NCT03166618

Study ID: VOLUMA-007

Title: A multicenter, single-blind, randomized, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for correction of temple hollowing

Protocol Date: 24 Feb 2017

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Study Title:	A multicenter, single-blind, randomized, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for correction of temple hollowing
Protocol Number:	VOLUMA-007 Amendment 3
Protocol Date	24 Feb 2017
Product Name:	JUVÉDERM VOLUMA XC injectable gel
Development Phase:	Pivotal
Sponsor:	Allergan [redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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

INVESTIGATOR SIGNATURE PAGE

Study Title:	A multicenter, single-blind, randomized, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for correction of temple hollowing
Protocol Number:	VOLUMA-007 Amendment 3
Protocol Date:	24 Feb 2017
Product Name:	JUVÉDERM VOLUMA XC injectable gel
Investigator:	
Study Location:	

I agree to:

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

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

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

RETURN TO ALLERGAN

Synopsis

NUMBER AND TITLE OF STUDY:
VOLUMA-007: A multicenter, single-blind, randomized, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for correction of temple hollowing

DEVELOPMENT PHASE: Pivotal

STUDY CENTERS: Up to 15 United States centers, including up to 3 centers for the feasibility phase

NUMBER OF SUBJECTS: Up to 189 subjects will be enrolled, including up to 30 subjects for the feasibility phase and up to 159 subjects for the pivotal phase

OBJECTIVES: The objectives of this study are to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC injectable gel in adult subjects seeking correction of temple hollowing.

STUDY DESIGN:

This is a prospective, multicenter, evaluator-blinded, randomized, parallel-group, controlled study to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC hyaluronic acid (HA) injectable gel to correct temple hollowing. [redacted]

At screening, after written informed consent has been given, the Treating Investigator (TI) will document the subject's demographics, height, weight, vital signs, Fitzpatrick skin phototype, race, and history of sun exposure, smoking, and medical, surgical, dental, and cosmetic procedures. Female subjects of childbearing potential will undergo urine pregnancy tests. The Evaluating Investigator (EI) will rate subjects on the 5-point photonumeric Allergan Temple Hollowing Scale (ATHS) to determine eligibility for the study. Subjects will be randomized 2:1 to the treatment group or the control group and 1:1 to receive the first treatment in the right or left temple. The same order must be used for all treatments.

FEASIBILITY PHASE:

Treatment group: [redacted] Pretreatment anesthesia will be applied as necessary. [redacted] Treatment of the second temple will follow the same treatment procedures as treatment of the first temple ([redacted]). [redacted]. Subjects will return for an office visit at 14 days after treatment of the second temple [redacted]

[redacted] Thirty days after treatment of the second temple, the subject and the TI will discuss the results of the initial treatment and determine whether correction has been achieved. If correction has not been achieved in 1 or both temples, the TI may perform a touch-up treatment. Touch-up treatment will be administered as described for initial treatment with each temple treated 1 or 2 days apart [redacted] The touch-up treatment visits, procedures, and follow-up are identical to those for the initial treatment. [redacted]

Routine follow-up visits for safety and effectiveness will occur at 1, 3, 6, 9, and 12 months after the last treatment. At each visit, [redacted]; the EI will rate subjects on the ATHS; the EI and subjects will separately assess improvement in the temple area using the Global Aesthetic Improvement Scale (GAIS); [redacted]

Control group: Subjects randomized to the control group will complete a 3-month no-treatment control period [redacted], and the EI will rate them on the ATHS and the GAIS at the month 1 and 3 visits. Subjects will exit the study after the month 3 procedures are complete.

PIVOTAL PHASE: TBD

Treatment group: In the pivotal phase, subjects randomized to the treatment group will undergo the visit(s) and procedures prior to, during (initial, touch-up, and repeat treatments), and after treatment identical to those for subjects randomized to the treatment group in the feasibility phase. Except that, in the pivotal phase, treatment of both temples from the same subject will occur on the same day, but will be separated by at least 30 minutes.

Control group: Pivotal phase subjects randomized to the control group will undergo the visit(s) and procedures during the no-treatment control period, prior to, during (optional initial and touch-up treatments), and after treatment identical to those for subjects randomized to the control group in the feasibility phase.

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION:

Adults with temple hollowing who are seeking restoration in the temple area

INCLUSION:

1. Age 22 or over and in good general health
2. [redacted]
3. TI considers the subject's temple hollowing to be amenable to temporary correction
4. [redacted]
5. [redacted]
6. [redacted]

EXCLUSION:

1. [redacted]
2. Has temple hollowing due to trauma, congenital malformations, or lipodystrophy, either congenital or acquired (eg, congenital myotonic dystrophy, HIV-associated lipodistrophy, or acquired generalized lipodystrophy)
3. [redacted]

4. Has ever received permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
5. Has ever undergone fat injections above the subnasale or is planning to undergo this procedure during the study
6. Has tattoos, piercings, facial hair (ie, beard, mustache), or scars above and including the subnasale that would interfere with visual assessment of the temple
7. Has undergone semipermanent dermal filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) in the temple or mid-face within 36 months before enrollment or is planning to undergo such treatment during the study
8. Has undergone dermal filler injections above the subnasale within 24 months before enrollment or is planning to undergo this procedure during the study
9. Has temporal arteritis or history of temporal arteritis
10. Has temporomandibular joint dysfunction
11. Has active or recurrent inflammation or infection in either eye
[redacted])
13. [redacted]
14. Has undergone mesotherapy or cosmetic treatment (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, liposuction, lipolysis, or other ablative procedures) anywhere in the face or neck or botulinum toxin injections above the subnasale within 6 months before enrollment or is planning to undergo any of these procedures during the study
15. Has experienced trauma to the temple area within 6 months before enrollment or has residual deficiencies, deformities, or scarring
16. Has a tendency to develop hypertrophic scarring
17. Has a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), hyaluronic acid products, or *Streptococcal* protein, or is planning to undergo desensitization therapy during the term of the study
18. Has porphyria or untreated epilepsy
19. Has active autoimmune disease
20. Has current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, above the subnasale (study device injection may be delayed for subjects with a history of recurrent oral herpes lesions who take prophylactic doses of antiviral/herpes medication for at least 2 days before study treatment administration)
21. Is on a concurrent regimen of lidocaine or structurally-related local anesthetics (eg, bupivacaine) or is on a concurrent regimen of drugs that reduce or inhibit hepatic metabolism (eg, cimetidine, beta-blockers)
22. [redacted]
23. [redacted]
24. [redacted]

25. [redacted]
26. [redacted]
27. [redacted]
28. [redacted]

TEST PRODUCT, DEVICE VOLUME, AND MODE OF ADMINISTRATION:

JUVÉDERM VOLUMA XC (a hyaluronic acid injectable gel with lidocaine) will be administered via the supplied needles (27G ½″) to the temple area. Appropriate injection volume for the temple will be determined by the TI [redacted]

DURATION OF STUDY:

Participation for each subject in the feasibility phase treatment group will encompass up to 1 month for screening, 1 month for treatment, and 12 months of follow-up after the last treatment (initial or touch-up).

Participation for each subject in the feasibility phase control group will encompass up to 1 month for screening and 3 months for the no-treatment control period.

RESPONSE MEASURES:

Effectiveness: The primary effectiveness measure is the EI assessment of temple hollowing using the ATHS (on a 5-point scale of convex to severe). [redacted]

Safety: [redacted]

STATISTICAL METHODS:

Sample Size Calculation: The sample size is determined to provide adequate power to demonstrate that the product is effective as well as safe. A total of 90 subjects in the treatment group and 45 subjects in the control group will provide at least 90% power to detect a difference of 30% in the responder rates between the groups. [redacted]

[redacted]

Effectiveness: The primary effectiveness endpoint will be met if the responder rate for the treatment group is statistically greater than that for the control group at month 3 and the responder rate at month 3 for the treatment group is 60% or greater. [redacted]

Safety: [redacted]

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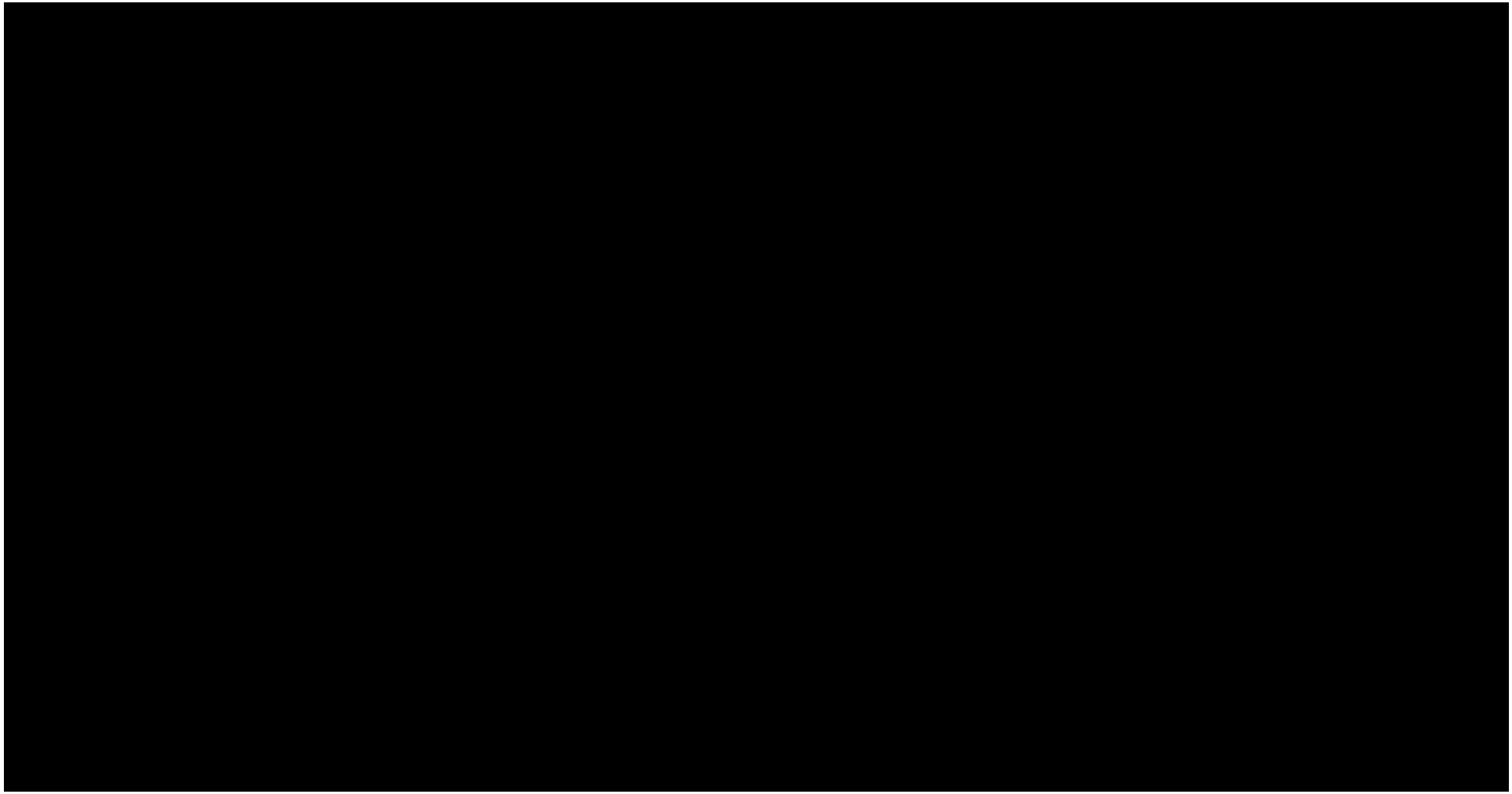
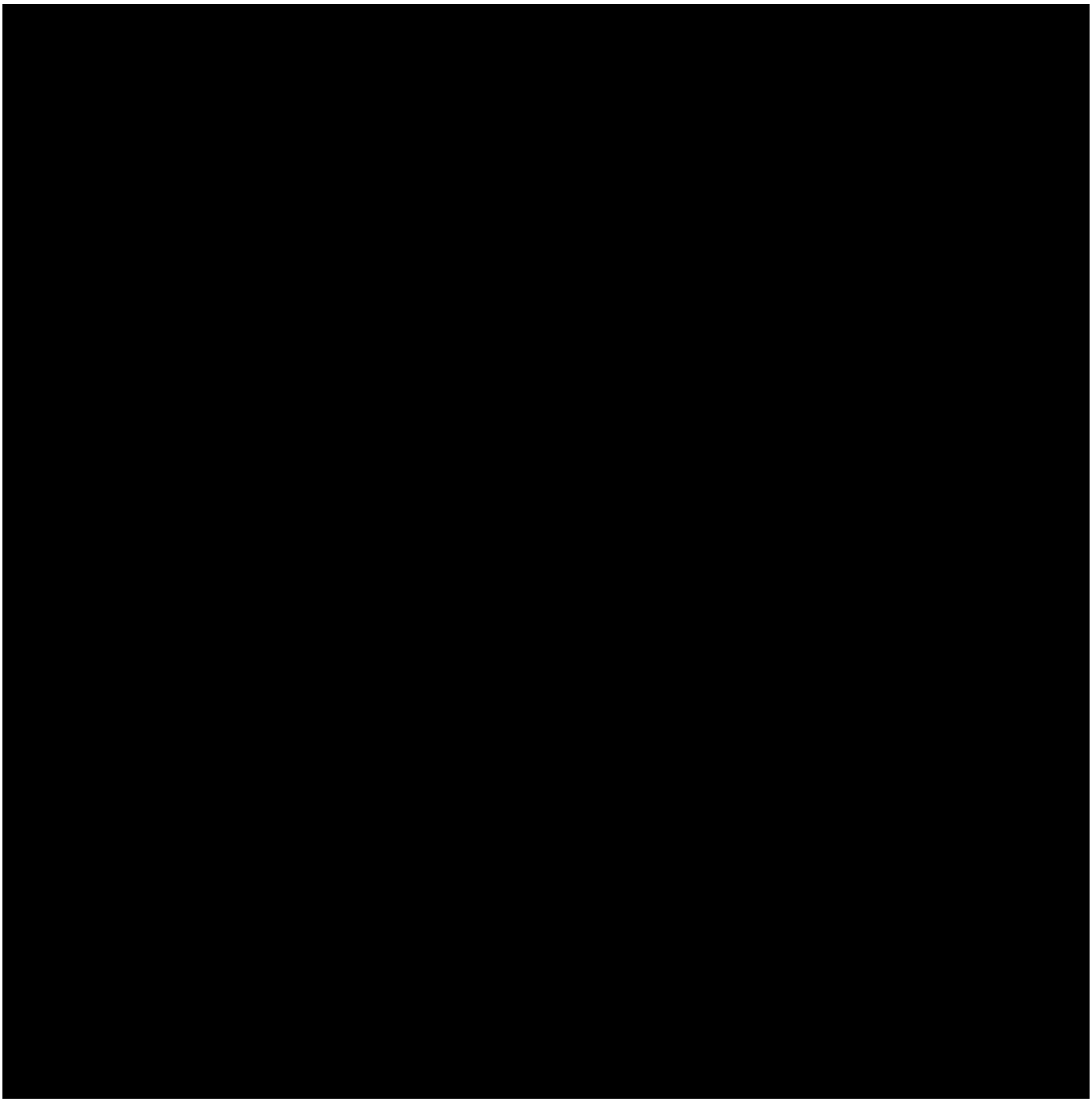




1. Abbreviations and Terms

Term/Abbreviation	Definition
3D	3-dimensional
ADE	adverse device event
AE	adverse event
ATHS	Allergan Temple Hollowing Scale
CE	Conformité Européene
CFR	Code of Federal Regulations
eCRF	electronic case report form
EI	Evaluating Investigator
DFU	directions for use
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
IC	informed consent
ICF	informed consent form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	injection site response
IWRS	interactive web response system
mITT	modified intent-to-treat
PP	per protocol
PT	preferred term
SADE	serious adverse device effect
SAE	serious adverse event
SITA	Swedish Interactive Threshold Algorithm
SOC	system organ class
TI	Treating Investigator
UADE	unanticipated adverse device effect
US	United States

2. Background, Risk and Benefit, and Clinical Rationale

2.1 Background

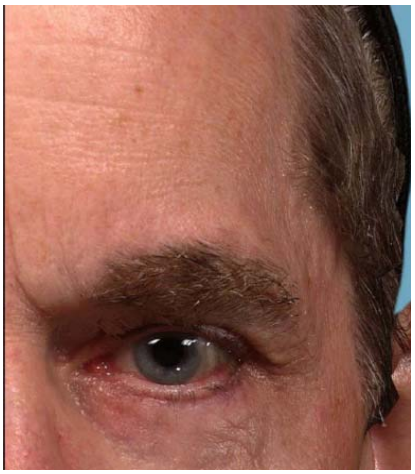
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

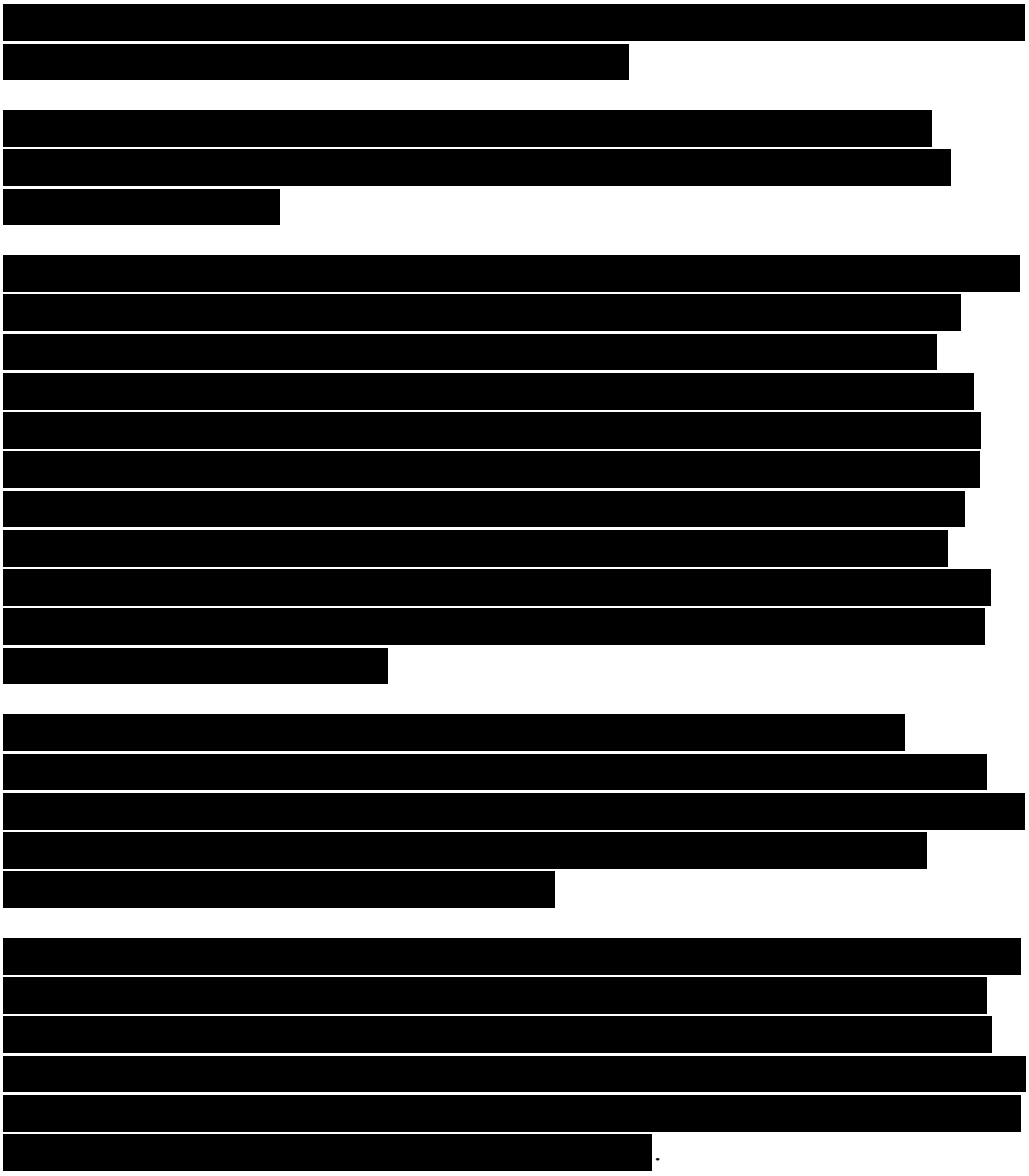


[redacted] These events were mild to moderate and resolved by week 2 (Moradi 2013).

[redacted]

2.2 Risk and Benefit

[redacted]



2.3 Clinical Rationale

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

implantation of JUVÉDERM VOLUMA XC for temple hollowing in adult subjects seeking aesthetic improvement.

3. Study Objectives and Clinical Hypotheses

3.1 Study Objectives

The objectives of this study are to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC injectable gel in adult subjects seeking correction of temple hollowing.

3.2 Clinical Hypothesis

The clinical hypothesis is that the percentage of pivotal phase subjects with a clinically significant change (defined as at least a 1-point improvement on the Allergan Temple Hollowing Scale [ATHS] score as assessed by the Evaluating Investigator [EI]) in temple hollowing from baseline to month 3 for both temples will be significantly greater in the JUVÉDERM VOLUMA XC treatment group than in the untreated control group and the percentage of the treatment group subjects with a clinically significant change in temple hollowing from baseline to month 3 for both temples will be 60% or greater.

4. Study Design

4.1 Structure

This is a prospective, multicenter, evaluator-blinded, randomized, parallel-group, controlled study to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC hyaluronic acid (HA) injectable gel to correct temple hollowing. This study will be conducted in 2 phases: an initial feasibility phase involving up to 30 subjects at up to 3 investigational sites to assess short-term safety of the treatment and a pivotal phase involving additional subjects and sites to assess the long-term safety and effectiveness of the treatment. [redacted]

4.2 Duration

Participation for each subject in the feasibility phase treatment group will encompass up to 1 month for screening, 1 month for treatment, and 12 months of follow-up after the last treatment (initial or touch-up).

Participation for each subject in the feasibility phase control group will encompass up to 1 month for screening and 3 months for the no-treatment control period.

4.3 Treatment Groups and Treatment Regimen

4.3.1 Study Treatment

JUVÉDERM VOLUMA XC injectable gel

4.3.2 Control Treatment

No treatment

4.3.3 Methods for Blinding

The EI and the image analysis technician will be blinded to treatment until after the month 3 visit when the control group subjects exit the study or receive the optional treatment. [redacted]

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

4.3.4 Retreatment Criteria

A subject may undergo a touch-up treatment 30 days after the initial treatment (ie, at the month 1 follow-up visit) if both the subject and TI determine that correction has not been achieved. [redacted]

[redacted]

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

Topical or injectable anesthesia may be used during treatment according to routine practice, but it must be limited to the treatment areas only.

[redacted]

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

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

4.4.2 Prohibited Medications/Treatments

[redacted]

[redacted]

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

4.4.3 Special Diet or Activities

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

[redacted]

4.5 Treatment Allocation Ratio

Subjects are randomized at an allocation ratio of 2:1 to treatment with JUVÉDERM VOLUMA XC or no treatment control group.

5. Study Population

5.1 Number of Subjects

Up to 189 subjects will be enrolled at up to 15 sites, [redacted]

5.2 Study Population Characteristics

Adult subjects with temple hollowing who are seeking restoration will be recruited. [redacted]

5.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Age 22 or over and in good general health
2. [redacted]
3. TI considers the subject's temple hollowing to be amenable to temporary correction
4. [redacted]
5. [redacted]
6. [redacted]

5.4 Exclusion Criteria

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

1. [redacted]
2. [redacted]
3. Has atrophic skin in the temple area that might not be suitable for injection, in the opinion of the TI
4. Has ever received permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
5. Has ever undergone fat injections above the subnasale or is planning to undergo this procedure during the study
6. Has tattoos, piercings, facial hair (ie, beard, mustache), or scars above and including the subnasale that would interfere with visual assessment of the temple
7. Has undergone semipermanent dermal filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) in the temple or mid-face within 36 months before enrollment or is planning to undergo such treatment during the study
8. Has undergone dermal filler injections above the subnasale within 24 months before enrollment or is planning to undergo this procedure during the study
9. Has temporal arteritis or history of temporal arteritis
10. [redacted]
11. Has active or recurrent inflammation or infection in either eye
12. Has a history of detached retina, retinal vascular occlusion (eg, vein or arterial occlusion), narrow angle glaucoma, or neovascular eye disease (eg, diabetic retinopathy, age-related wet macular degeneration)
13. Has ever received a facelift, browlift, or facial reconstructive surgery or is planning to during the study

14. Has undergone mesotherapy or cosmetic treatment (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, liposuction, lipolysis, or other ablative procedures) anywhere in the face or neck or botulinum toxin injections above the subnasale within 6 months before enrollment or is planning to undergo any of these procedures during the study
15. Has experienced trauma to the temple area within 6 months before enrollment or has residual deficiencies, deformities, or scarring
16. Has a tendency to develop hypertrophic scarring
17. Has a history of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), hyaluronic acid products, or *Streptococcal* protein, or is planning to undergo desensitization therapy during the term of the study
18. Has porphyria or untreated epilepsy
19. Has active autoimmune disease
20. Has current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, above the subnasale (study device injection may be delayed for subjects with a history of recurrent oral herpes lesions who take prophylactic doses of antiviral/herpes medication for at least 2 days before study treatment administration)
21. Is on a concurrent regimen of lidocaine or structurally-related local anesthetics (eg, bupivacaine) or is on a concurrent regimen of drugs that reduce or inhibit hepatic metabolism (eg, cimetidine, beta-blockers)
22. [redacted]
23. [redacted]
24. [redacted]
25. [redacted]

26. [redacted]

27. [redacted]

28. [redacted]

6. Procedures

6.1 Washout or Run-In Intervals

[redacted]

[redacted]	[redacted]

6.1.2 Run-in Intervals

[redacted]	[redacted]

6.2 Procedures to be Performed

The TIs will be trained in the injection technique, and TIs and EIs will be trained in the use of the ATHS prior to initiating enrollment.

Subjects will remove eyeglasses during all effectiveness assessments so that the eyeglasses do not obstruct the view of the temple area. Contact lens use during effectiveness assessments is allowed. The use of any corrective lenses during safety assessments of visual acuity is allowed, provided that the same lenses are used consistently throughout the study.

Throughout the study, to the extent possible, it is recommended that treatment and safety assessments for a particular subject be performed by the same TI, and effectiveness assessments (ATHS and Global Aesthetic Improvement Scale [GAIS]) be performed by the same EI. If it is not possible to use the same evaluator to follow the subject, it is recommended that evaluations overlap (examine the subject together and discuss findings) for at least 1 visit.

At each visit and safety telephone call, the TI (or designee) will solicit and record information about AEs and concomitant medications, therapies, and treatments. The TI (or designee) will begin by asking the subject a general, non-directed question, "How have you been feeling since the last visit?" [redacted] All reported AEs will be documented.

6.2.1 Screening Visit

A subject is considered enrolled when he/she has signed the Informed Consent Form (ICF) in the presence of the TI or a qualified designee. The site will then log onto the interactive web response system (IWRS) to obtain a unique subject number that will serve as the subject identification number on all study documents.

The EI will evaluate the subject's temple hollowing using the ATHS for each temple. Subjects who have an ATHS score of "Minimal", "Moderate", or "Severe" for each temple will be eligible for the study. Although both temples must qualify, each temple can have a different score (eg, one temple can be "Minimal" severity and the other "Moderate"). Subjects will complete the Satisfaction with Temples and Satisfaction with Facial Appearance Overall modules of the FACE-Q questionnaire.

The TI will ensure that each subject meets the study eligibility criteria and run-in and washout requirements (see Sections 5.3, 5.4, and 6.1). The TI will record the reasons for those subjects who do not meet the inclusion/exclusion criteria and who withdraw consent before randomization.

The TI (or designee) will collect and record the subject's demographic information, medical and surgical history, cosmetic and dental procedure history, smoking history, Fitzpatrick skin phototype, race, and sun exposure estimate. Physical measurements (height and weight) and vital signs, including blood pressure (systolic and diastolic, while subject is seated), temperature, pulse, and respiratory rate will also be collected and recorded.

A urine pregnancy test will be conducted for female subjects of childbearing potential. If the test is positive, the subject will be exited from the study.

The schedule of procedures to be conducted at screening are provided in Table 1 and Table 4.

6.2.2 Randomization Visit

The randomization visit may occur on the same day as the screening visit and must occur within 30 days after screening/signing of the ICF. Inclusion/exclusion criteria will be reviewed again to confirm subject eligibility, [redacted]

Subjects will be randomized in a 2:1 ratio to the treatment group or to the control group and 1:1 to receive the first treatment in the right or left temple. [redacted] Subjects randomized to the control group will finish the required procedures for the randomization visit and return for a month 1 and 3 visit during the control period.

The schedule of procedures to be conducted at randomization are provided in Table 1 and Table 4.

[redacted]

6.2.4 Treatment Group

In both phases, subjects randomized to the treatment group will receive initial treatment, touch-up treatment if needed, and follow-up visits throughout the 12-month posttreatment study period.

In the feasibility phase, treatment of the temples from the same subject will be staggered and separated by at least 1 day to allow for a retinal specialist examination after treatment of each temple. In the pivotal phase, treatment of both temples from the same subject will occur on the same day, but will be separated by at least 30 minutes.

6.2.4.1 Initial Treatment

The initial treatment visit will occur within 7 days after the retinal examination. Before treatment of the first temple, inclusion/exclusion criteria will be reviewed again to confirm subject eligibility. Female subjects of childbearing potential will take a urine pregnancy test; if the test is positive, the subject will not receive treatment and will be exited from the study. [redacted] The EI will not be present during any treatment procedures.

Anesthesia will be administered following the standard practice at each investigational site. The application of ice and topical anesthesia is allowed to reduce injection discomfort. Injectable anesthesia must be limited to the treatment area only. The TI will use aseptic skin preparation and will administer injections to the first temple according to the VOLUMA-007 DFU and Section 9.1.2 of this protocol.

The TI will determine the appropriate volume to inject to achieve optimal correction (at least 1-point improvement from baseline on the ATHS) based on clinical experience. [redacted]

[redacted]

[redacted]

Subjects will receive instructions on how to evaluate the treatment areas, assess the procedural pain on an 11-point scale, and complete the daily safety diary to record the presence or absence and severity of injection site responses (ISRs) starting on the day of treatment and for approximately 30 days after treatment.

Subjects will complete a safety follow-up telephone call at 3 days after treatment of the second temple. Subjects will return for an office visit at 14 days after treatment of the second temple [redacted]

Thirty days after treatment of the second temple, the subject and the TI will discuss the results of the initial treatment and determine whether correction has been achieved. If correction has not been achieved, the TI may perform a touch-up treatment.

Details regarding anesthesia use, treatment areas injected, volume injected, kit numbers, needle gauge, characteristics of the procedure [redacted] and characteristics of the product [redacted] will be recorded on the eCRF.

Concomitant medications, procedures, therapies, and AEs will be monitored continuously throughout the study. The procedures and evaluations for the treatment period are listed by visit in Table 1.

6.2.4.2 Touch-up Treatment

If the TI and subject agree that 1 or both temples have not reached optimal correction (at least 1-point improvement on the ATHS) at the Day 30 visit, a touch-up treatment may be administered. Touch-up treatment will be administered as described for initial treatment, with each temple treated 1 or 2 days apart [redacted]. Female subjects of childbearing potential will take a urine pregnancy test; if the test is positive, the subject will not receive touch-up treatment but will continue to be followed in the study.

[redacted]. The TI (or designee) will review the subject's daily safety diary and discuss any unusual signs/symptoms with the subject. If an ISR is ongoing at the touch-up treatment, it will be recorded in the touch-up safety diary.

The touch-up treatment visits, procedures, and follow-up are identical to those for the initial treatment. The procedures and evaluations for the touch-up treatment are provided in Table 1.

If no touch-up is needed, the subject will exit the treatment period and continue with the posttreatment follow-up visits and procedures.

6.2.4.3 Follow-up

Treatment group subjects will attend follow-up visits for safety and effectiveness at month 1, 3, 6, 9, and 12 after the last treatment (either initial treatment, if no touch-up is performed, or touch-up treatment). Safety assessments will be performed at all posttreatment follow-up visits. At all visits, [redacted], and the EI will evaluate the subject's temple area using the ATHS and global aesthetic improvement of the temple area using the GAIS and comparing to the digital images of the subject captured at baseline. [redacted], and also rate treatment effectiveness using the GAIS. [redacted] At the month 3 and 12 visits, subject's weight will be recorded and at the month 12 visit a urine pregnancy test will be administered to female subjects of childbearing potential. Subjects in

the feasibility phase will be exited from the study after all month 12 visit procedures are completed.

For the pivotal phase subjects, at the month 9 visit the TI and subject will discuss treatment results, and the subject will be offered a repeat treatment after completion of the month 12 visit. [redacted] If the subject chooses not to receive repeat treatment the subject will be exited from the study after all month 12 visit procedures are completed.

The procedures and evaluations to be performed during the follow-up period are listed by visit in Table 2.

6.2.4.4 Repeat Treatment

[redacted] The order in which temples are treated will be the same as that for initial treatment. Female subjects of childbearing potential will take a urine pregnancy test; if the test is positive, the subject will not receive repeat treatment and will be exited from the study. The repeat treatment visits and procedures are identical to those for the initial treatment during the pivotal phase. The repeat treatment will be administered as described for initial treatment, with each temple treated approximately 30 minutes apart [redacted]. Subjects will be followed for 1 month after the repeat treatment and will exit the study.

The procedures and evaluations to be performed during repeat treatment and follow-up are listed by visit in Table 3.

6.2.5 Control Group

6.2.5.1 Control Period

In both phases, control group subjects will return to the investigational site at months 1 and 3 after randomization.

Feasibility phase subjects randomized to the control group will exit the study at the month 3 visit.

At the month 1 visit, the pivotal phase subjects randomized to the control group will be offered an optional treatment after completion of the month 3 visit. [redacted]

who accept optional treatment will have a retinal specialist examination done within 7 days before the month 3 visit. Control group subjects who decline optional treatment will exit the study after the month 3 visit. The control period concludes after completion of the month 3 procedures.

The procedures and evaluations for the control group during the control period are listed by visit in Table 4.

6.2.5.2 Optional Treatment

In the pivotal phase, control group subjects who have optional treatment will be followed for safety only; no effectiveness assessments will be performed.

A urine pregnancy test will be conducted for female subjects of childbearing potential prior to the optional treatment. If the test is positive, the subject will not receive optional treatment and will be exited from the study.

The optional treatment can occur on the same day as the month 3 visit, [redacted] If the month 3 visit and optional treatment occur on the same day, all pretreatment study procedures that overlap with the month 3 procedures do not need to be repeated. If the optional treatment visit occurs after the month 3 visit, optional treatment must occur within 2 weeks after the month 3 visit or the start of the pivotal phase (whichever is last) [redacted]

The optional treatment visits, procedures, and follow-up are identical to those for the initial treatment of the treatment group in the pivotal phase, including the 30-minute waiting period between temples. The preparation process and performance of procedures after treatment administration will be the same as that described for the initial treatment of the treatment group in the pivotal phase. The procedures and evaluations for the optional treatment of the control group are listed by visit in Table 5.

6.2.5.3 Touch-up Treatment

Thirty days after the optional initial treatment, the subject and the TI will discuss the results of the initial treatment and determine whether correction has been achieved. If correction has not been achieved in 1 or both temples, the TI may perform a touch-up treatment. Female subjects of childbearing potential will take a urine pregnancy test; if the test is positive, the subject will not receive touch-up treatment but will continue to be followed in the study. The touch-up treatment visits, procedures, and follow-up are identical to those for the touch-up

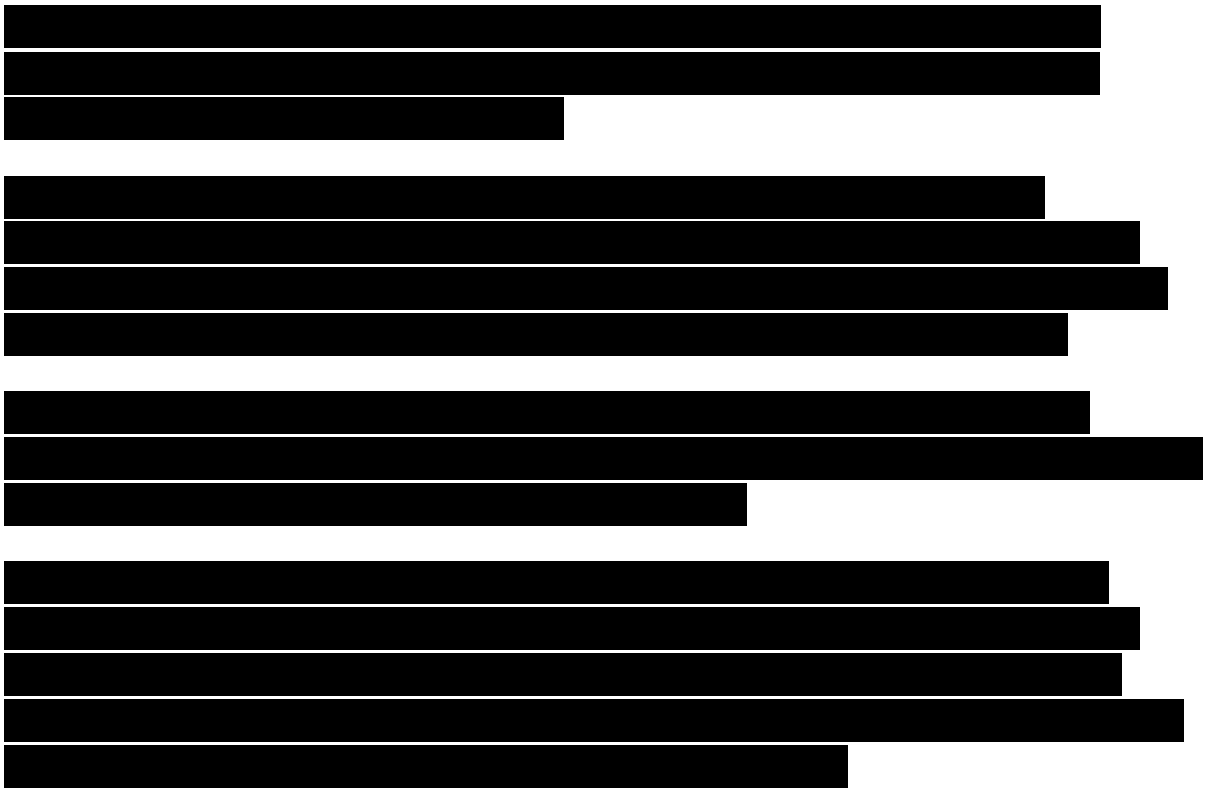
treatment of the treatment group in the pivotal phase. The procedures and evaluations for touch-up treatment are listed by visit in Table 5.

6.2.5.4 Follow-up

All treated control group subjects will be followed for 12 months for safety only. The procedures and safety assessments to be performed at the month 1, 3, 6, 9, and 12 visits after the last treatment (ie, either initial or touch-up) are listed by visit in Table 5.

6.3 Instructions for the Subjects

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



[redacted]

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

6.4 Unscheduled Visits

An unscheduled visit may occur for safety purposes [redacted] Applicable procedures will be performed and recorded on the eCRF.

[redacted]

6.5 Early Discontinuation of Subjects

Each subject reserves the right to withdraw from the study at any time without jeopardy to his/her future medical care. The procedures to be performed at early exit visits/final study visits are specified in Table 1 to 5. Subjects may also be administratively withdrawn if they do not return for follow-up visits through the final study visit. For any subject who withdraws from the study, the date and reason for withdrawal will be recorded on the eCRF. If an AE is ongoing at the time of withdrawal and is related to the study treatment, the TI will attempt to follow the subject until the AE has been resolved or follow-up is no longer possible. The TI shall ask for the subject's permission to follow his/her status/condition outside the study.

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

6.6 Withdrawal Criteria

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

[redacted]

7. Response Measures and Summary of Data Collection Methods

7.1 Effectiveness Measures

7.1.1 Primary Effectiveness Measure

The primary effectiveness measure is the EI's assessment of temple hollowing using the ATHS described in Table 6.

Table 6 Allergan Temple Hollowing Scale

Score	Grade	Description
0	Convex	Rounded temple
1	Flat	Flat temple; temporal fusion line may be visible
2	Minimal	Shallow depression or concavity with minimal volume loss; temporal fusion line may be visible
3	Moderate	Moderate depression or concavity with moderate volume loss; moderate prominence of temporal fusion line
4	Severe	Deeply recessed, sunken appearance; marked prominence of temporal fusion line and zygomatic arch

The ATHS is a 5-point ordinal scale developed by Allergan to grade the severity of temple hollowing. The ATHS contains photographic images of subjects representing different

Fitzpatrick skin types, race categories, and severities of temple hollowing (0 = Convex, 1 = Flat, 2 = Minimal, 3 = Moderate, 4 = Severe). A scale validation study (Study FSV-001) was conducted to assess the inter- and intra-rater reliability of the ATHS. Each of the 8 trained clinicians independently evaluated the subjects in-person and assigned each subject an ATHS grade based on the live evaluation. Three weeks later, the same 8 trained clinicians re-evaluated the same subjects, and assigned each subject an ATHS grade based on the live evaluation and without reliance on prior memory. Both the inter- and intra-rater agreement were substantial (> 0.60), indicating substantial agreement among the raters as well as within the raters between the 2 in-person evaluation sessions, respectively. Additionally, the results demonstrate that a 1-point difference or higher is clinically significant. Therefore, results confirmed that the ATHS is validated and appropriate to be used as a primary effectiveness measure for this study.

7.1.2 Secondary Effectiveness Measures

The secondary effectiveness measures include independent, noncollaborative assessments by both the EI and the subject of global aesthetic improvement in the temple area using the 5-point GAIS (Table 7).

Table 7 Global Aesthetic Improvement Scale

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

7.1.3 Other Effectiveness Measures

[redacted]

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

7.2 Safety Measures

[redacted]

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

[redacted]

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

[redacted]

7.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics to be collected include sex, age, race, height, weight, vital signs, [redacted] medical/surgical/cosmetic/dental procedure history, and prior medications.

7.4 [redacted]

[redacted]

7.5 Summary of Methods of Data Collection

Electronic data capture will be used to collect study-specific information, [redacted] Investigators will provide access to hospital files, medical records, and other source documents containing subject clinical/medical information. Source document verification will be performed.

[redacted]

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

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

8. Statistical Procedures

A separate statistical analysis plan will be prepared to provide specifications for all analyses. The plan will be finalized and approved prior to clinical database lock. The database will be locked and analyzed at the end of study (all data collected through the end of the study).

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

8.1 Analysis Populations

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

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

Unless specified otherwise, effectiveness analyses, whether performed on the mITT or PP population, will use the "as-randomized" assignment for each subject (eg, if a subject randomized to the control group is treated inadvertently at the start of the study, the

assessments for that subject will nonetheless be included in the control group analysis). The PP population will be used to perform sensitivity analyses for the primary effectiveness variable. All safety analyses will be conducted on the safety population, using the "as-treated" grouping for each subject (eg, if a subject randomized to the control group is treated at the start of the study, the subject will be analyzed in the treatment group).

8.2 Collection/Derivation of Primary and Secondary Effectiveness Assessments

8.2.1 Primary Effectiveness Variable

The primary effectiveness variable, the ATHS response, is derived from the EI's assessment of temple hollowing using the ATHS (on a 5-point scale of convex to severe, Section 7.1.1).

[redacted]

The primary effectiveness endpoint is the proportion of ATHS responders at month 3.

8.2.2 Secondary Effectiveness Variables

The 2 secondary effectiveness variables are:

- GAIS responder based on EI assessment of global aesthetic improvement [redacted]
- GAIS responder based on subject assessments of global aesthetic improvement [redacted]

8.3 Hypothesis and Methods of Analysis

8.3.1 Primary Effectiveness Analyses

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

8.3.2 Secondary Effectiveness Analyses

GAIS) at the month 3 visit

8.3.3 Other Effectiveness Analyses

[redacted]

8.3.4 Safety Analyses

[redacted]

[redacted]

8.5 Sample Size Calculation

The sample size is determined to provide adequate power to demonstrate that the product is effective as well as safe. A total of 90 subjects in the treatment group and 45 subjects in the control group will provide at least 90% power to detect a difference of 30% in the responder rates between the groups. [redacted]

[redacted]

[redacted]

[redacted]

9. Materials

9.1 Study Treatment

9.1.1 Product Description

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

9.1.2 Instructions for Use and Administration

[redacted]

[redacted]

The TIs will use aseptic injection technique, and the following procedures must be used to ensure subject safety. The detailed recommended injection technique is provided in the VOLUMA-007 DFU included in the Site Study Binder.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  severe pain.
- [redacted]

[redacted]

9.1.3 Treatment Regimen Adjustments

Up to 2 treatment sessions (initial and touch-up) per temple are allowed; [redacted]

9.2 Other Study Supplies

[redacted]

pressure cuff, and internet connection for eCRF completion and IWRS). The retinal specialist is responsible for supplies related to retinal exams (eg, retinal imaging equipment, Humphrey visual field analyzer).

10. Study Administration Procedures

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

10.1 Subject Entry Procedures

10.1.1 Overview of Entry Procedures

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

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

[redacted]

10.1.2 Informed Consent and Subject Privacy

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

[redacted]

10.1.3 Method for Assignment to Treatment Groups

At the time of randomization (ie, at or within 30 days after screening/signing of the ICF), eligible subjects will be assigned to 1 of 2 treatment groups (treatment and control) in a 2:1 ratio to receive JUVÉDERM VOLUMA XC or to the control group. [redacted]

[redacted] The IWRS will provide the site with the specific kit number(s) for each randomized subject at the time of randomization and at each subsequent treatment visit. Sites will dispense treatment according to the IWRS instructions provided by the system.

10.2 Compliance with Protocol

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

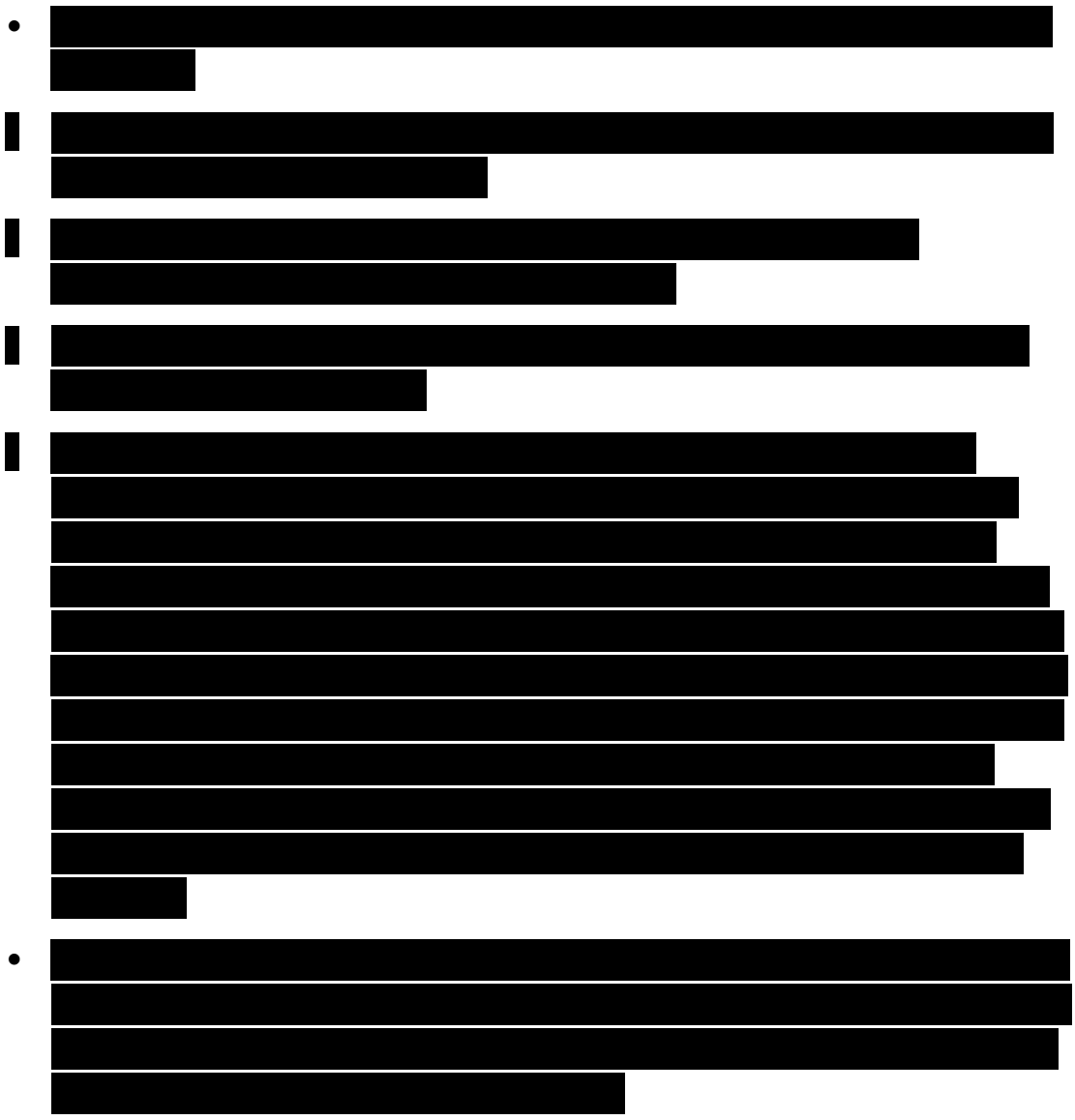
10.3 Pregnancy

If a female subject becomes pregnant after treatment, the TI will notify Allergan immediately after the pregnancy is confirmed. The TI will (1) instruct the subject to notify her physician of the presence of the investigational device and (2) will follow the pregnancy to term. Best practices are to be followed in order to ensure the welfare of the subject and the fetus. The Medical Safety Physician will contact the TI to obtain information about the pregnancy outcome. The subject will continue to be followed for safety, and the pregnancy will be documented as a protocol deviation.

Pregnancy by itself will not be considered an AE or serious adverse event (SAE). Hospitalization for a normal delivery or elective abortion of a normal fetus does not constitute an SAE. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an AE or SAE, and these are to be reported as described in Sections 11.1.4 and 11.1.5.

10.4 Study Termination

If conditions arise during the study that indicate that the study or an investigational site needs to be terminated, Allergan, the TI, Monitor, IRB, and/or regulatory agencies will discuss the situation and take appropriate action after consultation. [redacted]



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

11. Adverse Events

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

[redacted].

For a description of potential AEs, see Sections 2.2, 11.1.1, and the VOLUMA-007 DFU.

11.1 Definitions

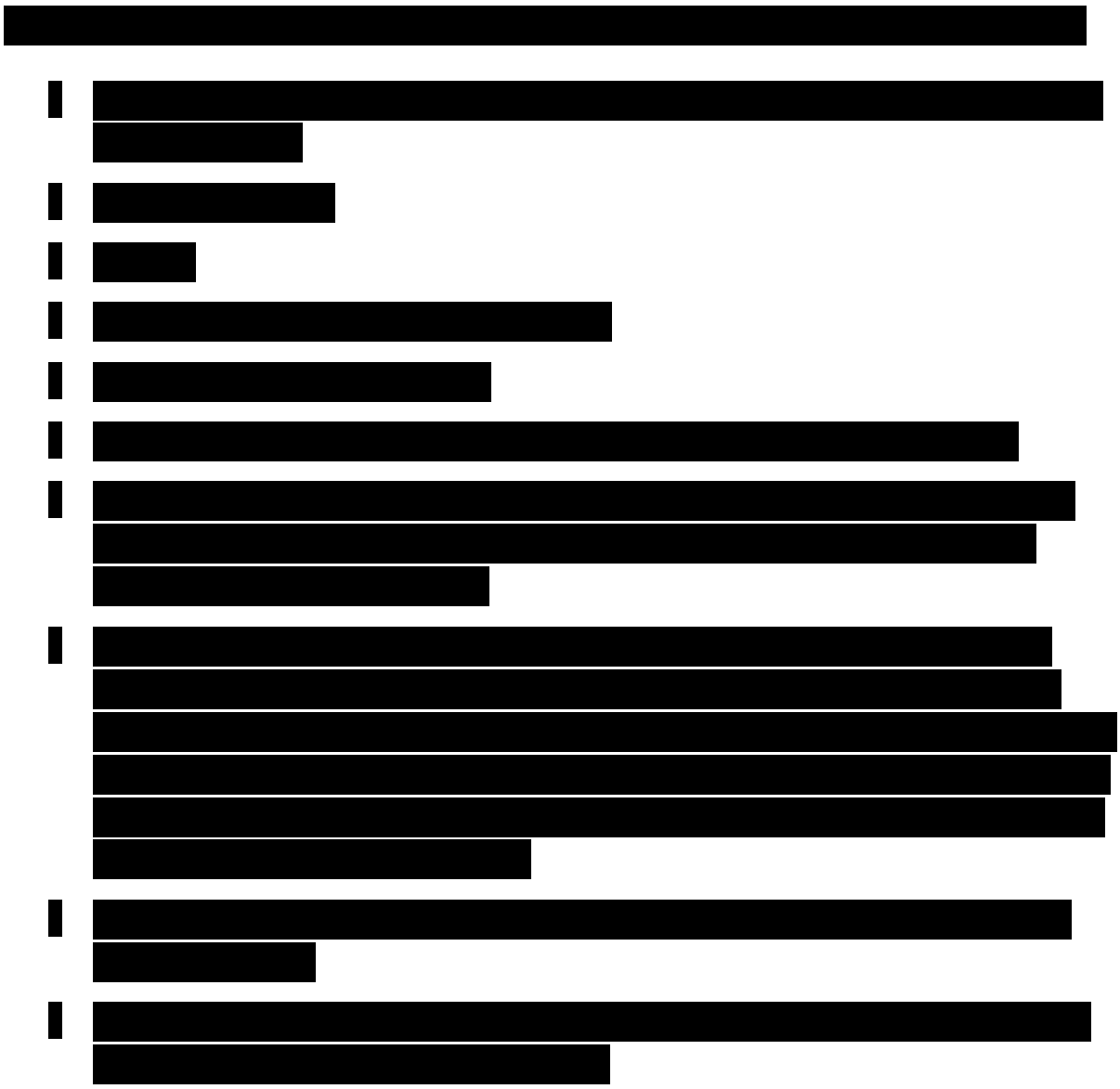
11.1.1 Adverse Event

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

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

AEs will be monitored throughout the study beginning with signing of the ICF. At each postscreening visit, the TI (or designee) will begin querying for AEs by asking each subject a general, non-directed questions, "Have you had any changes to your condition since your last visit?" [redacted] Previous AEs and changes in

therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate eCRF.



Unforeseeable risks or results are also a possibility. The risk of developing a serious complication is small. If a complication occurs, subjects will be advised to contact the TI who will use his/her medical judgment to do whatever is necessary to treat the subject.

11.1.2 Adverse Event of Special Interest

An AE of special interest is defined as any vision-related AE. See Section 11.3 for procedures for reporting an AE of special interest.

11.1.3 Serious Adverse Event

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

a) led to death,

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

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

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

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

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

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

11.1.4 Adverse Device Effect

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

See Section 11.3 for procedures for reporting an ADE.

11.1.5 Serious Adverse Device Effect

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

See Section 11.4 for procedures for reporting a SADE.

11.1.6 Unanticipated Adverse Device Effect

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

11.1.7 Device Deficiency

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

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

11.1.8 Severity

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

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

11.1.9 Relationship to Treatment

Relationship to a treatment refers to a determination of the relationship (if any) between an AE and the device or treatment procedure. A causal relationship is present if the TI determines that there is a reasonable possibility that the AE may have been caused by the device or is associated with the procedure, such as an event that can be attributed to other products, surgical techniques, or medications required specifically for the procedure. Relationship to the treatment must be determined by the TI and cannot be delegated to other study staff.

11.2 Timelines for Reporting

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

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

11.3 Procedures for Reporting an AE or ADE

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

The TI will report AEs of special interest to Allergan within 24 hours of awareness of the event by completing an AE eCRF and notifying Allergan study management personnel and the Medical Safety Physician by phone or email. Allergan will notify FDA of any AEs of special interest within 10 days of Allergan's awareness of the event.

11.4 Procedures for Reporting an SAE or SADE

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

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

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

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

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

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

12. Administrative Issues

12.1 Protection of Human Subjects

12.1.1 Compliance with Informed Consent Regulations

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

12.1.2 Compliance with IRB Regulations

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

12.1.3 Compliance with Good Clinical Practice

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

12.1.4 Financial Disclosure/Certification Form

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

- Any financial arrangement entered into between Allergan and the Investigator involved in the conduct of a covered clinical trial, whereby the value of the compensation to the Investigator for conducting the study could be influenced by the outcome of the study
- Any significant payments of other sorts from Allergan, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria
- Any proprietary interest in the tested product held by any Investigator involved in a study
- Any significant equity interest in Allergan held by any Investigator involved in any clinical study
- Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

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

12.1.5 Compliance with Electronic Records and Signature Regulations

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

12.2 Changes to the Protocol

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

12.3 Subject Confidentiality and Privacy

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

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

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

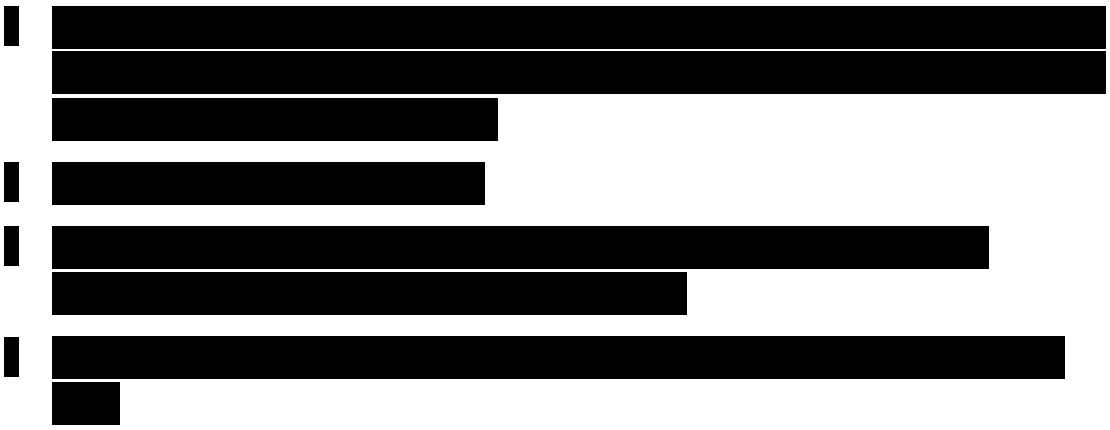
12.4 Documentation

12.4.1 Source Documents

Source documents may include a subject's medical records, hospital charts, laboratory notes, [redacted] and any other diagnostic tests that may be performed, [redacted] If the Serious Adverse Event Form and Pregnancy Surveillance Form are used in this study, they are also considered source documents. The TI's copies of the eCRFs serve as part of the TI's record of a subject's study-related data.

[redacted]

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



12.4.2 Case Report Form Completion

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

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

12.4.3 Investigator Reports

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

12.4.4 Retention of Documentation

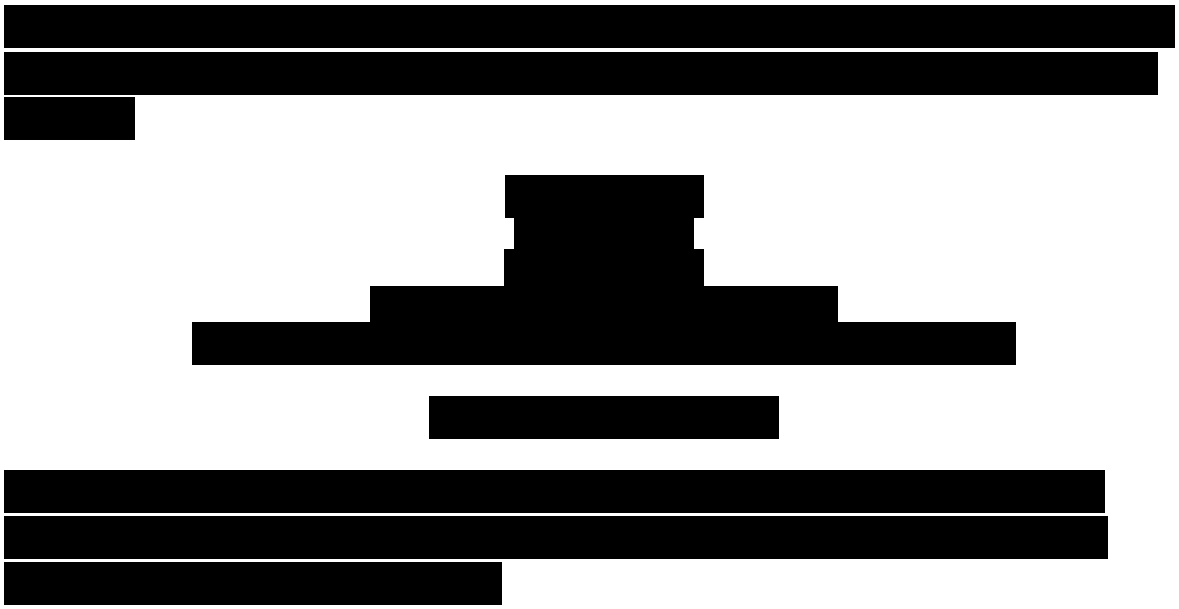
All study related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs are to be maintained on file.

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

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

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

12.5.1 Labeling/Packaging



12.5.2 Storage of Study Devices

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

JUVÉDERM VOLUMA XC must be stored at room temperature [redacted] with a continuous temperature monitoring device. Use of the device is required to ensure that the

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

12.5.3 Study Device Accountability

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

12.5.4 Return of Study Devices

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

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

12.6 Monitoring by Allergan

Appropriately trained representatives of Allergan will monitor the conduct of the trial at each investigational site, including visits to the site to review, audit, and retrieve copies of study-related documents. It is the responsibility of the TI to be present or available for consultation

and to assure that Allergan has access to all study-related records during scheduled monitoring visits.

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

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

12.7 Testing of Biological Specimens

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

12.8 Publications

This study will be registered and results posted on www.clinicaltrials.gov. Allergan, as the Sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study Investigators and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

13. References

13.1 Study Report References

Data from the following study are on file at Allergan.

Study Number	Study Title
FSV-001	Validation of Multiple Photonumeric Scales for Use in the Evaluation of Volume Deficits and Aging

13.2 Literature References

Alam M, Gladstone H, Kramer EM, Murphy JP Jr, Nouri K, Neuhaus IM, et al. American Society for Dermatologic Surgery. ASDS guidelines of care: injectable fillers. Dermatol Surg. 2008;34 Suppl 1:S115-S148.

Atherton DD, Joshi N, Kirkpatrick N. Augmentation of temporal fossa hollowing with Mersilene mesh. J Plast Reconstr Aesthet Surg. 2010;63(10):1629-1634.

Beer KR, Julius H, Dunn M, Wilson F. Remodeling of periorbital, temporal, glabellar, and crow's feet areas with hyaluronic acid and botulinum toxin. J Cosmet Dermatol. 2014;13(2):143-150.

Breithaupt AD, Jones DH, Braz A, Narins R, Weinkle S. Anatomical basis for safe and effective volumization of the temple. Dermatol Surg. 2015;41 Suppl 1:S278-S283.

Callan P, Goodman GJ, Carlisle I, Liew S, Muzikants P, Scamp T, et al. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of mid-face volume deficiency: A 24 month study. Clin Cosmet Investig Dermatol. 2013;6:81-89.

Carruthers J, Fagien S, Dolman P. Retro or peribulbar injection techniques to reverse visual loss after filler injections. Dermatol Surg. 2015;41 Suppl 1:S354-357.

Clauser LC, Tieghi R, Galie M, Carinci F. Structural fat grafting: facial volumetric restoration in complex reconstructive surgery. J Craniofac Surg. 2011;22(5):1695-1701.

Gosain AK. Hydroxyapatite cement paste cranioplasty for the treatment of temporal hollowing after cranial vault remodeling in a growing child. J Craniofac Surg. 1997;8(6):506-511.

Guo J, Tian W, Long J, Gong H, Duan S, Tang W. A retrospective study of traumatic temporal hollowing and treatment with titanium mesh. Ann Plast Surg. 2012;68(3):279-285.

Jones D, Flynn T. Hyaluronic acids: clinical applications. In: Jones D, editor. Injectable fillers: principles and practice. Oxford, UK: Wiley-Blackwell;2010. p. 158-174.

Jones D, Murphy DK. Volumizing hyaluronic acid filler for midface volume deficit: 2-year results from a pivotal single-blind randomized controlled study. Dermatol Surg. 2013;39(11):1602-1612.

Kim S, Matic DB. The anatomy of temporal hollowing: the superficial temporal fat pad. J Craniofac Surg. 2005;16(4):651-654.

Lowe NJ, Maxwell CA, Lowe P, Shah A, Patnaik R. Injectable poly-l-lactic acid: 3 years of aesthetic experience. Dermatol Surg. 2009;35(1 Suppl):344-349.

McNichols CH, Hatef DA, Cole P, Hollier LH, Thornton JF. Contemporary techniques for the correction of temporal hollowing: augmentation temporoplasty with the classic dermal fat graft. J Craniofac Surg. 2012;23(3):e234-e238.

Moradi A, Shirazi A, Moradi J. A 12-month, prospective, evaluator-blinded study of small gel particle hyaluronic acid filler in the correction of temporal fossa volume loss. J Drugs Dermatol. 2013;12(4):470-475.

Moradi A, Shirazi A, Perez V. A guide to temporal fossa augmentation with small gel particle hyaluronic acid dermal filler. J Drugs Dermatol. 2011;10(6):673-676.

Philip-Dormston WG, Hilton S, Nathan M. A prospective, open-label, multicenter, observational, postmarket study of the use of a 15 mg/mL hyaluronic acid dermal filler in the lips. J Cosmet Dermatol. 2014;13(2):125-134.

Raspaldo H. Volumizing effect of a new hyaluronic acid sub-dermal facial filler: a retrospective analoysis based on 102 cases. J Cosmet Laser Ther. 2008;10(3):134-142.

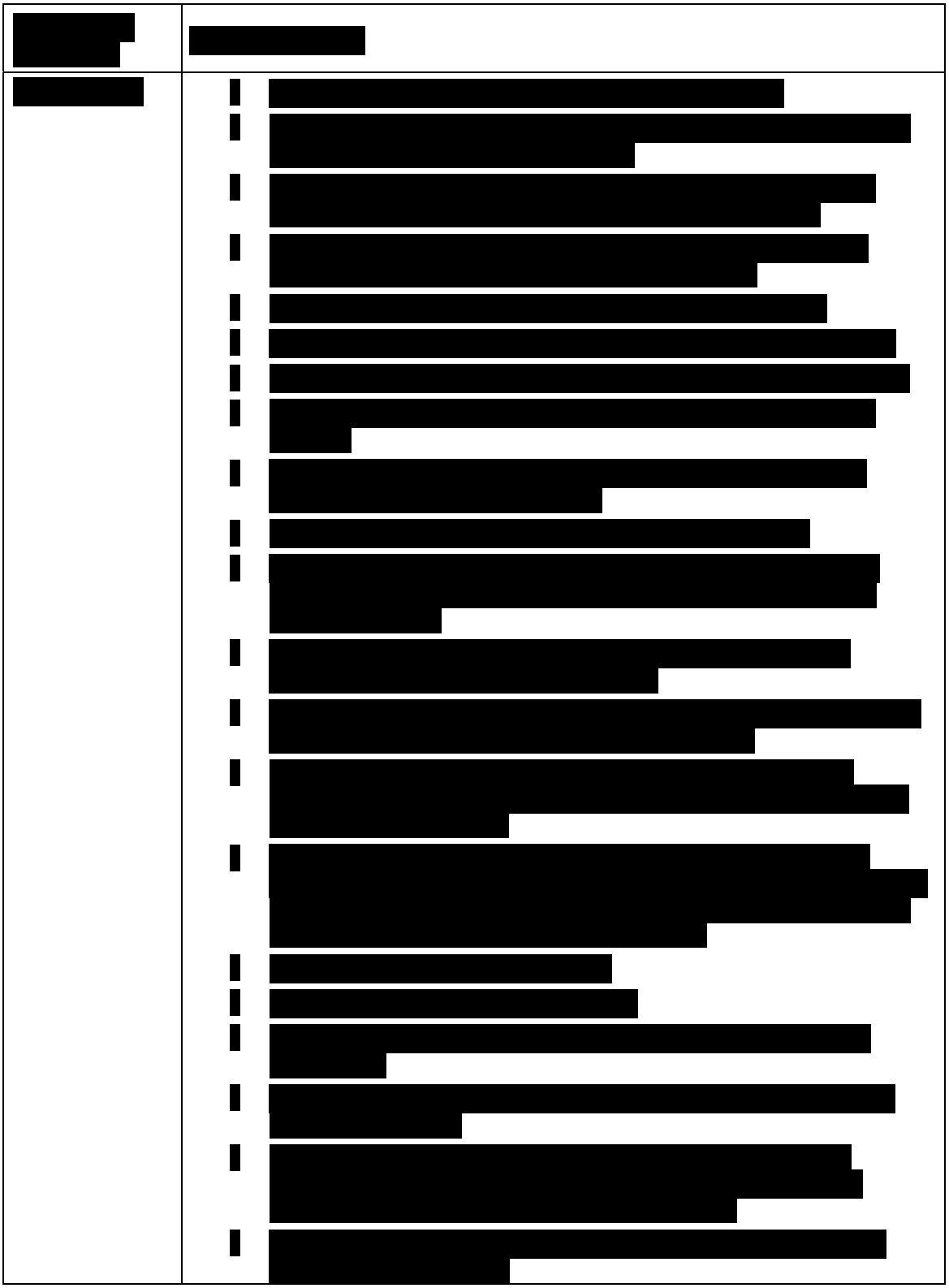
Rose AE, Day D. Esthetic rejuvenation of the temple. Clin Plast Surg. 2013;40(1):77-89.

Ross JJ, Malhotra R. Orbitofacial rejuvenation of temple hollowing with Perlane injectable filler. Aesthet Surg J. 2010;30(3):428-433.

Sykes JM. Applied anatomy of the temporal region and forehead for injectable fillers. J Drugs Dermatol. 2009;8(10 Suppl):s24-s27.

Sykes JM, Cotofana S, Trevidic P, Solish N, Carruthers J, Carruthers A, et al. Upper face: Clinical anatomy and regional approaches with injectable fillers. Plast Reconstr Surg. 2015;136(5 Suppl):204S-218S.

14. Protocol Amendment Summary



Version Date/ Amend. No.	Changes to Protocol
	• [redacted]

Version Date/ Amend. No.	Changes to Protocol
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ALLERGAN

Protocol VOLUMA-007 Amd 3

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
01-Mar-2017 16:02 GMT-080	[redacted]	[redacted]