questions regarding the look and feel of their mid-face (LAFM), self-perception of age (SPA), and facial appearance evaluation (FAE), which includes items for Subjects to self-assess their facial appearance related to gender, ethnicity, geographical area, and social group prior to treatment and at 1, 6, 12, 18 and 24 months post treatment.

At follow-up office visits after repeat treatment the Evaluating Investigators will assess MFVDS and GAIS. At each office visit, subjects will assess GAIS, SPA, FAE, and whether the treatment goal(s) have been met.

Volume change of the right and left cheeks (by mid-facial sub-unit, i.e., zygomaticomalar region, anteromedial cheek, and submalar region) will be estimated using 3D digital imaging at pre- and post-treatment visits.

Safety Measures: The presence, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), severity, and duration of common treatment site responses (CTRs) and any adverse events (AEs) will be assessed by a Subject diary for 30 days, by

telephone/e-mail follow-up with the Treating Investigator at 3 days and by office visits at 30 days after each treatment (including the repeat treatment), and by discussion of the Subject's observations and the Investigator's personal observation of the Subject at multiple scheduled timepoints (via telephone, e-mail and/or office visits) throughout the study. To maintain the study blinding, the Evaluating Investigators must not be present during the time of the safety evaluations.

Histological evaluation will be attempted in approximately 18 Subjects who volunteer to undergo biopsy, with a target of 2 biopsy specimens per timepoint. The biopsy visit for each volunteer will be randomly assigned to one of the 9 study follow-up visits (Month 1 through Month 24). Additionally, the depot injection site should undergo histological evaluation in any Subject with severe inflammatory symptoms in the treated or depot area.

GENERAL STATISTICAL METHODS AND TYPES OF ANALYSES:

Analysis Methods: Analyses will be performed on the modified Intent-to-Treat (mITT) population, i.e., all Subjects in the "treatment" and "control" groups. Subjects randomized to study treatment and having at least one study device treatment will be included in the "treatment group," and those randomized to no treatment will be included in the "control group" in the safety and effectiveness analyses. Primary effectiveness analyses are also planned for the Per Protocol (PP) population, which includes all mITT Subjects who are not considered to be major protocol violators. Primary effectiveness analyses will also be repeated on the mITT dataset with data imputation (mITT). Computation for all results will be performed using the SAS[®] computer software package (Version 9.1 or higher).

The primary effectiveness endpoint will be based on the average of the 2 blinded, independent Evaluating Investigators' pre-treatment and 6-month assessments of overall Mid-Face Volume deficit using the 6-point scale following treatment. A 2-sided Exact test at the 0.025 significance level will be used to determine if at least 70% of the Subjects treated with VOLUMA XC are responders (i.e., achieve a reduction of ≥ 1 grade in their MFVDS score compared to pre-treatment) at 6 months. In addition, clinical effectiveness will be demonstrated if the responder rate for Subjects treated with VOLUMA XC is statistically superior to the responder rate for the "no-treatment" control group at 6 months using a 2-group, 2-sided, Fisher's exact test at the 0.025 significance level.

Secondary effectiveness analyses will be performed only if the primary endpoint analysis is significant.

The estimated responder rates (with 95% confidence intervals) will be presented for the average of the blinded, independent Evaluating Investigators' GAIS assessments, where a "responder" is a subject that shows improvement of ≥ 1.0 grade ("Improved" or "Much Improved") at the 6-month visit following the last (initial or touch-up) treatment as well as for the average of the 2 blinded, independent Evaluating Investigators' assessments of the Subject's volume deficit **in each area treated**, where a "responder" is a subject that shows ≥ 1 grade improvement at 6 months in the respective treated area compared with the respective pre-treatment assessments.

Statistical adjustment for multiplicity for the secondary effectiveness analyses will use the Benjamini-Hochberg method,⁶ which controls the False Discovery Rate (FDR) at the significance level of α or smaller:

For k hypotheses to be tested:

1. Order the p-values $p_{(1)} < p_{(2)} < \dots < p_{(k)}$, and let $H_{(1)}, H_{(2)}, \dots, H_{(k)}$ be the corresponding null hypotheses
2. Compare $p_{(k)}$ to α
 - a. If $p_{(k)} < \alpha$, reject all of $H_{(1)}, \dots, H_{(k)}$ and stop
 - b. If $p_{(k)} \geq \alpha$, do not reject $H_{(k)}$ and continue
3. Compare $p_{(k-1)}$ to $(k-1) \alpha/k$
 - a. If $p_{(k-1)} < (k-1) \alpha/k$, reject all of $H_{(1)}, \dots, H_{(k-1)}$ and stop
 - b. If $p_{(k-1)} \geq (k-1) \alpha/k$, do not reject $H_{(k-1)}$ and continue
4. Continue in this fashion until a stop or until no hypotheses are rejected

Additionally, a survival analysis after 6 months will be used to determine duration of effect in each treatment area, i.e., the timepoint when the averages of the blinded Evaluating Investigators' assessments of the Subject's MFVDS (overall, zygomatico-malar region, anteromedial cheek, and submalar region) return to or exceed the respective averages pre-treatment score.

Sample Size Calculation: Using a 4-point volume loss scale (range 1-4) for his retrospective case record review, a single, unblinded European physician reported that 98% of 102 aesthetic patients demonstrated ≥ 1 grade improvement (score reduction) following treatment with VOLUMA.²⁶ In contrast, the current prospective, controlled pivotal study protocol employs a primary effectiveness analysis based on the average scores from 2 blinded, independent Evaluating Investigators pre- and post-treatment as well as statistical superiority over a "no treatment" control group. This study design significantly reduces or eliminates investigator bias by including untreated subjects in the

evaluations. Thus, the estimated responder rate should be less than 98% and is arbitrarily set at 90%.

To achieve 85% power with a 2-sided Exact test at the 0.05 significance level a minimum sample size of 36 subjects is needed to detect a difference between the null hypothesis proportion (70%) and the alternate hypothesis proportion (90%), i.e., to demonstrate that $\geq 70\%$ of treated Subjects will be improved by ≥ 1 grade on the 6-point MFVDS at 6 months compared with the pre-treatment MFVDS assessment. A sample size of 36 control subjects and 216 treated subjects will provide $>99\%$ power for a 2-sided 2-group Fisher's exact test at the 0.025 significance level to demonstrate statistical superiority of the treatment group over the control group if the assumed responder rate in the control group is less than 40% at 6 months. Allowing for 20% attrition (drop-outs and protocol deviations) in the control group and 10% in the treatment group, the number of randomized Subjects is set at 45 "no treatment" control Subjects and 240 treated Subjects. Each site may treat up to 2 run-in Subjects (up to 30 total). Thus, overall enrollment will be at least 315 Subjects, which includes up to 240 subjects in the treatment group, at least 45 subjects in the "no-treatment" control group, and 30 run-in subjects.

For adequate power in covariate modeling and subgroup analyses, enrollment targets are set at ≥ 40 Subjects within specific subgroups [*Gender*: ≥ 40 Males, ≥ 40 Females; *Race*: ≥ 40 Caucasians, ≥ 40 African Americans, ≥ 40 Hispanics, and ≥ 40 Asians/Pacific Islanders; *Fitzpatrick Skin Phototype*: $\geq 20\%$ (48) I/II, $\geq 20\%$ (48) III/IV, and $\geq 20\%$ (48) V/VI; *Geography*: ≥ 40 Northeast, ≥ 40 Southeast, ≥ 40 Midwest, ≥ 40 Northwest, and ≥ 40 Southwest U.S., and ≥ 40 Canadian; *Treatment Site*: ≥ 40 zygomaticomalar region, ≥ 40 anteromedial cheek, and ≥ 40 submalar region; *Treatment Plane*: ≥ 40 suprapariosteal and ≥ 40 subdermal; and *Treatment Technique*: ≥ 40 Tunneling, ≥ 40 Fanning, ≥ 40 Antegrade, ≥ 40 Retrograde, and ≥ 40 Other].

Table 1: Enrollment and Randomization Period: All Subjects

Screening, Enrollment, and Randomization Procedure/Assessment	Visit 1
Study Informed Consent (ICF), Authorization to Use and Release of Health and Research Study Information (HIPAA)	X
Demographics; Medical and Cosmetic Procedures Histories; Concomitant Medications, Therapies, and Treatments (DEM, MED HX, COSM HX, CM)	X
Urine Pregnancy Testing in Females of Child-Bearing Potential (UPT)	X
3D Digital Imaging (Preparation of Wax Bite Mold)	X
Treating Investigator Assessments: <ul style="list-style-type: none"> • Photometric Mid-Face Volume Deficit Scale (MFVDS) • Nasolabial Fold Photo Severity Scale (NLFS) • Other Aesthetic Features of the Mid-Face (OAFM) 	X X X
Evaluating Investigators #1 and #2 Assessments: <ul style="list-style-type: none"> • Photometric Mid-Face Volume Deficit Scale (MFVDS) • Nasolabial Fold Photo Severity Scale (NLFS) • Other Aesthetic Features of the Mid-Face (OAFM) 	X X X
Subject Self-Assessments: <ul style="list-style-type: none"> • Mid-Face Volume, Goal Setting, and Satisfaction with Mid-Facial Regions Before Treatment (GOAL1) • Nasolabial Fold Photo Severity Scale (NLFS) • Self-Perception of Age (SPA) • Facial Appearance Evaluation (FAE) • Look and Feel of the Mid-Face (LAFM) 	X X X X
Treating Investigator Confirmation of Eligibility (ELIG)	X
Randomization	X

Table 2: Schedule of Study Visits and Procedures: “No Treatment” Control Group

Study Period	Blinded Follow-up Period ^a		
	2C	3C	4C
Visit Number			
Study Day/Month ^c	Month 1 (± 5 Days)	Month 3 (± 10 Days)	Month 6 ^b (± 15 Days)
3D Digital Imaging	X	X	X
Evaluating Investigator Assessments:			
• Photometric Mid-Face Volume Deficit Scale (MFVDS)	X	X	X
• Guess at Subject Randomization Assignment (MFVDS 6 Mo)			X
• Global Aesthetic Improvement Scale (GAIS)	X	X	X
• Nasolabial Fold Photo Severity Scale (NLFS)	X	X	X
• Other Aesthetic Features of the Mid-Face (OAFM)	X	X	X
Adverse Events (AEs)	Continuous monitoring ^c		
Concomitant Medications, Therapies, and Treatments	Continuous monitoring ^d		

a At every study visit the Treating Investigator, Study Coordinator, and the Subject must do their best to assure that the Evaluating Investigators do not discover that the control subjects did not undergo VOLUMA XC treatment. Evaluating Investigators should also not discuss the randomized assignments nor their assessments with each other.

b Following completion of all randomized Subjects' 6-month blinded follow-up visits at each investigational site, the control Subjects will be allowed to undergo treatment with VOLUMA XC without randomization (see Table 3).

c At each office visit the Treating Investigator and/or Study Coordinator will solicit information from the Subject regarding any new or ongoing adverse events (AEs), including symptom, sign, or diagnosis; location; severity; onset and resolution dates; causality; any action taken; and the outcome.

d At every study visit the Treating Investigator and/or Study Coordinator will inquire whether the Subject has used any prescription or OTC medications or other anti-wrinkle products or procedures since the previous visit

e Day 0 for the “no treatment” control group is calculated as the Month 1 visit date minus 30 days

Table 3: Schedule of Study Periods, Visits, and Procedures: Treatment Group

Study Period Visit Number	Treatment Period		Primary Safety and Effectiveness (Blinded) Follow-up Period ^g			Extended Follow-up Period	
	TA	TB (Possible Touch-Up)	2T	3T	4T	5, 6, 7, 8, 9, 10	
Procedure/Assessment	Study Day/Month	Day -30/ Day 0	Day 0	Month 1 (± 5 Days)	Month 3 (± 10 Days)	Month 6 (± 15 Days)	Months 9, 12, 15, 18, 21 & 24 (± 15 Days)
Evaluating Investigators #1 and #2 Assessments: <ul style="list-style-type: none"> • Photometric Mid-Face Volume Deficit Scale (MFVDS) • Guess at Subject Randomization Assignment (MFVDS 6 Mo) • Global Aesthetic Improvement Scale (GAIS) • Nasolabial Fold Severity Scale (NLFS) • Other Aesthetic Features of the Mid-Face (OAFM) 	See Table 1: Enroll- ment and Random- ization Period			X	X	X	X
Subject Self-Assessments: <ul style="list-style-type: none"> • Mid-Face Volume (MFVDS), Goal Achievement and Satisfaction with Mid-Facial Regions After Treatment (GOAL2) • Global Aesthetic Improvement Scale (GAIS) • Nasolabial Fold Severity Scale (NLFS) • Self-Perception of Age (SPA) • Facial Appearance Evaluation (FAE) • Look and Feel of the Mid-Face (LAFM) 		X ^a	X	X	X	X	X
Treating Investigator Procedures: <ul style="list-style-type: none"> • 3D Imaging • Urine Pregnancy Testing for Females of Child-Bearing Potential (UPT) • Biopsy for Histology (BXS) 		X ^a X ^a	X	X	X	X	X
Treating Investigator: Study Treatment/Touch-up: <ul style="list-style-type: none"> • Pre-treatment Anesthesia (PREP) • Injection Sites, Plane of Injection, Volume Injected & Techniques (TXS) • Biopsy Depot (BXS) 		X ^b X X ^c					
Treating Investigator Safety Evaluations: <ul style="list-style-type: none"> • Telephone/e-mail Contact by Investigator (DAY 3) • Subject Diary for Common Treatment Site Responses (CTRs) 		X (3 days) X ^c (30 days)	X (3 days) X ^c (30 days)				
<ul style="list-style-type: none"> • Adverse Events (AEs) • Concomitant Medications, Therapies, and Treatments 				Continuous monitoring ^e Continuous monitoring ^d			

- a These evaluations must be done within 10 days prior to touch-up treatment. If the urine pregnancy test is positive, the Subject may not undergo treatment.
- b A touch-up treatment may be performed at Visit TB if the Treating Investigator and Subject determine that volume augmentation of the Subject's mid-face has not been optimized, the Subject's allotment of VOLUMA XC has not been used up, and the Treating Investigator believes that additional VOLUMA XC will improve the facial appearance. If no touch-up is performed, the Subject enters the Primary Safety and Effectiveness Follow-up Period and Visit TB becomes the 1-month visit (Visit 2T).
- c For 30 days after initial and touch-up treatment(s) the Subject will maintain a diary of the presence or absence, severity, and location of common treatment site responses (CTRs). At each office visit the Treating Investigator and/or Study Coordinator will solicit information from the Subject regarding any new or ongoing CTRs or other adverse events (AEs), including symptom, sign, or diagnosis; location; severity; onset and resolution dates; causality; any action taken; and the outcome.
- d At every study visit the Treating Investigator and/or Study Coordinator will inquire whether the Subject has used any prescription or OTC medications or other anti-wrinkle products or procedures since the previous visit
- e For possible later biopsy each subject will receive a subdermal depot injection of ~0.05 mL of VOLUMA XC in the medial aspect of the upper inner arm or behind the ear during the initial treatment. Histological evaluation will be attempted in approximately 18 Subjects who volunteer to undergo biopsy, with a target of 2 biopsy specimens per timepoint. The biopsy visit for each volunteer will be randomly assigned to one of the 9 study follow-up visits (Month 1 through Month 24). Additionally, the depot injection site should undergo histological evaluation in any Subject with severe inflammatory symptoms in the treated or depot area.
- f These procedures should only be performed at Months 12, 18, and 24, unless the extended follow-up period ends at Month 15 or 21, at which point they should be performed.
- g At every study visit the Treating Investigator, Study Coordinator, and the Subject must do their best to assure that the Evaluating Investigators do not discover that the control subjects did not undergo VOLUMA XC treatment. Evaluating Investigators should also not discuss the randomized assignments nor their assessments with each other.

Table 4: Schedule of Repeat Treatment Periods, Visits, and Procedures: All Subjects (Optional)

	<u>Study Period</u>	<u>Repeat Treatment</u>	<u>Repeat Treatment Follow-up</u>	
	Visit Number	R1 (Optional)	R2	R3, R4, R5, R6, R6+ ^e
Procedure/Assessment	Study Day/Month	Month > 12 ≤ 27	1 Month Post Repeat Treatment (± 5 Days)	3, 6, 9, 12 & 12+ Months Post Repeat Treatment (± 15 Days)
Evaluating Investigators #1 and #2 Assessments:				
• Photometric Mid-Face Volume Deficit Scale (MFVDS)		X ^a	X	X
• Global Aesthetic Improvement Scale (GAIS)		X ^a	X	X
Subject Self-Assessments:				
• Goal Achievement			X	X
• Global Aesthetic Improvement Scale (GAIS)		X ^a	X	X
• Self-Perception of Age (SPA)		X ^a	X	X
• Facial Appearance Evaluation (FAE)		X ^a	X	X
Treating Investigator Procedures:		X ^b		
• Urine Pregnancy Testing for Females of Child-Bearing Potential (UPT)				
Treating Investigator: Repeat Treatment:				
• Pre-treatment Anesthesia (PREP)		X		
• Injection Sites, Plane of Injection, Volume Injected & Techniques (TXS)		X		
Treating Investigator Safety Evaluations:				
• Telephone/e-mail Contact by Investigator (DAY 3)		X (3 days)		X
• Subject Diary for Common Treatment Site Responses (CTRs)		X ^c (30 days)		
• Adverse Events (AEs)		Continuous monitoring ^c		
• Concomitant Medications, Therapies, and Treatments		Continuous monitoring ^a		

- a If the repeat treatment occurs at the same visit as the end of the extended follow-up period, this evaluation does not need to be repeated for the repeat treatment.
- b This evaluation must be done within 10 days prior to repeat treatment. If the urine pregnancy test is positive, the Subject may not undergo treatment.
- c For 30 days after repeat treatment the Subject will maintain a diary of the presence or absence, severity, and location of common treatment site responses (CTRs). At each office visit the Treating Investigator and/or Study Coordinator will solicit information from the Subject regarding any new or ongoing CTRs or other adverse events (AEs), including symptom, sign, or diagnosis; location; severity; onset and resolution dates; causality; any action taken; and the outcome.
- d At every study visit the Treating Investigator and/or Study Coordinator will inquire whether the Subject has used any prescription or OTC medications or other anti-wrinkle products or procedures since the previous visit
- e Visits at Month 3 through Month 12 can be an in-person office visit or a telephone contact, not both. If the follow-up is an office visit, all safety and effectiveness assessments for that visit will be performed. If the follow-up is a telephone contact, only safety evaluations will be performed. Only subjects who had already traversed the Month 12 follow-up window before Amendment 12 may be reconsented for a single 12+ Month follow-up office visit.

1. Background and Rationale

The youthful face is characterized by a round, full mid-face across the cheek and malar area with prominent cheekbones.^{8,11,13,28} Although gender, ethnic, and cultural differences must also be considered,⁹ the zygomaticomalar complex has been described as the “hallmark of youth.”²⁴ Universally, the mid-facial striated muscles, combined with the skin and subdermal fat, create an anterior convexity from the lower eyelid onto the cheeks, forming a smooth S-shape (“ogee curve”) when viewed from an oblique angle.^{13,23}

Volumetric facial aging appears as a gravity-induced descent and forward drift of the soft tissues from the malar region into the nasolabial fold zone and from the submalar region into the jowl such that a heart-shaped face gradually transitions to a rectangular or pear-shaped face.²³ As the inferior bony orbit resorbs and the soft tissue in the malar area descends, the ‘ogee curve’ flattens.

Aging baby boomers are again driving emerging trends. They are healthier and more active in their middle age with greater life expectancy than any prior generation. They are bothered by their tired and volume-depleted mid-faces. They want to look as young as they feel without looking overdone or unnatural, they want a minimally invasive procedure, and many do not want the downtime or permanence of surgery, liposuction and autologous fat transfer, or permanent fillers.

In response to their patients’ desires, the community of cosmetic physicians and surgeons has made a paradigm shift in their approach to facial rejuvenation. Volume restoration via injection of HA-based fillers in the mid-face and lower face is now the recommended first step to restore a youthful appearance.⁹ Initial treatment with fillers in the mid-face (zygomaticomalar region, anteromedial cheek, and/or submalar region) often provides a lifting effect in adjacent areas that reduces the severity of the nasolabial folds and nasojugal grooves such that minimal further treatment of these areas may be needed. The addition of volume to the temples, pre-jowl sulcus, chin, and mandible can also have a rejuvenating effect.

Because injections to restore volume are often made with more robust materials that are placed under the skin and/or muscle (as opposed to intradermal injection), a thorough knowledge of the facial anatomy; appreciation for the characteristics of the product being injected; an eye for beauty, harmony, and proportion; an understanding of the patient’s goals and aesthetic potential; and a meticulous approach with skilled and steady hands are the pre-requisites for safe and effective outcomes in this new arena.

Standardized facial lipoatrophy/volume loss scales and appropriate patient-reported outcomes (PRO) measures are emerging for use in evaluating the effectiveness of these new treatment algorithms in a reliable and reproducible way. Ascher et al. defined lipoatrophy as the “loss of facial fat due to aging, trauma, or disease, manifested by flattening or indentation of normally convex contours” and developed a 6-point classification system (range 0-5) with grade 0 representing no facial lipoatrophy and grade 5 representing severe indentation of one or more facial regions, severe prominence of bony landmarks, and clear visibility of underlying structures.²

Global Aesthetic Improvement Scales (GAIS) have become a commonly used measure of patient satisfaction in recent dermal filler studies.^{5,25} However, a PRO instrument is more than just the vague notion of patient satisfaction, but rather it should attempt to measure the patient’s degree of physical, mental, and social well-being.¹ Standardized PRO instruments, e.g., the Freiberg Questionnaire on Aesthetic Dermatology and Cosmetic Surgery (FQAD I and II)⁴ and the Dermatology Quality of Life Index (DLQI),¹⁶ have been used with injections of botulinum toxin type A (BoNTA)¹⁰ and VOLUMA.⁵ Yet, these instruments were designed for use with more invasive procedures or with medical dermatology conditions (i.e., liposuction under tumescent anesthesia or a “skin problem,” respectively), and many of the items are unsuited to minimally-invasive, cosmetic enhancements, e.g., volumizing and recontouring with dermal fillers. Alsarraf reports on four PROs developed for specific cosmetic procedures, i.e., facelift (FOE), rhinoplasty (ROE), blepharoplasty (BOE), and skin resurfacing (SOE). Each PRO is validated with the specific procedure; includes items that measure physical, mental, and social elements; and uses a 5-point Likert Scale format in each of its 6 items (which are very similar across the four procedure-specific instruments.)¹

Two new PRO instruments have been used in studies to correct upper facial lines (glabella, forehead, crow’s feet) with BoNTA.¹⁰ The Facial Lines Outcomes (FLO-11 or FLO-7) 11- or 7-item questionnaire uses an 11-point Likert Scale (0=not at all, 5=somewhat, and 10=very much) to assess the patient’s level of concern about their upper facial lines during the previous 7-day period. In a recent study of JUVÉDERM® ULTRA Injectable Gel, adaptations of the FLO-11 [i.e., the Look and Feel (LAF) and Function and Sensation (FAS) questionnaires] demonstrated dramatic improvements without significant change in function and sensation as assessed by subjects treated for aesthetic enhancement of the lips and perioral area.²¹ Very simple to administer as well as being relevant to a patient’s treatment goal, the Self-Perception of Age (SPA) measure demonstrated that BoNTA treatment helps

patients feel younger than their current age.¹⁴ Adaptations of the validated FLO, FOE/ROE/BOE/SOE, LAF, and SPA scales will be employed in the current study.

In June 2006, 3 members of the JUVÉDERM[®] family of HA-based dermal fillers, known as JUVÉDERM[®] 30, JUVÉDERM[®] Ultra, and JUVÉDERM[®] Ultra Plus Injectable Gels, were approved by the U.S. Food and Drug Administration (FDA) for the correction of moderate to severe facial wrinkles and folds such as nasolabial folds.²⁰ A new member of the JUVÉDERM[®] family, JUVÉDERM[®] VOLUMA Injectable Gel (VOLUMA), is commercially available in Europe, Canada, Australia, Russia, Israel, and Brazil, and has been specifically developed for volumizing by injection into deeper tissue, e.g., to augment facial volume for aesthetic improvement. VOLUMA is formulated from the same raw materials [hyaluronic acid, 1,4-butanediol diglycidyl ether (BDDE), and phosphate buffer] as other members of the JUVÉDERM[®] family of products, but it differs in its HA concentration (20 mg/mL vs. 24 mg/mL), and the rate and efficiency of crosslinking, which affects the percentage of un-crosslinked and partially crosslinked HA chains as well as the density of the 3-dimensional (3D) gel matrix. The result is a gel with increased gel strength while maintaining the cohesive nature of the JUVÉDERM[®] family of dermal fillers. For clinical testing in the U.S. the addition of 0.3% Lidocaine during formulation may enhance patient comfort during and shortly after the injection procedure without changing the physical or chemical properties of VOLUMA. These characteristics make VOLUMA XC (with Lidocaine) a suitable option for restoration of facial volume by means of deep injections over a large area, with large quantities of gel distributed in small aliquots.

As is evident from the plethora of literature on minimally invasive facial volume restoration, FDA-approved HA fillers are frequently used “off-label” to improve the contours of the mid-face (zygomaticomalar region, anteromedial cheek, and submalar region) and lower face (chin and prejowl sulcus). JUVÉDERM[®] VOLUMA XC Injectable Gel is especially suited for volume enhancement with its robust viscosity and cohesivity compared with other HA fillers. In non-U.S. markets where VOLUMA is currently available, thousands of patients have been treated with VOLUMA with minimal reported side effects.[†]

This protocol is designed as a pivotal study to collect safety and effectiveness data associated with the implantation of VOLUMA XC for cheek augmentation to correct age-related

[†] Post market surveillance data on file, Allergan.

volume deficit in the mid-face in normal, healthy subjects desiring aesthetic improvement, the first HA formulation to be studied under an IDE for this indication.

2. Study Objectives

To demonstrate the safety and effectiveness of VOLUMA XC for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face

3. Clinical Hypotheses

At least 70% of Subjects treated with VOLUMA XC will be responders, i.e., the average of the blinded, independent Evaluating Investigators' assessments of the Subject's overall mid-face volume deficit at 6 months following the last VOLUMA XC treatment will be improved (reduced) by ≥ 1 grade compared with the pre-treatment assessment. In addition, clinical effectiveness will be demonstrated if the responder rate for Subjects treated with VOLUMA XC is statistically superior to the responder rate for the "no-treatment" control group at 6 months.

4. Overall Study Design

This is a multicenter, single-blind, randomized, "no treatment" control study. Eligible Subjects will be randomized either to undergo up to 2 treatments with VOLUMA XC for cheek augmentation to correct age-related volume deficit in the mid-face at the outset of the study or to delay treatment with VOLUMA XC at least 6 months. Duration of participation for Subjects randomized to treatment with VOLUMA XC (and run-in Subjects) may last up to 40 months after randomization and up to 40 months after enrollment for run-in subjects (1-month treatment period, 6-month primary safety and effectiveness period, 18-month extended follow-up period, 3-month repeat treatment period, and 12-month post repeat treatment follow-up). Participation for Subjects randomized to the "no-treatment" control group may last up to 46 months after randomization (6 months with no treatment, 1-month treatment period, 6-month primary safety and effectiveness period, 18-month extended follow-up period, 3-month repeat treatment period, and 12-month post repeat treatment follow-up).

The Treating Investigator will determine the appropriate volume of VOLUMA XC to be injected during initial and touch-up treatment as well as at repeat treatment after the extended follow-up period. For possible later biopsy each subject will also receive a subdermal depot

injection of ~0.05 mL of VOLUMA XC in the medial aspect of the upper inner arm or behind the ear during the initial treatment.

Injectable anesthesia (nerve block and/or local infusion) as well as topical anesthesia is allowed. The type, dose, and time of anesthesia will be recorded. The study treatment sites are the Right and Left cheeks, described in this study by mid-facial sub-unit, i.e., zygomaticomalar region, anteromedial cheek, and submalar region. Treatment of the tear troughs, nasojugal folds, nasal sidewall, nasolabial folds, and upper lip are not permitted; however, contour improvement may be indirectly achieved in these areas by increased volume in the treated areas.

Treatment details, e.g., plane of injection, injection technique, and volume injected will be recorded for each area, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region. Through the use of a subject diary for 30 days after each treatment, common treatment site responses (CTRs) will be tracked by presence, severity, and location (treatment area). Other related and unrelated adverse events (AEs) and use of medications will be monitored by the Treating Investigator throughout the study.

Each Subject will complete the extended follow-up period at 24 months after the last study treatment or at/after the 12-month visit if the average of the blinded, independent Evaluating Investigators' assessments of zygomaticomalar region, anteromedial cheek, and submalar region, and overall mid-face volume deficit (MFVDS) return to or exceed the respective pre-treatment average, whichever occurs first.

5. Study Population

5.1 Number of Subjects

Up to 345 subjects will be enrolled at up to 15 U.S. and Canadian sites including up to 30 run-in Subjects, up to 240 in the treatment group who will be treated with VOLUMA XC at the study outset, and at least 45 Subjects in the “no-treatment” control group whose treatment with VOLUMA XC will be delayed at least 6 months.

Enrollment will be monitored and randomization may become restricted by the Sponsor to meet treatment group enrollment targets for subgroup analyses: *Gender*: ≥ 40 Males, ≥ 40 Females; *Race*: ≥ 40 Caucasians, ≥ 40 African Americans, ≥ 40 Hispanics, and ≥ 40 Asians/Pacific Islanders; *Fitzpatrick Skin Phototype*:¹⁵ $\geq 20\%$ (48) I/II, $\geq 20\%$ (48) III/IV, and $\geq 20\%$ (48) V/VI; *Geography*: ≥ 40 Northeast, ≥ 40 Southeast, ≥ 40 Midwest, ≥ 40 Northwest, and ≥ 40 Southwest U.S., and ≥ 40 Canadian; *Treatment Site*: ≥ 40 zygomaticomalar region, ≥ 40 anteromedial cheek,

and ≥ 40 submalar region; *Treatment Plane*: ≥ 40 supraperiosteal and ≥ 40 subdermal; and *Treatment Technique*: ≥ 40 Tunneling, ≥ 40 Fanning, ≥ 40 Antegrade, ≥ 40 Retrograde, and ≥ 40 Other.

5.2 Study Population Characteristics

Normal, healthy adults who desire cheek augmentation to correct mid-facial volume deficit related to aging will be recruited.

5.3 Inclusion Criteria

The following are requirements for entry into the study. The Subject must:

1. Be male or female, 35–65 years of age
2. Sign the IRB-approved Informed Consent form and the Authorization for Use and Release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed
3. Have zygomaticomalar region, anteromedial cheek, submalar region, and/or overall mid-facial volume deficit assessed by the Treating Investigator as grade 3, 4, or 5 on the photometric Mid-Face Volume Deficit Scale (MFVDS)
4. Desire cheek augmentation to correct age-related volume deficit in the mid-face, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region, as recommended by the Treating Investigator
5. Accept the obligation not to receive any other facial procedures or treatments affecting facial volume deficit at any time during the study
6. Be able to follow study instructions and likely to complete all required visits, as assessed by the Investigator
7. If the subject is a female of child-bearing potential (sexually active and not sterile nor postmenopausal for at least 1 year), have a urine pregnancy test evaluated as negative within 10 days prior to enrollment, have used contraception for at least 30 days prior to enrollment, and agree to use a reliable method of contraception for the duration of the study

5.4 Exclusion Criteria

The Subject must not:

8. Have received (or is planning to receive) anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (oral/injectable corticosteroids or NSAIDs, e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., Vitamin E, garlic, ginkgo), from 10 days pre- to 3 days post injection [Study

device injections may be delayed as necessary to accommodate this 10-day wash-out period.]

9. Have undergone cosmetic facial plastic surgery (with the exception of rhinoplasty more than 2 years prior to enrollment), tissue grafting, or tissue augmentation with silicone, fat, or other permanent, or semi-permanent or be planning to undergo any of these procedures at any time during the study
10. Have undergone temporary facial dermal filler with hyaluronic acid-based fillers within 12 months, porcine-based collagen fillers within 24 months, or neuromodulator injections, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) within 6 months prior to entry in the study or be planning to undergo any of these procedures at any time during the study
11. Have begun use of any new over-the-counter or prescription, oral or topical, anti-wrinkle products in the treatment area within 90 days prior to enrollment or be planning to begin use of such products at any time during the study. [NOTE: Use of sunscreens and continued therapy with some cosmeceuticals (e.g., alpha hydroxyl acids, glycolic acids, retinol, or retinoic acids) is allowed if the regimen was established ≥ 90 days prior to enrollment]
12. Have very thin skin in the mid-facial region, tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, i.e., significant convexity or projection from the infraorbital fat pads
13. Have mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or HIV-related disease
14. Have a history of anaphylaxis, multiple severe allergies, atopy, or allergy to lidocaine (or any amide-based anesthetic), hyaluronic acid products, or *Streptococcal* protein, or have plans to undergo desensitization therapy during the term of the study
15. Have noticeable acne scarring, an active inflammation, infection, cancerous or pre-cancerous lesion, or unhealed wound or have undergone radiation treatment in the area to be treated
16. Be pregnant, lactating, or planning to become pregnant at any time during the study
17. Have received any investigational product within 30 days prior to study enrollment or be planning to participate in another investigation during the course of this study
18. Be an employee (or a relative of an employee) of the Evaluating Investigators, Treating Investigator, Sponsor, or representative of the Sponsor

19. Have a condition or be in a situation that, in the Treating Investigator's opinion, may put the Subject at significant risk, may confound the study results, or may interfere significantly with the Subject's participation in the study

5.5 Withdrawal Criteria

Subjects may withdraw from the study at any time. They may also be administratively withdrawn if they do not return for follow-up (see Section 8.4.3).

6. Response Measures

6.1 Effectiveness Measures

6.1.1 Primary Effectiveness Variable

The primary effectiveness measure is the blinded Evaluating Investigator assessment of the Subject's overall mid-face volume deficit on the 6-point photometric Mid-Face Volume Deficit Scale (MFVDS). Two (2) blinded Evaluating Investigators will provide independent MFVDS assessments prior to treatment and at all follow-up visits.

6-Point Mid-Face Volume Deficit Scale (MFVDS)

Score	Grade	Description
5	Severe	<ul style="list-style-type: none"> • Wasting • Severe concavity in the zygomaticomalar region, anteromedial cheek, 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	<ul style="list-style-type: none"> • Significant concavity in the zygomaticomalar region, anteromedial cheek, 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	<ul style="list-style-type: none"> • Moderate concavity in the zygomaticomalar region, anteromedial cheek, 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	<ul style="list-style-type: none"> • Mild concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar areas • Mild tear troughs and/or nasolabial folds
1	Minimal	<ul style="list-style-type: none"> • Flattening in the zygomaticomalar region, anteromedial cheek, and/or submalar areas
0	None	<ul style="list-style-type: none"> • Moon face • Fullness (convexity) in the zygomaticomalar region, anteromedial cheek, and/or submalar region

The verbal descriptions above have been combined with frontal, oblique, and top-down photographs of 2 individuals deemed to be representative of each grade by a board-certified dermatologist with experience in the use of dermal fillers for facial volume restoration (see Attachment 13.1.1, Photometric Mid-Face Volume Deficit Scale). These representative individuals were selected from a non-treatment, screening and photo collection study involving approximately 289 subjects.

To validate the scale and to determine the grade change that is clinically significant prior to study enrollment, the 2 Evaluating Investigators and the Treating Investigator from each site will independently compare pairs of digital images to assess whether they represent clinically significant differences in mid-face volume deficit. They will then be trained in the use of the MFVDS scale and will independently rate a set of 3D images [some that were used during the initial scale validation and some that were not, including images compared for clinical significance and of non-study subjects before and after volumizing treatment with VOLUMA in the mid-face (in a region where VOLUMA is commercially available)].

In addition to rating the overall MFVDS score, they will rate each image for volume deficit of the zygomaticomalar region, anteromedial cheek, and submalar region. These regions are demarcated by the following reference lines super-imposed on frontal and oblique views of a mannequin (see Figures 1 and 2, below, which are also included as Attachments 13.1.2 and 13.1.3).

- A line drawn from the inferior orbital rim to the upper tragus
- A line drawn from the nasal alar base to the middle tragus
- A line drawn from the lateral commissure to the lower tragus
- A line drawn from the lateral commissure to the lateral canthus
- A line drawn from the nasal ala along the nasofacial sulcus, the natural concavity between the nasal sidewall and medial cheek

NOTE: The tear trough and nasolabial fold areas are shaded for reference only. These areas may not be treated as part of this protocol.

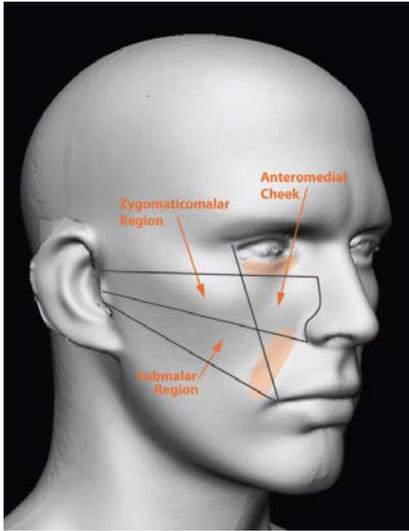


Figure 1

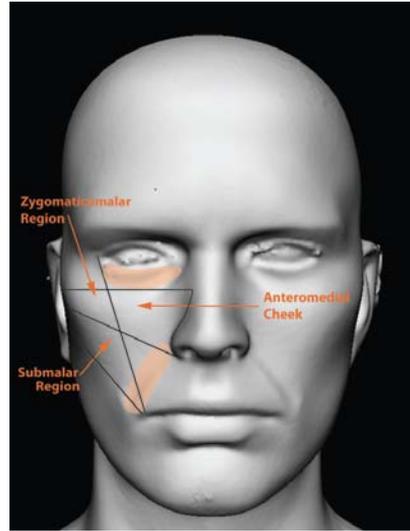


Figure 2

At least 14 days later the Evaluating and Treating Investigators will again independently rate the same set of 3D images. The MFVDS grade difference that corresponds with a clinically significant difference as well as the inter-rater and intra-rater agreement for overall MFVDS and by treatment area (zygomaticomalar region, anteromedial cheek, and submalar region) will be determined from these data.

Reproducible use of the scale by each Investigator and across all Investigators over the duration of the study is essential to assure the reliability of the study results, and substantial agreement (0.60 or greater)¹⁷ is expected. For this reason, the Treating Investigators must be board-certified dermatologists, plastic surgeons, and/or facial, maxillofacial or oculoplastic surgeons with at least 3 years of experience with the use dermal fillers for cosmetic volumizing. Evaluating Investigators will also be board-certified dermatologists, plastic surgeons, and/or facial, maxillofacial or oculoplastic surgeons, or physicians of other specialties if they are board-certified in their respective specialties and have documentation of experience in the evaluation of patients undergoing cosmetic filler treatments.

If the inter-rater or intra-rater agreement is less than 0.60, the outlying Investigator(s) with a low pair-wise inter-rater agreement or a low intra-rater agreement will be identified and will undergo additional training and a retest at least 14 days later. If after retest, agreement is still less than 0.60, the disparate Investigator(s) will not participate in the study.

6.1.2 Criteria for Effectiveness

To be considered a “responder” to VOLUMA XC, the average of the 2 blinded, independent Evaluating Investigators’ assessments of the Subject’s overall Mid-Face Volume Deficit

(MFVDS) at 6 months following the initial or touch-up treatment (whichever is last) will be improved (reduced) by ≥ 1 grade compared with the average of the pre-treatment MFVDS assessments.

6.1.3 Secondary Effectiveness Variables

The blinded Evaluating Investigators will independently assess the Subject’s level of improvement on the 5-point Global Aesthetic Improvement Scale, comparing the live Subject with his/her pre-treatment digital image, at all follow-up visits.

5-Point Global Aesthetic Improvement Scale (GAIS)

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

Additionally, the blinded, independent Evaluating Investigators will use the MFVDS to independently assess the Subject’s mid-face volume deficit for each treatment area (zygomaticomalar region, anteromedial cheek, and/or submalar region), (see Attachment 13.1).

6.1.4 Additional Effectiveness Measures

Prior to treatment, the Treating Investigator will examine the Subject’s mid-face from multiple angles, in repose and in animation, and will assess the Subject’s mid-face volume deficit using the MFVDS to determine eligibility, nasolabial fold severity using the NLFS (see below), and Other Aesthetic Features of the Mid-face, such as symmetry, proportion, and shape, using an 11-point scale (range 0–10).

5-Point NLF Severity Scale (NLFS)

Score	Severity Descriptions	
4	Extreme	Very deep wrinkle, redundant fold (overlapping skin)
3	Severe	Deep wrinkle, well-defined edges (but not overlapping)
2	Moderate	Moderately deep wrinkle
1	Mild	Shallow, just perceptible wrinkle
0	None	No wrinkle

In consultation with the Treating Investigator prior to treatment, the Subject will assess his/her level of mid-face volume and treatment goal(s) using the MFVDS and will record his/her current level of satisfaction with 5 mid-facial areas. Independently, the Subject will assess NLFS. Due to the lack of suitable validated patient reported outcome (PRO) instruments, Subject outcome measures for this study have been adapted from previously validated PROs, including self-perception of age¹⁴ and self-evaluation of facial appearance (with the first 6 questions patterned after the validated ROE, BOE, FOE, and SOE instruments¹ and with additional items to explore the relation of facial appearance to gender, ethnic, and cultural aspects). Using an 11-point scale (range 0–10) patterned after the FLO-11 questionnaire¹⁰ and the LAF CRF,²¹ Subjects will complete a series of questions regarding their level of satisfaction with the look and feel of their mid-face.

The Evaluating Investigators will examine the Subject’s mid-face from multiple angles, in repose and in animation, and will independently assess NLFS and OAFM.

At all follow-up visits the Subject will independently assess current MFVDS, whether the goal(s) of treatment have been met, level of satisfaction with the 5 mid-facial areas, level of improvement (compared with his/her pre-treatment digital image) on the 5-point Global Aesthetic Improvement Scale (GAIS), and NLFS. At 1, 6, 12, 18, and 24 months post treatment, Subjects will complete the SPA, FAE, and LAFM. At post repeat treatment follow-up office visits, Subjects will independently assess whether the goal(s) of treatment have been met and will complete GAIS, SPA, and FAE.

At 6 months after treatment the Evaluating Investigators will independently guess the Subject’s randomization assignment, i.e. treated or not treated, and will give the reasons for their guesses.

Digital images of the right and left cheeks (by mid-facial sub-unit, i.e., zygomaticomalar region, anteromedial cheek, and submalar region) at pre- and post-treatment visits will be used by Canfield Scientific, Inc. to estimate volume change with 3D digital imaging software.

6.2 Safety Measures

The presence, severity, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), and duration of common treatment site responses (CTRs) and any adverse events (AEs) will be assessed by a Subject diary for 30 days, by telephone/e-mail follow-up with the Treating Investigator at 3 days, at office visits at 30 days after each treatment (including the optional repeat treatment), and by discussion of the Subject's observations and the Treating Investigator's personal observation of the Subject at multiple scheduled office visits throughout the study. To maintain the study blind, the Evaluating Investigators must not be present during the safety evaluations.

Histological evaluation will be attempted in approximately 18 Subjects who volunteer to undergo biopsy, with a target of 2 biopsy specimens per timepoint. The biopsy visit for each volunteer will be randomly assigned to one of the 9 study follow-up visits (Month 1 through Month 24). Additionally, the depot injection site should undergo histological evaluation in any Subject with severe inflammatory symptoms in the treated or depot area. The biopsied tissue will be placed in formalin prior to shipment to a central CLIA-certified laboratory that will prepare the tissue specimens using established techniques and stains, e.g., hematoxylin and eosin (H&E), tri-chrome, and colloidal iron. A single board-certified dermatopathologist who is experienced in histological evaluation following dermal filler injections will evaluate all tissue specimens from the study and will comment on the types and relative quantities of cells observed, the presence and status of the implant, the overall level of inflammation (minimal, mild, moderate, or marked) and fibrosis at the implant site, and any other interesting features.

7. Materials

7.1 Study Treatment

7.1.1 Study Device

JUVÉDERM[®] VOLUMA Injectable Gel (VOLUMA without lidocaine) is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant (dermal filler) that is currently available in Europe, Canada, Australia, Russia, Israel, and

Brazil. Clinical data is limited to European experience,^{3,5,19,22,26} and the product is investigational, i.e., not approved by the U.S. Food and Drug Administration (FDA). It consists of crosslinked hyaluronic acid (HA) formulated to a concentration of 20 mg/mL, suspended in a physiological buffer. The HA in JUVÉDERM[®] Gel and VOLUMA XC is produced by *Streptococcus equi* bacteria. The HA is mixed with phosphate buffer and 0.3% Lidocaine and crosslinked by adding a minimum amount of BDDE (1,4-butanediol diglycidyl ether) to form a 3-dimensional HA gel. For clinical testing in the U.S. VOLUMA XC has been formulated with 0.3% Lidocaine to enhance patient comfort.

JUVÉDERM[®] 30, JUVÉDERM[®] Ultra, and JUVÉDERM[®] Ultra Plus Injectable Gels were approved by the U.S. Food and Drug Administration (FDA) in June 2006 as Class III devices for injection into the mid- to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). JUVÉDERM[®] VOLUMA XC is formulated from the same raw materials [hyaluronic acid, 1,4-butanediol diglycidyl ether (BDDE), and phosphate buffer) as the other members of the JUVÉDERM[®] family of products, i.e., 30, Ultra, and Ultra Plus), but VOLUMA XC includes an additional molecular weight raw material HA and 0.3% lidocaine. It also differs in its HA concentration (20 mg/mL vs. 24 mg/mL) and degree of crosslinking. The result is a gel with increased gel strength (resistance to flow, “stiffness”). All JUVÉDERM[®] Injectable Gels are significant risk devices as defined in 21 CFR Part 812.3(m)(1).

VOLUMA XC is provided sterile in glass or COC (cyclic olefin copolymer) syringes filled to 1.0 mL. The Sponsor is supplying 25G x 1” UTW (ultra thin wall) and 27G x ½” UTW needles for the implantation procedure separately (see the current Instructions for Use document).

VOLUMA XC is an investigational device and will bear a label similar to the following:

CAUTION: Investigational Device
Limited by U.S. (federal) law to investigational use

7.1.2 Instructions for Use and Administration

The Treating Investigator will inject VOLUMA XC deeply (subcutaneous and/or supraperiosteal plane) for cheek augmentation to correct age-related volume deficit in the mid-face, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region. Deep, volumizing injections should only be performed by experienced injectors and only after they have mastered the injection techniques for wrinkle correction with less robust products, such as JUVÉDERM® Ultra or Ultra Plus injectable gel. All Treating Investigators will have at least 3 years of experience using HA and/or other injectable fillers for cheek augmentation to correct age-related volume deficit of the mid-face. The Treating Investigators will undergo product-specific training by a physician who has personal experience injecting VOLUMA. Details for the implantation of VOLUMA XC will be provided in a separate “Instructions for Use” document (IFU), which will include written guidelines for pre-treatment evaluation and treatment planning as well as for temporary marking of the mid-facial treatment area(s). In general, the plane of injection will be subcutaneous except in the zygomaticomalar region and the anteromedial cheek, where supraperiosteal placement of VOLUMA XC may be indicated. The Treating Investigators will review and discuss the IFU treatment guidelines in detail before beginning study enrollment. Their conclusions will be included in a revised IFU as indicated. The first 2 Subjects at each site will be treated as run-in Subjects, allowing the Treating Investigator 2 practice cases to gain experience with injection characteristics of VOLUMA XC.

7.1.3 Treatment Regimen/Volume Allowances

Up to 2 treatment sessions are allowed (Day -30 and/or Day 0). The Treating Investigator will determine the appropriate treatment area, plane of injection, injection technique, and volume (dosage). If > 2 syringes (2 mL) are injected per treatment site and treatment session, the material should be distributed in small aliquots over a large area to reduce the risk of persistent lumpiness. The maximum total volume allowed for each Subject is 12 syringes (12 mL) of VOLUMA XC for initial and touch-up treatments combined. The study treatment sites are the Right and Left cheeks. Treatment details, e.g., treatment area, plane of injection, injection technique, and volume injected will be recorded for each treatment site by mid-

facial sub-unit, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region. For (optional) later biopsy each subject will also receive a subdermal depot injection of ~0.05 mL of VOLUMA XC in the medial aspect of the inner upper arm or behind the ear during the initial treatment. Treatment of the tear troughs, nasojugal folds, nasal sidewall, nasolabial folds, and upper lip are not permitted; however, contour improvement may be indirectly achieved in these areas by increased volume in the treated areas. At the optional repeat treatment the maximum volume allowance per Subject is also 12 syringes (12 mL).

7.2 Other Study Supplies

Urine pregnancy test kits, digital imaging equipment, biopsy needles/punches, and other supplies specific to this study will be provided by the Sponsor. The Investigator is responsible for routine supplies related to pre-and post treatment care, e.g., antiseptics, drapes, gloves, gauze, anesthesia, post-biopsy sutures (if needed), etc. The Treating Investigator may use only ice or FDA-approved topical and injectable anesthetic products, e.g., EMLA[®] Cream (AstraZeneca), ELAMax[®] Cream (Ferndale Laboratories), Pliaglis[™] Cream (Galderma), Xylocaine[®] Injection or Xylocaine[®] Injections with Epinephrine (AstraZeneca et al).

8. Study Methods and Procedures

8.1 Subject Entry Procedures

8.1.1 Pre-Entry Procedures

All incoming patients who are interested in cheek augmentation to correct age-related volume deficit in the mid-face (“prospective subjects”) will be considered for entry into this study. Use of any pre-screening script or study advertising will be pre-approved by the reviewing IRB.

8.1.2 Informed Consent and Subject Privacy

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential Subject. Prior to any study-related procedures or change in treatment, Subjects wishing to participate must give their written informed consent. The Subject must also give Authorization for Use and Release of Health and Research Study

Information (HIPAA) and other written documentation required by local regulations and/or the reviewing IRB prior to any study-related procedures or change in treatment. Attachment 13.2 contains generic forms for informed consent (IC) and HIPAA authorization to be prepared in the language(s) of the potential study population. The Sponsor will provide updated IC and HIPAA forms for IRB review and approval as appropriate.

The person who conducts the informed consent discussion will document in the Subject's medical records the acquisition of informed consent and the Subject's agreement or refusal to notify his/her primary care physician about the study. The Subject should personally sign and date the IC and HIPAA forms. The Investigator will retain the original copy of the signed forms, and the Subject will receive a copy of each. Upon signing the informed consent and authorization forms, 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 should be assigned in ascending order, and numbers should not be omitted or reused. The Subject Number is coupled with the site identification number for unique identification of each Subject.

8.1.3 Run-In and Washout Intervals

8.1.3.1 Run-In Intervals

To be eligible to participate, females of child-bearing potential must have used contraception for at least 30 days prior to study treatment and agree to continue using contraception throughout the study.

8.1.3.2 Washout Intervals

A 10-day washout before treatment is required if the Subject has taken oral corticosteroids, aspirin, NSAIDs or other pharmaceutical, vitamin, or herbal preparations with clinically significant anti-coagulation effects.

Subjects are not allowed to receive any other investigational product or begin using over-the-counter or prescription anti-wrinkle treatments in the mid-face (i.e., from the lower orbital rim superiorly to the oral commissures inferiorly and from the nasolabial fold medially to the zygomatic bone and sub-zygomatic cheek area laterally) within 90 days of study treatment.

However, use of sunscreens and continued therapy with some cosmeceuticals (e.g., alpha hydroxyl acids, glycolic acids, retinol, or retinoic acids) is allowed if the regimen was established ≥ 90 days prior to enrollment.

A 6-month wash-out prior to treatment is required if the Subject has undergone neuromodulator injections, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures). A 12-month washout is required if the Subject has undergone hyaluronic acid-based filler injections, and 24 months if the Subject has undergone collagen-based filler injections.

8.1.4 Procedures for Final Study Entry

A Subject is considered “Enrolled” when s/he has signed the IRB-approved consent form(s) and HIPAA authorization in the presence of the Investigator or designee, who will then collect and record the Subject’s demographic information and medical and cosmetic histories and will perform 3D digital imaging (see Attachment 13.3). Females of child-bearing potential must have pregnancy test results evaluated as negative no more than 10 days prior to study treatment.

The Treating Investigator will assess the Subject’s mid-face volume deficit using the 6-point photometric Mid-Face Volume Deficit Scale (MFVDS), nasolabial fold severity using the 5-point NLF Photo Severity Scale (NLFS), and Other Aesthetic Features of the Mid-Face (OAFM).

In consultation with the Treating Investigator, Subjects will complete their assessments of mid-facial volume, goal setting, and satisfaction with mid-facial regions (GOAL1).

Independently, they will complete their NLF Severity (NLFS) assessments, Self-Perception of Age (SPA) assessments, the Look and Feel of the Mid-Face questionnaires (LAFM), and their Facial Appearance Evaluations (FAE).

The Evaluating Investigators will independently assess the Subject’s mid-face volume deficit using the 6-point photometric Mid-Face Volume Deficit Scale (MFVDS), nasolabial fold

severity using the 5-point NLF Photo Severity Scale (NLFS), as well as the Other Aesthetic Features of the Mid-Face (OAFM).

The Treating Investigator is responsible to assure that each Subject meets the run-in and washout requirements as well as other eligibility criteria (see Sections 5.3, 5.4, and 8.1.3) and will notify the Sponsor as each new Subject becomes eligible for randomization.

8.1.5 Method for Assignment to Treatment or Control

The first 2 Subjects at each site (up to 30 in total) will be treated as run-in Subjects, allowing each Treating Investigator 2 practice cases to gain experience with injection characteristics of VOLUMA XC. As each subsequent Subject qualifies for entry, the Investigator will contact Allergan Clinical Research department with the subject's ID number and initials, date of screening visit, demographic information, and treatment plan. Allergan will provide the next sequential Randomization Number and assignment (treatment or control) or will add the subject to a randomization waiting list if the Subject's subgroup enrollment targets have been met (*Gender*: ≥ 40 Males, ≥ 40 Females; *Race*: ≥ 40 Caucasians, ≥ 40 African Americans, ≥ 40 Hispanics, and ≥ 40 Asians/Pacific Islanders; *Fitzpatrick Skin Phototype*: $\geq 20\%$ (48) I/II, $\geq 20\%$ (48) III/IV, and $\geq 20\%$ (48) V/VI; *Geography*: ≥ 40 Northeast, ≥ 40 Southeast, ≥ 40 Midwest, ≥ 40 Northwest, and ≥ 40 Southwest U.S., and ≥ 40 Canadian; *Treatment Site*: ≥ 40 zygomaticomalar region, ≥ 40 anteromedial cheek, and ≥ 40 submalar region; *Treatment Plane*: ≥ 40 suprapariosteal and ≥ 40 subdermal; and *Treatment Technique*: ≥ 40 Tunneling, ≥ 40 Fanning, ≥ 40 Antegrade, ≥ 40 Retrograde, and ≥ 40 Other).

Each Subject will be randomized either to the treatment group, who undergo treatment with VOLUMA XC at the outset of the study, or to the "no-treatment" control group, whose VOLUMA XC treatment will be delayed at least 6 months. Among randomized Subjects the ratio of treated to untreated subjects is approximately 5.3:1 (up to 240 Subjects in the treatment group and at least 45 Subjects in the "no-treatment" control group).

The statistician will prepare a randomization schedule. Allergan will control the central randomization procedure, and, when the treatment group enrollment targets have been met, will contact the Treating Investigators with randomization assignments for subjects on the randomization waiting list on a first-eligible/first-randomized basis up to 240 treated

subjects. It is possible that subjects on the randomization waiting list will be terminated from the study by the Sponsor without being randomized.

Only the Treating Investigator or Study Coordinator at each site may have access to the Subject's randomization assignment. They will secure the study records from discovery by the Evaluating Investigators. The Treating and Evaluating Investigators should not discuss any details or guesses about the randomization assignment (treatment or control group), study treatment (or deferral of study treatment), or their assessments, and in particular, Evaluating Investigators should also not discuss any of their guesses or assessments with each other. The Treating Investigator and Study Coordinator will explain to each Subject that, to assure scientific rigor and unbiased results from this clinical trial, it is essential that s/he not divulge her/his randomization assignment (treatment or control group) to either of the Evaluating Investigators. To maintain the study blind, the Evaluating Investigators must not be present during the safety evaluations.

8.2 Concurrent Therapies

The use of and indication for any (prescription or over-the-counter) concurrent medication, therapy, or treatment will be recorded on the Subject's Cosmetic History or Concomitant Medications, Therapies, and Treatments CRFs. This includes concurrent prescription or over-the-counter cosmetic or therapeutic procedures or treatments to the face or neck performed by a medical professional from 90 days prior to enrollment and for the duration of the study.

Concurrent enrollment in another clinical investigation for a medicinal product or device is prohibited.

8.2.1 Permissible Medications/Treatments

All medications and treatments are permitted with the exception of the restricted medications and treatments described in Section 8.2.2.

8.2.2 Prohibited Medications/Treatments

Subjects must not undergo any type of facial plastic or reconstructive surgery or cosmetic procedure [e.g., plastic surgery; tissue grafting; tissue augmentation with silicone, fat, or

other permanent, semi-permanent, or temporary dermal fillers; neuromodulator injections; mesotherapy; or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures)] at any time during this study.

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. If the permissibility of a specific medication/treatment is in question, please contact an Allergan representative before the prohibited medication/treatment is administered.

8.2.3 Escape Medications

Although several authors have reported that hyaluronidase (Vitrase™ or Amphadase®) is effective to reverse the effects of misplaced or excess HA-based dermal fillers,^{7,27} no product has been approved for this indication. Therefore, administration of hyaluronidase is considered to be “off-label” and should not be performed during this study.

8.2.4 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.

8.3 Examination Procedures

8.3.1 Overall Introduction

Prior to enrollment of any study Subjects, the Treating Investigators will undergo product-specific injection training for VOLUMA XC, review of facial anatomy, as well as training on the use of the MFVDS, GAIS, and NLFS scales and other specifics of the protocol. The research staff will undergo training to perform digital imaging (Attachment 13.3).

Throughout the study, Subjects will be instructed to report any unusual signs or symptoms to the Treating Investigator, who will solicit and record information about common treatment site responses (CTRs), other adverse events (AEs), and concomitant medications, therapies and treatments. Treated Subjects will maintain a diary for 30 days and telephone/e-mail contact with the Treating Investigator at 3 days after each treatment. At each post-treatment

visit, phone call, or e-mail contact, the Treating Investigator (or designee) will begin by asking the Subject a general, non-directed question such as ‘How have you been feeling since the last visit?’ Directed questioning and examination will then be done as appropriate. All reported AEs and CTRs will be documented on the appropriate case report form.

Whenever possible, the same Treating and Evaluating Investigators will continue to perform their respective evaluations throughout the study. If that is not possible, the substitute Investigator will undergo scale training and intra- and inter-rater reliability testing and must meet the acceptable level of agreement as described in Section 6.1.1 prior to performing any study evaluations. Additionally, evaluations by the departing Investigator and substitute Investigator should overlap for at least one visit at which they will examine the Subject together and discuss their findings.

8.3.2 Run-In Subjects

To ensure that Treating Investigators have adequate experience with VOLUMA XC, each will treat up to 2 run-in subjects prior to randomization and treatment of any study subjects. The run-in Subjects must sign the same study documentation, meet the same inclusion and exclusion criteria, and will follow the same visit schedule as Treated Subjects (see Sections 8.3.4-8.3.9). Data collected from these run-in subjects will be collected and analyzed separately from data collected for subjects in the “No Treatment” Control and Treatment Groups.

8.3.3 “No Treatment” Control Group

After completing all study entry procedures and randomization (see Section 8.3.1), the “no treatment” control Subjects will not undergo treatment but will be asked to return in 1, 3, and 6 months (Visits 2C, 3C, and 4C) for the same effectiveness assessments by the Evaluating Investigators as described for the treatment group (see Section 8.3.5). Because “no treatment” control Subjects do not attend a Day 0 treatment visit, Day 0 will be defined as 30 days prior to their Month 1 visit date. After all Subjects at the investigational site have completed the 6-month follow-up visit, the “no treatment” control Subjects will cross-over to the Treatment Group and will undergo VOLUMA XC treatment and follow-up as detailed below (see Sections 8.3.4-8.3.9). Prior to initiation of VOLUMA XC treatment, the Treating

Investigator will reconfirm that the Subject meets all study eligibility criteria (see Sections 5.3 and 5.4).

8.3.4 Treatment Group: Study Treatment Period

8.3.4.1 Visit TA (Day -30 or Day 0)

After completing all study entry procedures and randomization (see Section 8.1), each Subject that has been randomized to treatment at the study outset is prepared for treatment. The Treating Investigator will use the recommended anesthesia, aseptic skin preparation, and injection techniques outlined in the current Instructions for Use (IFU). The study treatment sites are the Right and Left cheeks, i.e., the zygomaticomalar region, anteromedial cheek, and submalar region. Treatment of the tear troughs, nasojugal folds, nasal sidewall, nasolabial folds, and upper lip are not permitted; however, contour improvement may be indirectly achieved in these areas by increased volume in the treated areas.

In general, the plane of injection will be subcutaneous except in the zygomaticomalar region and anteromedial cheek, where supraperiosteal placement of VOLUMA XC may be indicated. Using a surgical pen or other temporary marker, the Treating Investigator will “sketch” or mark where s/he plans to inject directly onto both sides of the Subject’s mid-face. The Treating Investigator will document the Subject’s “treatment plan” using the 3D imaging system prior to treatment.

Treatment details regarding anesthesia usage, area(s) treated, injection procedure, plane of injection, volume injected, device lot number, and ease of injection will be recorded on the CRF. The maximum total volume of VOLUMA XC allowed per Subject is 12 syringes (12 mL) for initial and touch-up treatments combined.

For possible later biopsy each subject will also receive a subdermal depot injection of ~0.05 mL of VOLUMA XC in the medial aspect of the inner upper arm or behind the ear. To locate the depot injection site later, the depot site will be photographed to include a ruler and nearby landmarks, e.g., nevus, freckle, scar. The research staff will contact the Sponsor for a biopsy randomization code and biopsy schedule for Subjects who consent to undergo (optional) later biopsy.

After treatment, the Treating Investigator will document the Subject's immediate post-treatment appearance using the 3D imaging system after treatment. Subjects will receive instruction on how to record the absence or presence, location, and severity of common treatment site responses (CTRs) at the end of each day for 30 days, and the Treating Investigator (or designee) will follow-up with the Subject by telephone/e-mail at 3 days and an office visit at 30 days.

The Investigator will record the reasons for those Subjects who withdraw consent prior to treatment or who do not meet the inclusion/exclusion criteria.

8.3.4.2 *Visit TB (Day 0; possible Visit 2, Month 1)*

Subjects in the treatment group will return to the study center approximately 30 days after treatment. The Treating Investigator (or designee) will begin by asking the Subject a general, non-directed question such as 'How have you been feeling since the last visit?' Directed questioning and examination will then be done as appropriate, e.g., symptoms experienced, actions taken. The research staff will obtain digital images of the Subject.

If the Treating Investigator and the Subject determine that the volume augmentation of the Subject's mid-face has not been optimized, if the Subject's allotment of VOLUMA XC has not been exhausted, and if the Treating Investigator believes that additional VOLUMA XC will improve the volume augmentation, the Treating Investigator may perform a touch-up treatment. The Treating Investigator will use the recommended anesthesia and injection techniques outlined in the current IFU. Women of childbearing potential must have pregnancy test results evaluated as negative within 10 days prior to touch-up treatment. Treatment details regarding anesthesia usage, areas treated, injection procedure, plane of injection, volume injected, device lot numbers, and ease of injection will be recorded on the CRF. The maximum total volume of VOLUMA XC allowed per Subject is 12 syringes (12 mL) for initial and touch-up treatments combined.

After treatment, Subjects will receive instruction on how to record the absence or presence, location, and severity of common treatment site responses (CTRs) at the end of each day for

30 days, and the Treating Investigator (or designee) will follow-up with the Subject by telephone/e-mail at 3 days.

If a touch-up treatment is not performed, the Subject has entered the primary safety and effectiveness follow-up period, and this visit is considered the 1-month follow-up visit (See Section 8.3.5, Visit 2T).

8.3.5 Treatment Group: Primary Safety and Effectiveness Follow-up Period

Subjects in the treatment group will attend study follow-up visits at 1, 3, and 6 months (Visits 2T-4T) after the last treatment to the mid-face (Visit TA/TB). The Treating Investigator (or designee) will begin by asking the Subject a general, non-directed question such as ‘How have you been feeling since the last visit?’ Directed questioning and examination will then be done as appropriate, e.g., symptoms experienced, actions taken. The Treating Investigator (or designee) will then inquire about any changes in medications, therapies or treatments. To maintain the study blind, the Evaluating Investigators must not be present during the safety evaluations.

At each follow-up visit the research staff will obtain digital images of the Subject. The Subject will complete the GOAL2, GAIS, NLFS. At the Month 1 and Month 6 visits the Subject will also complete the SPA, FAE, and LAFM. The Evaluating Investigators will independently complete the MFVDS, GAIS, NLFS, and OAFM at all follow-up visits. With the 6-month MFVDS assessment the Evaluating Investigators will independently guess the Subject’s randomization assignment, i.e., treated or not treated, and will give the reasons for their guesses.

Histological evaluation will be attempted in approximately 18 Subjects who volunteer to undergo biopsy, with a target of 2 biopsy specimens per timepoint. The biopsy visit for each volunteer will be randomly assigned to one of the 9 study follow-up visits (Month 1 through Month 24). Additionally, the depot injection site should undergo histological evaluation in any Subject with severe inflammatory symptoms in the treated or depot area.

8.3.6 Treatment Group: Extended Follow-up Period

All Subjects will attend quarterly study follow-up visits (Months 9, 12, 15, 18, 21, and 24; Visits 5-10) after the last study treatment to the mid-face or until the average of the Evaluating Investigators' assessments of the Subject's zygomaticomalar region, anteromedial cheek, and submalar region, and overall MFVDS return to or exceed the pre-treatment level.

The Treating Investigator (or designee) will begin by asking the Subject a general, non-directed question such as 'How have you been feeling since the last visit?' Directed questioning and examination will then be done as appropriate, e.g., symptoms experienced, actions taken. The Treating Investigator (or designee) will then inquire about any changes in medications, therapies or treatments. To maintain the study blind, the Evaluating Investigators must not be present during the safety evaluations.

The research staff will obtain digital images of the Subject. The Subject will complete the GOAL2, GAIS, and NLFS. At Months 12, 18, and 24, the Subject will complete the SPA, FAE, and LAFM. If the extended follow-up period ends at Months 15 or 21, Subjects will complete these evaluations at that time. The Evaluating Investigators will independently complete the MFVDS, GAIS, NLFS, and OAFM at all follow-up visits.

8.3.7 Treatment Group: End of Extended Follow-up

Subjects will complete the extended follow-up period at Month 24 (Visit 10) or at any visit after Month 12 if the average of the 2 blinded, independent Evaluating Investigators' assessments of the Subject's zygomaticomalar region, anteromedial cheek, and submalar region, and overall MFVDS return to or exceed the average of their respective MFVDS scores from the pre-treatment visit. At the final visit in the extended follow-up period the Evaluating Investigators and the Subject should complete all evaluations (MFVDS, OAFM, GAIS, NLFS, GOAL2, SPA, FAE, and LAFM), respectively, including urine pregnancy testing if the Subject is a female of child-bearing potential. If Subjects decline a repeat treatment (described in Section 8.3.8), they will be exited from the study, and the Treating Investigator will ask the reason for declining.

8.3.8 Treatment Group: Repeat Treatment (*Visits R1 through R6 or R6+*)

Subjects who complete the extended follow-up period as described above will be offered an optional, complimentary repeat treatment to be performed at the Treating Investigator and Subject's convenience but no later than 3 months after the end of the extended follow-up period. Women of childbearing potential must have pregnancy test results evaluated as negative within 10 days prior to repeat treatment. If the repeat treatment takes place after the final visit in the extended follow-up period, the Evaluating Investigators should assess MFVDS and GAIS, and the Subject should assess GAIS, SPA, and FAE at the repeat treatment visit (prior to treatment).

The Treating Investigator will use the recommended anesthesia, aseptic skin preparation, and injection techniques outlined in the current IFU. Details regarding anesthesia usage, area(s) treated, treatment plane, injection procedure, and volume injected, lot numbers, and ease of injection will be recorded on the CRF. For the repeat treatment a maximum of 12 syringes (12 mL) per Subject is allowed. Subjects opting for repeat treatment will receive instruction on how to record the absence or presence, location, and severity of common treatment site responses (CTRs) at the end of each day for 30 days, and the Treating Investigator will follow-up with the Subject by telephone/e-mail at 3 days after repeat treatment.

The Subject will attend an office visit 1 month after the repeat treatment. The Subject will either attend office visits or have telephone contact with the Treating Investigator (or designee) at 3, 6, 9, and 12 months after the repeat treatment. The Treating Investigator (or designee) will begin by asking the Subject a general, non-directed question such as 'How have you been feeling since the last visit?' Directed questioning and examination will then be done as appropriate, e.g., symptoms experienced, actions taken. The Treating Investigator (or designee) will then inquire about any changes in medications, therapies or treatments. In addition, if the Subject attends an in-person office visit, the Evaluating Investigators will assess MFVDS and GAIS. The subject will independently complete GAIS, SPA, and FAE and assess whether the treatment goal(s) were met. If Subjects have exited the study after a repeat treatment and prior to protocol Amendment 12, they may re-enter the study. The subjects who have not traversed the Month 12 follow-up visit window should be re-

consented and their scheduled follow-up visits should be based on their repeat treatment date. Subjects who have traversed the Month 12 follow-up visit window may be re-consented and they will attend a single, Month 12+ follow-up office visit with the Treating Investigator (or designee), as described above.

8.3.9 Instructions for the Subjects

During each office visit Subjects will be required to remove all creams, oils, makeup and lipstick from the face to avoid interference with the live assessments and digital photographs. Subjects will be given detailed instructions for completing the diary and reminded to contact the Investigator or his/her research staff to report any unexpected symptoms or to ask any questions about the study. Creams/oils and makeup may be re-applied at the discretion of the Investigator.

Subjects should avoid strenuous exercise, consumption of alcoholic beverages and extended exposure to sun or heat for at least 24 hours after treatment to reduce the risk of post treatment redness, swelling, and/or itching. Subjects should also avoid taking oral corticosteroids, aspirin, NSAIDs or other pharmaceutical, vitamin, or herbal preparations with clinically significant anti-coagulation effects for at least 10 days before and 3 days after study treatment.

The Treating and Evaluating Investigators should not discuss any details or guesses about the randomization assignment (treatment or control group), study treatment (or deferral of study treatment), or their assessments, and in particular, Evaluating Investigators should also not discuss any of their guesses or assessments with each other. The Treating Investigator and Study Coordinator will explain to each Subject that, to assure scientific rigor and unbiased results from this clinical trial, it is essential that s/he not divulge her/his randomization assignment (treatment or control group) to either of the Evaluating Investigators. To maintain the study blind, the Evaluating Investigators must not be present during the safety evaluations.

Subjects who undergo biopsy of a depot site will receive instructions to keep the area clean and dry and, if the Treating Investigator sutures the biopsy site, to return for suture removal within 7 – 10 days.

8.4 Schedule of Visits and Procedures

8.4.1 Scheduled Visits

Refer to the Synopsis, Tables 1, 2, 3, and 4, and Section 8.3, above, regarding the procedures and assessments to be performed at each scheduled study visit.

8.4.2 Unscheduled Visits

Each time the Subject returns to the study site the Treating Investigator (or designee) will solicit and record information about common treatment site responses (CTRs), other adverse events (AEs), and concomitant medications, therapies and treatments. An interim or unscheduled visit may replace a scheduled visit if it occurs within the acceptable time window for a scheduled visit or if the scheduled visit was missed. All applicable procedures should be performed.

8.4.3 Early Discontinuation/Withdrawal

Subjects reserve the right to withdraw from the study at any time without jeopardy to future medical care. All follow-up assessments and procedures should be performed at the final study visit. They 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 CRF. If an AE or CTR is ongoing at the time of the withdrawal, the Treating Investigator will attempt to follow the Subject until the AE or CTR has resolved or stabilized or until follow-up is no longer possible.

If the Subject misses a scheduled study visit, the Treating Investigator or the Study Coordinator 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.

Subjects who withdraw before treatment may be replaced by another suitable Subject; the new Subject will be assigned to the next sequential Subject Number. A Subject Number or Randomization Number should not be reassigned to a different subject.

8.5 Compliance with Protocol

The Treating Investigator is considered the Principal Investigator and is responsible for compliance with the protocol at the investigational site. The Principal Investigator is also responsible for reporting all issues of protocol non-compliance to the respective IRB and to the Sponsor. A representative of the Sponsor will make frequent contact with the Principal (Treating) Investigator 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, e.g., Subject eligibility criteria, wash-out periods, randomization assignments, volume of product injected, procedures performed, and follow-up visit schedule.

8.6 Discontinued Subjects

The Treating Investigator will record on the CRF and will report to the Sponsor and the IRB the reasons that Subjects discontinue from the study, including Subjects who sign the Informed Consent Form but do not proceed to treatment.

8.7 Study Termination

If conditions arise during the study that indicate that the study or an investigational site should be terminated, the Sponsor, Investigator, 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 the Sponsor to suspend or discontinue testing, evaluation, or development of the study device
- Failure of the Investigator to comply with pertinent national or state regulations, IRB-imposed conditions, or protocol requirements
- Submission of knowingly false information from the Investigator to the Sponsor, Monitor, IRB, or any regulatory agency

8.8 Study Duration

Study participation for an individual Subject is expected to last between 2½ and 4 years. Participation for subjects completing a Month 12+ visit or telephone contact could be extended by up to approximately 1 year. Study duration at each investigational site may last up to 4 ½ years (3 months for recruitment, enrollment, and initial treatment; 1 month for touch-up treatments; 6 months for the primary safety and effectiveness follow-up period; 7 months for “no treatment” control group treatment, touch-up, and 6-month primary follow-up; 18 months for the extended follow-up period; 3 months for the repeat treatment period; 12 months for post repeat treatment follow-up; and 4 months for final database lock and study close-out).

9. Adverse Events

Throughout the course of the study (from the date of informed consent and for at least 30 days after study exit), all common treatment site responses (CTRs) and adverse events (AEs) will be monitored and reported on the Subject Diary and/or AE case report form. If an adverse event occurs, the first concern will be the safety of the study participants. All AEs and CTRs occurring after study device administration will be followed throughout the study. All AEs and CTRs related to study treatments or procedures will be followed until resolved or stabilized or until follow-up is no longer possible.

9.1 Definitions

9.1.1 Adverse Events (AEs)

An adverse event (AE) is defined as any undesirable physical, psychological or behavioral effect experienced by a Subject during his/her participation in a study, in conjunction with the use of the device, whether or not it is considered related to the procedure or the product. AEs may include, but are not limited to, subjective or objective symptoms spontaneously offered by the Subject, solicited via Subject interviews, uncovered by review of concomitant medications, therapies, and treatments, and/or observed by the Investigator. The Investigator will record the description (sign, symptom, or diagnosis), location, onset, resolution,

seriousness, severity, cause, and action taken for any event on the AE CRF. To maintain the study blind, the Evaluating Investigators must not be present during the safety evaluations.

Disease signs and symptoms that existed prior to the study injections 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.

9.1.2 Common Treatment Site Responses (CTRs)

Commonly-reported treatment site responses (CTRs) following treatment with dermal fillers (including VOLUMA) include redness, pain, firmness, swelling, lumps/bumps, bruising, itching, and discoloration. For 30 days after each treatment Subjects will maintain a diary record of the absence or presence, severity, and location of any CTRs. Via telephone/e-mail at 3 days post treatment and at every study visit, the Treating Investigator will solicit and record the location, onset, resolution, severity, cause and action taken for these and any other Subject responses to treatment. NOTE: CTRs that persist longer than 30 days (i.e., ongoing at the end of the diary period) will be recorded and followed to resolution on the AE CRF. The depot injection site should undergo histological evaluation in any subject with severe inflammatory symptoms at the treatment or depot site.

9.1.3 Serious Adverse Events and Unanticipated Adverse Device Effects

A *Serious Adverse Event (SAE)* is any AE that results in any of the following:

- Death
- Life-threatening injury or illness – any AE that places the Subject, in the view of the reporter, at immediate risk of death from the AE as it occurred (It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity – any AE that results in a substantial disruption of the Subject’s ability to conduct normal life functions
- Important medical events that may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed above

An *Unanticipated Adverse Device Effect (UADE)* is any device-related SAE that meets one or more of the following criteria:

- Is not identified in nature, severity or frequency in current literature on the product

- Is life threatening, even if temporary in nature
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Also considered an UADE is any device malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. The Investigator will promptly notify Allergan’s Clinical Research department of any device malfunction, and the Clinical Research representative will provide instruction for the return of any faulty syringe for evaluation.

As required by 21 CFR §812.46(b)(2), if the Sponsor determines that an UADE presents an unreasonable risk to study Subjects, the Sponsor will terminate the investigation within 5 working days of the unreasonable risk determination.

9.1.4 Severity

Definitions for classification of severity appear below. The Investigator will review these definitions with the Subject for use when completing the Subject Diary. For events reported on the AE CRF, e.g., CTRs that persist beyond the diary period and other AEs, the Investigator will determine the severity classification based on these definitions, his/her clinical experience in the use of dermal fillers, and/or the Subject’s description of the event. [Note: A “severe” AE is not the same as an “SAE” (serious adverse event), which is defined above.]

Mild: Symptoms are barely noticeable or do not make the Subject uncomfortable. The AE/CTR does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

Moderate: Symptoms are of sufficient severity to make the Subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.

Severe: Symptoms are of sufficient severity to cause the Subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

Not applicable: In some cases, an AE/CTR may be an ‘all or nothing’ finding that cannot be graded.

9.1.5 Relationship to Study Device

The Investigator will determine whether the Subject’s symptom or problem is most likely unrelated to the study treatment or is possibly/probably related to the anesthesia employed, the study device, or the injection procedure.

9.2 Procedures for Reporting Adverse Events

All adverse events (AEs), including common treatment site responses (CTRs), should be recorded on the appropriate Case Report Form (CRF) page.

9.3 Procedures for Reporting Serious Adverse Events (SAEs)

All Serious Adverse Events (SAEs) that occur after the time of informed consent through 30 days after study exit must be reported to Allergan. All subjects with an SAE must be followed and the outcomes reported. The Investigator should supply the Sponsor and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy reports and terminal medical reports). The Sponsor shall evaluate all SAEs and determine and document in writing whether they meet the definition of an Unanticipated Adverse Device Effect (UADE). These shall be reported to all participating investigators, the regulatory authorities, and IRBs as required by national regulations. In the event of an SAE, the Investigator must:

1. Notify Allergan within 24 hours of the Investigator’s awareness of the event by contacting the Medical Monitor at the emergency number listed on the front page of this protocol.
2. Obtain and maintain 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, including copies of supporting reports (e.g., progress notes, laboratory reports) and a statement from the Investigator as to whether or not the event was related to the use of the investigational device
4. Promptly inform the governing IRB of the event, if it is device-related. For other SAEs, notify the governing IRB as required by the IRB, local regulations, and the governing health authorities.

10. Statistical Procedures

Computation for all results will be performed using the SAS[®] computer software package (Version 9.1 or higher). All data collected will be listed. Data will be summarized descriptively. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized by the number of subjects, mean, mean difference from baseline (when appropriate), median, standard deviation, 95% confidence interval, and minimum and maximum values for each evaluated timepoint.

The Statistical Analysis Plan will be finalized and appropriate clinical and statistical personnel will document their decisions concerning the inclusion or exclusion of data for each subject prior to the interim and final database locks for analyses. The primary effectiveness analysis will be performed after all subjects have completed Month 6 (Visit 4). A survival analysis will be performed after all subjects have completed the extended follow-up period (up to 24 months after treatment).

10.1 Analysis Populations

All analyses will be performed on the modified Intent-to-Treat (mITT) population, i.e., all Subjects in the "treatment" and "control" groups. Subjects randomized to study treatment and having at least one study device treatment will be included in the "treatment group," and those randomized to no treatment will be included in the "control group" in the safety and effectiveness analyses. Primary effectiveness analyses are also planned for the Per Protocol (PP) population, which includes all mITT Subjects who are not considered to be major protocol violators. Data will be pooled across investigational sites. All analyses will also be performed separately for the run-in Subjects.

10.2 Collection and Derivation of Primary Effectiveness Assessments

The primary effectiveness endpoint will be based on the average of the 2 blinded, independent Evaluating Investigators' assessments of the Subject's overall mid-face volume deficit using the validated 6-point photometric Mid-Face Volume Deficit Scale (MFVDS, see Attachment 13.1.1). Improvement (reduction) in MFVDS grade from baseline (pre-treatment) to 6 months will be analyzed.

10.3 Hypothesis and Methods of Analysis

The study device will be determined to be clinically effective if at least 70% of subjects are responders and the responder rate for Subjects treated with VOLUMA XC is statistically superior to the responder rate for the “no-treatment” control group at 6 months after treatment with VOLUMA XC.

Primary effectiveness analyses will be repeated on three datasets, namely, the mITT dataset without data imputation, the mITT dataset with data imputation, and the PP dataset without data imputation. Data imputation techniques will include “all missing as failure,” “all missing as success,” “half of the missing as success,” “worst case,” and “best case.”

Sensitivity analyses will be performed to compare the mITT results with and without data imputation analyses to determine if the missing data and the data imputation technique have an impact on the conclusions. A “tipping point” analysis will be performed to consider various proportions of success and failure to determine the point at which imputation of missing data changes the overall study conclusion. Further, a sensitivity analysis will also be performed to compare the results between the mITT (without data imputation) and PP analyses to determine if the protocol violations have an impact on the conclusions.

10.3.1 Primary Effectiveness Analyses

The primary effectiveness measure will be based on the average of the 2 blinded, independent Evaluating Investigators’ assessments of the Subject’s overall mid-face volume deficit using the validated 6-point photometric Mid-Face Volume Deficit Scale (MFVDS). To be considered a “responder” to VOLUMA XC the average of the blinded Evaluating Investigators’ assessments of the Subject’s overall mid-face volume deficit will be improved (reduced) by ≥ 1 grade compared with the average of the pre-treatment MFVDS assessment. A 2-sided Exact test at the 0.025 significance level will be used to determine if at least 70% of the Subjects treated with VOLUMA XC are responders (i.e., achieve a reduction of ≥ 1 grade in their MFVDS score compared to pre-treatment) at 6 months. In addition, clinical effectiveness will be demonstrated if the responder rate for Subjects treated with VOLUMA XC at 6 months is statistically superior to the responder rate for the “no-treatment” control group using a 2-sided, 2-group, Fisher’s exact test at the 0.025 significance level.

10.3.2 Secondary Effectiveness Analyses

Secondary effectiveness analyses will be conducted only if the primary endpoint is significant. Statistical adjustment for multiplicity for the secondary effectiveness analyses will use the Benjamini-Hochberg method,⁶ which controls the False Discovery Rate (FDR) at the significance level of α or smaller:

For k hypotheses to be tested:

1. Order the p-values $p_{(1)} < p_{(2)} < \dots < p_{(k)}$, and let $H_{(1)}, H_{(2)}, \dots, H_{(k)}$ be the corresponding null hypotheses
2. Compare $p_{(k)}$ to α
 - a. If $p_{(k)} < \alpha$, reject all of $H_{(1)}, \dots, H_{(k)}$ and stop
 - b. If $p_{(k)} \geq \alpha$, do not reject $H_{(k)}$ and continue
3. Compare $p_{(k-1)}$ to $(k-1) \alpha / k$
 - a. If $p_{(k-1)} < (k-1) \alpha / k$, reject all of $H_{(1)}, \dots, H_{(k-1)}$ and stop
 - b. If $p_{(k-1)} \geq (k-1) \alpha / k$, do not reject $H_{(k-1)}$ and continue
4. Continue in this fashion until a stop or until no hypotheses are rejected

The estimated responder rate (with 95% confidence intervals) for the treatment group will be presented for the average of the blinded, independent Evaluating Investigators' GAIS assessments, where a "responder" is a subject that shows improvement ≥ 1.0 point ("Improved" or "Much Improved") at the 6-month visit following the last treatment (initial or touch-up) treatment as well as for the average of the 2 blinded, independent Evaluating Investigators' assessments of the Subject's volume deficit **in each area treated**, where a "responder" is a subject that shows ≥ 1 grade improvement at 6 months in the respective treated area compared with the respective pre-treatment assessments.

For follow-up data after 6 months, a survival analysis will be performed using Kaplan-Meier estimates to determine the duration of effect of VOLUMA XC in each treatment area based on the timepoint when the averages of the 2 blinded Evaluating Investigators' assessments of the Subject's MFVDS (overall, zygomaticomalar region, anteromedial cheek, and/or submalar region) return to or exceed the averages of the respective pre-treatment scores.

10.3.3 Additional Effectiveness Measures

Additional effectiveness analyses will include summary results for each scheduled timepoint for the following measures.

- Evaluating Investigators' assessments and the Subject's self-assessments of nasolabial fold severity using the NLFS
- Evaluating Investigators' assessments of other aesthetic features using the OAFM
- Evaluating Investigators' guesses and reasons for their guesses of Subject's randomization assignment (MFDVS 6 Mo)
- Subject's self-assessment of improvement using the GAIS
- Subject's self assessments of mid-face volume and treatment goal(s) using the MFVDS (GOAL1/GOAL2)
- Subject's level of satisfaction with 5 mid-facial areas (GOAL1/GOAL2)
- Subject's self-perception of age (SPA)
- Subject's facial appearance evaluation (FAE)
- Subject's assessment of the look and feel of the mid-face (LAFM)
- Treating Investigator's pre-treatment assessment of MFVDS, NLFS, and OAFM for eligibility

For MFVDS, change from pre-treatment will also be summarized. Subject satisfaction with mid-facial regions (GOAL1/GOAL2) will be summarized by gender, ethnicity and geographical location (investigational site).

Relative to the pre-treatment scores, an average improvement of 3 points for the LAFM, a 10% reduction in self-perception of age (SPA), or a statistically significant improvement (increase) in average post-treatment FAE score^{*} will be considered clinically significant.

To determine whether the Evaluating Investigators' guesses of Subject's randomization assignment are random, a Chi-square test at a 0.05 significance level will be used to test if

^{*} The FAE score is based on the total score for the first 6 items, divided by 24 (the maximum possible total score), and multiplied by 100; the overall FAE satisfaction score ranges from 0 to 100 where 0 represents the least and 100 represents the most satisfaction.¹

the observed proportions of correct identifications in the treated and control group match the expected proportions under the hypothesis of guessing at random, i.e., a proportion of 84% (240/285) for the treated group and 16% (45/285) for the control group.

Volume change estimates for the Right and Left cheeks by mid-facial sub-unit, i.e., zygomaticomalar region, anteromedial cheek, and submalar region, from 3D images will be summarized in terms of mean, standard deviation, range, and confidence intervals.

10.3.4 Safety Analyses

Common treatment site responses (CTRs) will be tabulated by severity, duration, and location for initial, touch-up, and repeat treatment. Safety data will be collected from Subject Diaries and the AE CRFs. Subject-reported CTRs will be tabulated by location, maximum severity, and duration. Adverse events (AEs) will be tabulated by location and duration as well as the Investigator's assessment of maximum severity, causality, action taken, and outcome. AEs occurring prior to and those occurring after repeat treatment will be summarized separately. Results of histological evaluations will be tabulated.

10.4 Subgroup Analyses

Subgroup analyses for the primary effectiveness variable, i.e., responder rate among treated subjects, will include stratification by pre-treatment score, gender, ethnicity, Fitzpatrick Skin Phototype, geographical location (investigational site) location, injection plane, injection technique, and volume injected. Within each subgroup, an estimate of the responder rate and the 95% confidence intervals will be provided, where responder rate is the percent of subjects that show ≥ 1 grade improvement in the average of 2 blinded, independent Evaluating Investigators' assessments of the Subject's overall Mid-Face Volume Deficit (MFVDS) at 6 months following the last treatment compared with the average of the respective pre-treatment MFVDS assessments. Covariates for subgroup analyses will include pre-treatment score, gender, ethnicity, Fitzpatrick Skin Phototype, geographical location (investigational site), injection plane, injection technique, and volume injected. To determine the impact of covariates on the responder rate, logistic regression with responder rate as the dependent variable and the covariates as independent variables will be employed as shown below:

$$\text{Logit (responder rate)} = \alpha + \beta_1 * \text{Pre-treatment Score} + \beta_2 * \text{Gender} + \beta_3 * \text{Ethnicity} + \beta_4 * \text{Fitzpatrick Skin Phototype} + \beta_5 * \text{Geographical Location} + \beta_6 * \text{Subcutaneous plane of injection} + \beta_7 * \text{Supraperiosteal plane of injection} + \beta_8 * \text{injection technique as Tunneling} + \beta_9 * \text{injection technique as Fanning} + \beta_{10} * \text{injection technique as Antegrade}$$

+ β_{11} *injection technique as Retrograde + β_{12} *Other injection technique + β_{13} *Volume Injected

Significance of a covariate at the 10% level of significance ($\beta \neq 0$) would imply that the covariate is predictive of the response.

Subgroup analyses will be performed for the safety variable, i.e., incidence rate of a common treatment site response (CTR) by injection site, may include stratification volume of product injected, injection plane, and injection technique. Incidence rates and their 95% confidence intervals will be provided within each subgroup for each treatment area. To determine the impact of covariates on the incidence rate of a CTR, logistic regression as shown below with incidence rate of a CTR as the dependent variable and the covariates as independent variables will be employed separately for each treatment area:

Logit (incidence rate of a CTR) = α + β_1 *Volume Injected + β_2 *Subcutaneous plane of injection + β_3 *Supraperiosteal plane of injection + β_4 *injection technique as Tunneling + β_5 * injection technique as Fanning + β_6 *injection technique as Antegrade + β_7 *injection technique as Retrograde + β_8 *Other injection technique

Volume injected (mL) will be a continuous covariate. Significance of a covariate at the 10% level of significance ($\beta \neq 0$) would imply that the covariate has an effect on the safety profile corresponding to that CTR and treatment area.

Additionally, all safety and effectiveness results will be summarized separately for the run-in Subjects.

10.5 Sample Size Calculation

Using a 4-point volume deficit scale (range 1-4) for his retrospective case record review, a single, unblinded European physician reported that 98% of 102 aesthetic patients demonstrated ≥ 1 grade improvement (score reduction) following treatment with VOLUMA.²⁶ In contrast, the current prospective, controlled pivotal study protocol employs a primary effectiveness analysis based on the average scores from 2 blinded, independent Evaluating Investigators pre- and post-treatment as well as statistical superiority over a "no treatment" control group. This study design significantly reduces or eliminates investigator bias by including untreated subjects in the evaluations. Thus, the estimated responder rate would be less than 98% and is arbitrarily set at 90%.

To achieve 85% power with a 2-sided Exact test at the 0.05 significance level a minimum

sample size of 36 is needed to demonstrate that $\geq 70\%$ of Subjects will be improved by ≥ 1 grade on the 6-point MFVDS at 6 months compared with the pre-treatment MFVDS assessment. A sample size of 36 control subjects and 216 treatment group subjects will provide $>99\%$ power for a 2-sided 2-group Fisher's exact test at the 0.025 significance level to demonstrate statistical superiority of the treatment group over the control group if the assumed responder rate in the control group is less than 40% at 6 months. Allowing for 20% attrition (drop-outs and protocol deviations) in the control group and 10% in the treatment group, the number of randomized Subjects is set at 45 "no treatment" control group Subjects and 240 treatment group Subjects. Each site may treat up to 2 run-in Subjects (up to 30 total). Thus, the overall enrollment is 315 Subjects, which includes 240 subjects in the treatment group, 45 subjects in the "no-treatment" control group, and 30 run-in subjects.

For adequate power in covariate modeling and subgroup analyses, enrollment targets are set at ≥ 40 Subjects within specific subgroups (*Gender*: ≥ 40 Males, ≥ 40 Females; *Race*: ≥ 40 Caucasians, ≥ 40 African Americans, ≥ 40 Hispanics, and ≥ 40 Asians/Pacific Islanders; *Fitzpatrick Skin Phototype*: $\geq 20\%$ (48) I/II, $\geq 20\%$ (48) III/IV, and $\geq 20\%$ (48) V/VI; *Geography*: ≥ 40 Northeast, ≥ 40 Southeast, ≥ 40 Midwest, ≥ 40 Northwest, and ≥ 40 Southwest U.S., and ≥ 40 Canadian; *Treatment Site*: ≥ 40 zygomaticomalar region, ≥ 40 anteromedial cheek, and ≥ 40 submalar; and *Treatment Plane*: ≥ 40 suprapariosteal and ≥ 40 subdermal; and *Treatment Technique*: ≥ 40 Tunneling, ≥ 40 Fanning, ≥ 40 Antegrade, ≥ 40 Retrograde, and ≥ 40 Other).

10.6 Interim Analyses

Data through 6 months post treatment will be summarized in an interim analysis although no prospectively determined early stopping of the study is planned. The interim results may be submitted in a Pre-Market Approval Application (PMA) while the study continues, i.e., the "no treatment" control group will undergo treatment and begin follow-up, and the treatment group enters the Extended Follow-up Period.

11. Administrative Issues

This protocol will be conducted in accordance with the applicable U.S. Food and Drug Administration (FDA) regulations and guidelines and Good Clinical Practice (GCP), i.e., the International Conference on Harmonisation (ICH) Guideline on Good Clinical Practice.

11.1 Protection of Human Subjects

11.1.1 Compliance with Informed Consent Regulations (21 CFR Part 50)

Written informed consent will be obtained from each Subject prior to enrollment into the study, i.e., before performing any screening evaluations or procedures.

11.1.2 Compliance with Institutional Review Board (IRB) Regulations (21 CFR Part 56)

This study will be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). The Investigator 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 Investigator should be provided to Allergan.

11.1.3 Compliance with the Principles of Good Clinical Practice (ICH E6)

This protocol will be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines (ICH E6).

11.1.4 Compliance with Electronic Records; Electronic Signatures Regulations (21 CFR Part 11)

This study will be conducted in compliance with the regulations on electronic records and electronic signature (21 CFR Part 11).

11.2 Changes to the Protocol

The Investigator should not implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval 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 (e.g., change in monitors, change of telephone numbers).

11.3 Subject Confidentiality

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 the Sponsor of the study (Allergan), the governing health authorities, or the FDA (U.S. Food and Drug Administration) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

11.3.1 Subject Privacy

Written authorization will be obtained from each Subject prior to enrollment into the study in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information, "HIPAA").

11.4 Documentation

The Investigator will maintain a confidential Subject Contact List with the names and contact information for all Subjects recruited for participation in the study (i.e., received a copy of the IRB-approved consent form for review), whether s/he enrolled (i.e., signed a copy of the consent form in the presence of the Investigator or designee), and reason(s) for those who do not enroll.

Each enrolled Subject will receive a unique Subject Number. The Subject Contact List will link the Subject by name and Subject Number to this study. The Investigator will track the participation of enrolled Subjects on a Study Visit Log, which identifies Subjects by number and initials only.

11.4.1 Source Documents

Individual Subject records will be maintained in the Investigator's Source Documents (SDs). Source documentation is generally considered to be the document on which the information or data point was first recorded. SDs may include a Subject's medical records, hospital charts, clinic charts, and the Investigator's study files as well as the results of diagnostic tests

such as X-rays, laboratory tests, and electrocardiograms. The Investigator's copy of the CRF may also serve as part of the Investigator's source record for a Subject's study-related data.

The following information should be entered into the Subject's medical record:

- a. Subject's name
- b. Subject's contact information
- c. The date that the Subject entered the study and the Subject number assigned
- d. The study title and/or the protocol number of the study and the Sponsor's name (Allergan)
- e. A statement of the informed consent process and the date that informed consent and HIPAA authorization were obtained
- f. Records of previous and current dermatological treatments and/or therapies
- g. Dates of all subject visits
- h. List of all prescription and non-prescription concurrent medications, therapies, and treatments (up to 90 days prior to enrollment through the final visit of the study) and any changes to the list of medications
- i. Occurrence and status of any adverse events and common treatment site responses
- j. The date the Subject exited the study, and a notation as to whether the Subject completed the study or reason for discontinuation
- k. The reason for declining repeat treatment, when applicable
- l. The results of urine pregnancy testing, if performed

Study-specific information, such as Investigator and Subject effectiveness and safety assessments, may be recorded directly on the CRF. With no prior written or electronic record, these data are considered to be source data and will be maintained in the Investigator's study files. Pertinent records related to the study, e.g., the Subject's medical chart, will be made available to the Sponsor representative on request with due precaution to protect the privacy of the Subject. Personal identifying information (except Subject initials) will be redacted on any photocopies of relevant medical records and replaced with the unique Subject Number before submission to the Sponsor. The Investigator will protect the

confidentiality of all Subjects' records within applicable federal/national, state/provincial, and local laws.

11.4.2 Case Report Form (CRF) Completion

The Investigator is responsible for ensuring that data are properly recorded on each Subject's CRFs and related documents. The Evaluating and Treating Investigators must sign the protocol signature page and will personally sign and date where indicated on the respective CRF pages to certify that the observations and findings are recorded on the case report forms correctly and completely.

All required data will be recorded on the CRFs for this study, which will be designed and provided by the Sponsor. Effectiveness assessments, the Subject diary, and study treatment and biopsy depot details may be recorded directly on the CRFs. Draft CRFs are available upon request.

All CRF entries must be in ink; black is preferred. An error will be corrected by a single line drawn through it, and the correct data, recorder's initials and correction date will be entered adjacent to the error. All errors must remain legible. Erasure or obliteration of errors on the CRF or other permanent study record is strictly prohibited.

The reason for any missing CRF data will be explained:

- Not performed or not done = ND
- Cannot be determined or approximated, unknown = UNK or UU
- Does not apply, not applicable = NA
- No data are available = NAV

Original CRF pages will be collected by the Sponsor's Monitor after review and verification of the completion and accuracy of the study data. As needed, the Principal (Treating) Investigator will be contacted to clarify illegible, inconsistent, or incomplete CRF entries.

11.4.3 Study Summary

On a regular basis the Principal Investigator will submit to the Sponsor copies of the Study Visit Log, which lists all enrolled Subjects by Subject Number, initials, and dates of completed visits. The Investigator will submit a final progress report to his/her reviewing

IRB within 3 months of study completion at the site. The Investigator will also provide additional reports to the IRB or to the Sponsor upon request.

The Sponsor will submit the study results to the FDA in an IDE progress report(s) and/or as part of a pre-market approval application (PMA).

11.4.4 Retention of Documentation

Essential documents are any records that demonstrate the compliance of the Subject, Investigator, Sponsor, and Monitor with the study protocol, with standards of Good Clinical Practice (GCP), and with all applicable regulatory requirements. Essential documents (including but not limited to study-related correspondence, Subject records, Subject privacy documentation, records of the distribution and use of all investigational devices, and copies of CRFs) should be retained and available for audit by the Sponsor's auditor and regulatory authorities until at least 2 years after the latest among the following scenarios: completion or termination of the study, the last approval of a marketing application, no pending or contemplated marketing applications, or formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if mandated by the applicable regulatory requirements, by conditions imposed by the IRB, or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained. Allergan requires that it be notified in writing if the Investigator chooses to store the records at a different physical address than the site address or if the Investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

11.5 Labeling, Packaging, Storage and Return of Study Devices

11.5.1 Labeling/Packaging

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

CAUTION: Investigational Device
Limited by U.S. (Federal) law to investigational use

Each individual syringe package and each syringe will bear a label with the product name, lot number, and expiry date. The syringe label will also include mL gradations.

11.5.2 Storage of Study Devices

VOLUMA XC should be stored at 2°C to 25°C, not frozen or exposed to extreme heat, and not used if the package is open or damaged or if the product is not clear. The inventory of VOLUMA XC for this study should be stored in a secure area with access limited to research staff members so authorized by the Principal (Treating) Investigator.

11.5.3 Clinical Supply Inventory

Each shipment from the Sponsor will include a packing list that details the lot numbers and quantity of VOLUMA XC syringes provided for the study. Upon receipt and verification of the contents, the Investigator must sign, date, and retain the packing list with the study records. The Investigator will record the shipment (date received, quantity, and lot numbers) on a Device Inventory Record (DIR). As each Subject is treated, the date, Subject Number, and number of syringes used will also be recorded on the DIR. Study devices must be administered only to Subjects entered into the clinical study and in accordance with the conditions specified in this protocol and the current Instructions for Investigational Use.

11.5.4 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 destroyed after inspection and verification against the CRF by the Monitor. Unused syringes will be returned to the Sponsor unless other disposition arrangements are agreed upon in writing with the Sponsor.

Devices that are damaged during shipment or at the site or that malfunction during use, e.g., faulty syringe or plunger, must be accounted for and returned. The Investigator will promptly notify Allergan's Clinical Research department of any device malfunction (see Sections 9.1.3 and 9.3). The Clinical Research representative will provide instruction for the return of any faulty syringe for evaluation.

11.6 Monitoring by the Sponsor

Appropriately trained representatives of the Sponsor 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 the Monitor has access to all study-related records during scheduled monitoring visits.

The Monitor will review device accountability records and completed CRFs to ensure completeness and consistency with the source records and compliance with the protocol requirements.

11.7 Handling of Biological Specimens

Prior to each study treatment and at study exit, a trained research staff member will perform pregnancy testing on urine samples of women of child-bearing potential. The urine pregnancy test employed should have a sensitivity of at least 50 mIU/mL for human chorionic gonadotropin (hCG). Dermal/subdermal biopsy samples for histological evaluation will be placed in formalin, securely sealed, and shipped to a central laboratory for processing using established techniques and stains, e.g., hematoxylin and eosin (H&E), tri-chrome, and/or colloidal iron. The laboratory will have Clinical Laboratory Improvement Amendments (CLIA) certification. A single board-certified dermatopathologist who is experienced in histological evaluation following dermal filler injections will evaluate all slides from the study and will comment on the types and relative quantities of cells observed, the presence and status of the implant, the overall level of inflammation (minimal, mild, moderate, or marked) and fibrosis at the implant site, and any other interesting features.

At the conclusion of the study, the laboratory and the dermatopathologist will submit all tissue samples and slides to Allergan for retention with other essential study records (see Section 11.4.4). The tissue samples and slides will not be used for any other purpose. Subject privacy concerns and biohazard handling precautions will be paramount.

11.8 Publications

Allergan, as the Sponsor, has a proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation among multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

12. References

12.1 Study Report References

Data from the following studies are on file at Allergan.

STUDY NUMBER	STUDY TITLE
JD-ZZ-001	A multi-center, randomized, within-patient controlled study to evaluate the safety and efficacy of Juvéderm® Hyaluronate Gel Implants vs. Zyplast® Collagen Implant for the correction of nasolabial folds
JD-002	A multi-center follow-up evaluation of efficacy and safety after repeat treatment with Juvéderm® hyaluronate gel implants for the correction of nasolabial folds
JD-003	Interim study report: A multi-center, open label feasibility study of the safety and effectiveness of JUVÉDERM® Ultra Injectable Gel in subjects who desire lip enhancement.
UE041M01	JUVÉDERM® VOLUMA European Expert Evaluation, preliminary report

12.2 Literature References

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13. Attachments

Attachment 13.1 Photographic References

13.1.1 Allergan Photometric Mid-Face Volume Deficit Scale (MFVDS)

13.1.2 Mid-facial Subunits (frontal view)

13.1.3 Mid-facial Subunits (oblique view)

Attachment 13.2 Sample Informed Consent and HIPAA Authorization

Attachment 13.3 Canfield VECTRA Quick Reference Guide

Attachment 13.4 Glossary of Abbreviations

AE	Adverse event
BDDE	1,4 Butanediol diglycidyl ether
BOE	Blepharoplasty Outcomes Evaluation
C	Celsius
CFR	U. S. Code of Federal Regulations
COC	Cyclic olefin copolymer
CRF	Case report form
CTR	Common treatment site response
DIR	Device inventory record
DLQI	Dermatology Quality of Life Index
EMLA	Topical anesthetic (a eutectic mixture containing Lidocaine and Prilocaine)
FAS	Function and Sensation (Lips and Perioral Area)
FDA	Food and Drug Administration
FLO	Facial Lines Outcome
FOE	Facelift Evaluations Outcome
FQAD	Freiburg Questionnaire on Aesthetic Dermatology and Cosmetic Surgery
G	Gauge
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic acid or Hyaluronan
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LAFM	Look and Feel of the Mid-face
MFVDS	Mid-FaceVolume Deficit Scale
mITT	Modified Intent-to-Treat
NSAIDs	Non-steroidal anti-inflammatory drugs
OAFM	Other Aesthetic Features of the Mid-Face
PMA	Pre-market approval
PRO	Patient-Reported Outcomes Measure
ROE	Rhinoplasty Outcomes Evaluation
SAE	Serious adverse event
SAS	Statistical Analysis Software
SOE	Skin Rejuvenation Outcomes Evaluation
SPA	Subject Self-Perception of Age
UADE	Unanticipated adverse device effect
UPT	Urine pregnancy test

ALLERGAN

Protocol VOLUMA-002 Amendment 12

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
25-Jan-2013 15:46 GMT-080	Murphy_Diane	Clinical Development Approval
25-Jan-2013 15:48 GMT-080	Avelar_Rui	Clinical Development Approval
25-Jan-2013 16:34 GMT-080	Eaton_Laura	Study Director Approval
29-Jan-2013 11:55 GMT-080	Gross_Todd	Biostatistics Approval