NCT03418545

Study ID: 1932-701-008

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

Protocol Amendment 1 Date: 10Oct2017

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Study Title:	A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLBELLA® XC injectable gel for correction of infraorbital hollowing
Protocol Number:	1932-701-008 Amendment 1
Product Name:	JUVÉDERM VOLBELLA® XC injectable gel
Development Phase:	Pivotal
Sponsor:	Allergan 2525 Dupont Drive Irvine, CA 92612
Manufacturer:	Allergan Industrie, SAS Route de Proméry Zone Artisanale de Pré-Mairy 74370 Pringy France
[redacted]	[redacted]

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

INVESTIGATOR SIGNATURE PAGE

Study Title:	A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLBELLA® XC injectable gel for correction of infraorbital hollowing
Protocol Number:	1932-701-008 Amendment 1
Product Name:	JUVÉDERM VOLBELLA 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) 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

RETURN TO ALLERGAN

Synopsis

NUMBER AND TITLE OF STUDY:
1932-701-008: A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLBELLA® XC injectable gel for correction of infraorbital hollowing

DEVELOPMENT PHASE: Pivotal

STUDY CENTERS: Up to 15 United States centers

NUMBER OF SUBJECTS: Up to 175 subjects will be enrolled and 140 subjects will be randomized

OBJECTIVES:
The objective of this study is to evaluate the safety and effectiveness of JUVÉDERM VOLBELLA XC injectable gel (hereafter, VOLBELLA XC) in adult subjects seeking correction of infraorbital hollowing.

Study design:

This is a prospective, multicenter, evaluator-blinded, randomized, controlled study to evaluate the safety and effectiveness of VOLBELLA XC hyaluronic acid (HA) injectable gel to correct infraorbital hollowing. Once screened, subjects will be randomized to either the treatment or control group. The treatment group will receive treatment at the start of the study and an optional touch-up treatment 1 month later. They will be followed for safety and effectiveness for 12 months with the option for a repeat treatment and an additional month of follow-up. The control group will complete a 3-month control phase after randomization and will be offered optional treatment and optional touch-up treatment 1 month later. They will be followed only for safety for 9 months.

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, 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 Infraorbital Hollows Scale (AIHS) to determine eligibility for the study. The TI will ensure the subject's anatomy is amenable to correction to an AIHS rating of 0 or 1 [redacted] Before randomization, subjects will undergo [redacted] All subjects will be randomized 3:1 to the treatment group or the control group, and will also be randomized 1:1 to receive the first treatment on the right or left side. The same order must be used for all treatments.

Treatment group: Before treatment, subjects randomized to the treatment group will complete the following assessments:

- FACE-Q Appraisal of Lower Eyelids questionnaire
- TI (or designee) safety assessments
  - Snellen visual acuity using a Snellen eye chart
  - confrontational visual fields
  - ocular motility

The TI will use supplied 32G ½″ needles or 27G 1½" cannulas (as provided by Allergan) based on the TI's preference to inject VOLBELLA XC submuscularly/supraperiostially to correct infraorbital hollowing. Topical or local anesthesia or ice will be applied as necessary. [redacted] The following assessments will be performed on the treatment day after treatment:

- TI assessments
  - product moldability
  - Snellen visual acuity [redacted])
  - confrontational visual fields ([redacted])
  - ocular motility ([redacted])
  - adverse events (AEs)

Approval Date: 10-Oct-2017

- recording of concomitant medications and procedures

- Subject assessments
  - procedural pain on an 11-point scale
  - daily safety diary to record the presence and severity of injection site responses (ISRs) for 30 days after treatment

Subjects will receive a safety follow-up telephone call at 3 days after treatment. Subjects will return for an office visit at 14 days after treatment to undergo [redacted], and the TI will perform all safety assessments. The subject will not see the blinded EI at the Day 14 visit. Thirty days after treatment, the subject and the TI will discuss the results of the initial treatment. [redacted] ptional touch-up treatment may be performed if agreed upon by the subject and TI. The touch-up treatment visits, procedures, and follow-up are identical to those for the initial treatment. If no touch-up is performed, that visit becomes the Month 1 visit, and the visit is conducted as described below.

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, the following assessments will be performed:

[redacted]

- TI (or designee) safety assessments
  - ocular motility
  - AEs
  - recording of concomitant medications and concurrent procedures
- EI effectiveness assessments
  - AIHS
  - improvement in the infraorbital hollows using the Global Aesthetic Improvement Scale (GAIS)
- subject's assessments
  - improvement in the infraorbital hollows using the GAIS, [redacted]
  - FACE-Q Appraisal of Lower Eyelids questionnaire

[redacted]

After completion of the Month 12 visit, subjects will be offered an optional repeat treatment. Alternatively, subjects will complete the study after all Month 12 visit procedures are complete. The procedures and assessments to be performed at repeat treatment and at follow-up visits after repeat treatment are identical to those after the initial treatment, with the exception that no touch-up will be offered. Subjects will be followed for 1 month after repeat treatment and then exit the study.

Control group: Subjects randomized to the control group will complete a 3-month no-treatment control period with office visits at Months 1 and 3. At randomization and at each of these office visits, the following assessments will be performed:

- AEs
- recording of concomitant medications and concurrent procedures
- EI effectiveness assessments
  - AIHS

[redacted]

  - improvement in the infraorbital hollows using the GAIS (Months 1 and 3 only)

After the Month 3 procedures are complete, subjects will be offered optional treatment and will be followed for safety only for 9 months after last treatment. Control group subjects who decline optional treatment will exit the study after the Month 3 visit procedures are complete.

The optional treatment visit for the control group will be identical to the treatment visit for the treatment group. Control subjects who receive treatment will follow the same follow-up visit schedule as the treatment group, including optional touch-up, for 9 months after last treatment; however only the following assessments will be performed at follow-up visits:

- [redacted]
- TI (or designee) safety assessments:
  - Snellen visual acuity [redacted]
  - confrontational visual fields [redacted]
  - ocular motility [redacted]
  - AEs
  - recording of concomitant medications and procedures

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION:

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

INCLUSION:

1. Age 22 or over and in good general health
2. Has "Moderate" or "Severe" infraorbital hollowing (grade 2 or 3 on the AIHS) for each eye as assessed by the EI (ie, both eyes must qualify but do not need to have the same score)
3. TI considers the subject's anatomy to be amenable to improvement to an AIHS grade of 0 or 1 (None or Minimal)
4. Is able to complete effectiveness self-assessments without the use of glasses (contact lens use is acceptable if they will be used for all subject self-assessments)
5. Ability to follow study instructions and likely to complete all required visits
6. Written informed consent has been obtained

EXCLUSION:

1. Has atrophic skin in the tear trough region as determined by the TI
2. Has large lower lid fat pads that would mask improvement, as determined by the TI
3. Has hyperpigmentation in the infraorbital area (does not include dark circles under the eyes not due to hyperpigmentation)
4. Has significant volume loss in the midface
5. Has a cornea that projects farther forward than the most anteriorly projected part of the cheek
6. 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
7. Has ever undergone fat injections above the subnasale or is planning to undergo this procedure during the study
8. Has tattoos, piercings, facial hair (ie, beard, mustache), or scars that would interfere with visual assessment of the infraorbital hollows
9. Has undergone volume augmentation with semipermanent dermal fillers (eg, calcium hydroxyapatite, poly-L-lactic acid) or temporary dermal fillers in the malar area, temples, or around the eyes within

12 months before enrollment or is planning to undergo such treatment during the study

10. Has active or recurrent inflammation or infection in either eye
11. Has ever received a blepharoplasty, facelift, browlift, or is planning to during the study
12. 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
13. Has experienced trauma to the infraorbital area within 6 months before enrollment or has residual deficiencies, deformities, or scarring in the periorbital or cheek areas
14. Has a tendency to develop hypertrophic scarring
15. 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
16. Has active autoimmune disease
17. 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
18. Has received any investigational product within 30 days prior to study enrollment or is planning to participate in another investigation during the course of this study
19. Has begun using any new over-the-counter or prescription oral or topical, anti-wrinkle products within 30 days before enrollment or is planning to begin using such products during the study (subjects who have been on a regimen of such products for at least 30 days are eligible for the study if they intend to continue their regimen throughout the study)
20. Females who are pregnant, nursing, or planning a pregnancy
21. Is an employee (or a relative of an employee) of the TI, EI, or Allergan, or a representative of Allergan
22. Has a condition or is in a situation which in the TI'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

TEST PRODUCT, DEVICE VOLUME, AND MODE OF ADMINISTRATION:

VOLBELLA XC (a HA injectable gel with lidocaine) will be administered via the supplied needles (32 G ½ inch) or 27 G 1½ inch cannulas to the infraorbital and adjacent area. The appropriate injection volume will be determined by the TI but is not to exceed a maximum total volume of 2.2 mL per side for initial and touch-up treatments combined, and not to exceed a maximum total volume of 2.2 mL per side for repeat treatment.

DURATION OF STUDY: Treatment group: up to 1 month for screening, 1 month for treatment, 12 months of follow-up after the last treatment (initial or touch-up), and 1 month of follow-up after optional repeat treatment. **Control group**: up to 1 month for screening, 3 months for the no-treatment control period, 1 month for optional treatment, and 9 months of follow-up after the last treatment (initial or touch-up)

RESPONSE MEASURES:

Effectiveness:

The primary effectiveness measure is the EI assessment of infraorbital hollowing using the AIHS. Separate AIHS scores will be provided for each infraorbital hollow. Secondary effectiveness measures include independent, noncollaborative assessments by both the EI and the subject of global aesthetic improvement in the infraorbital area using the 5-point GAIS below and subject responses on the validated FACE-Q Appraisal of Lower Eyelids questionnaire. For GAIS and FACE-Q questionnaires, one overall assessment will be provided to encompass both sides.

[redacted]

STATISTICAL METHODS:

Sample Size Calculation: [redacted]

Effectiveness: The primary effectiveness endpoint is the responder rate at month 3 after the last treatment. A responder is defined as subjects who show at least 1-point improvement from baseline on the AIHS in both infraorbital areas based on EI assessment. Baseline is defined as the EI assessment at screening.

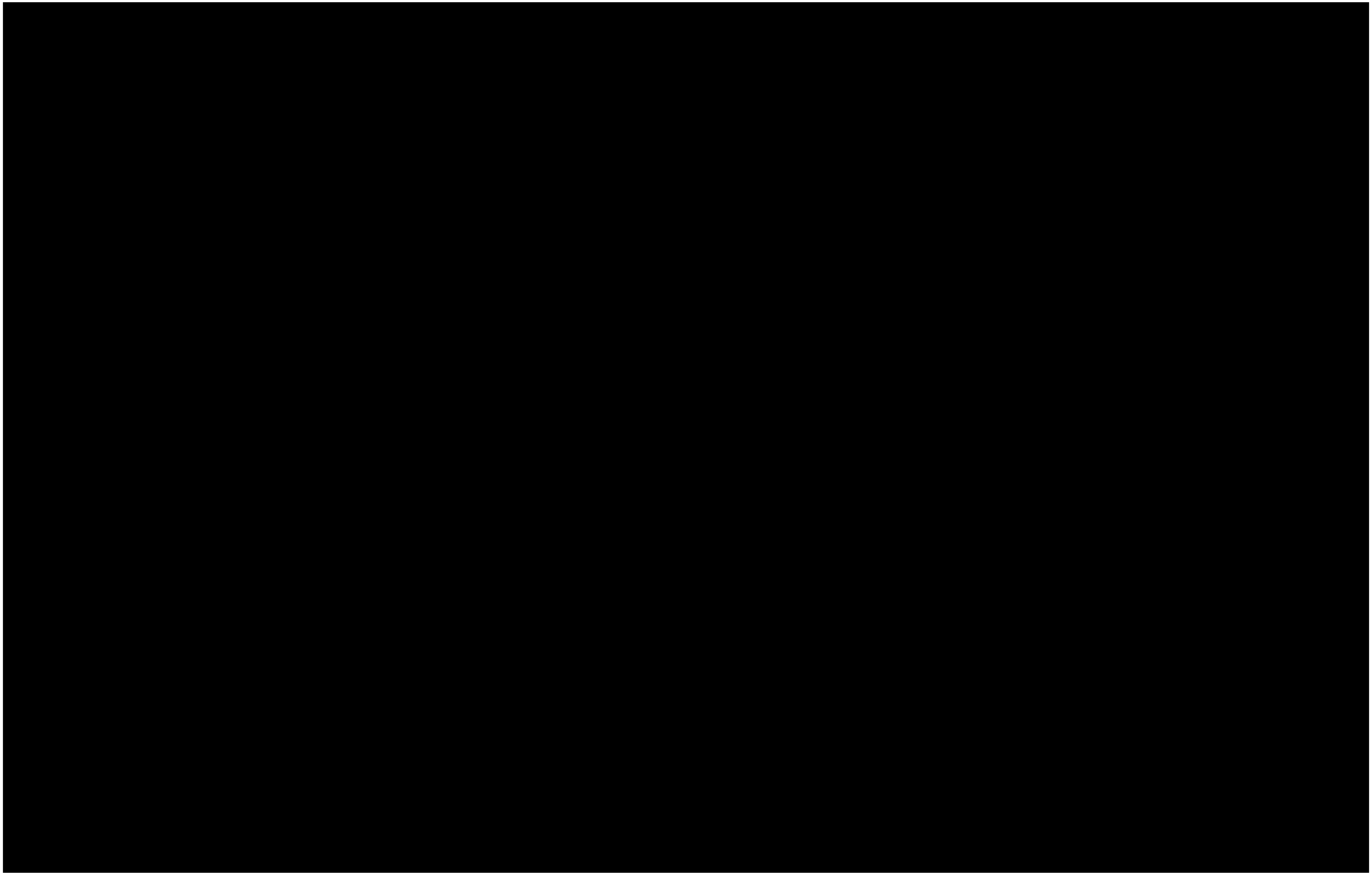
For the primary effectiveness analysis, a 2-sided, Fisher's exact test at the 5% level will be used to test whether the responder rate at month 3 in the treatment period is significantly greater than that in the control group at month 3 in the control period.

The secondary effectiveness analyses will include the responder rates with 95% CIs for the treatment group based separately on the EI and subject assessments of GAIS, where a "responder" is a subject who shows improvement in the overall aesthetic assessment in the infraorbital area (Improved or Much Improved on GAIS) at the Month 3 visit, and subject responses on the Appraisal of Lower Eyelids module of the validated FACE-Q questionnaire. A 2-sided paired t-test at the 5% level will be used to demonstrate that the mean overall satisfaction score at Month 3 visit is statistically greater than that at baseline for the treatment group.

The effectiveness analyses will be performed on the modified intent-to-treat population.

[redacted]

Table of Contents



[redacted]

1. Abbreviations and Terms

Term/Abbreviation	Definition
[redacted]	[redacted]
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AIHS	Allergan Infraorbital Hollows Scale
CFR	US Code of Federal Regulations
eCRF	Electronic case report form
EI	Evaluating Investigator
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed consent
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDFU	Investigational directions for use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	Injection site response
IWRS	Interactive web response system
mITT	Modified intent-to-treat
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TI	Treating Investigator
UADE	Unanticipated Adverse Device Effect

2. Background, Risk and Benefit, and Clinical Rationale

2.1 Background

The youthful face is characterized by a fullness that is supported by striated muscle, subdermal fat, and skin. Predominant components of the skin—collagen, elastin, and glycosaminoglycans, (eg, hyaluronic acid [HA])—lend the skin its strength, elasticity, and plumpness. Chronic reduction in any one of these components as well as a loss of muscle and fat mass contribute to the facial volume loss that characterizes the aging face. The desire to maintain and restore a youthful looking face has led to a widespread increase in the number of cosmetic procedures being performed. While part of this increase has been in the area of surgical procedures, the largest growth in cosmetic procedures has occurred in the area of nonsurgical procedures, including injectable products, such as botulinum toxin, HA, and other dermal fillers.

An early sign of periorbital aging is the development of dark circles under the eyes lending a fatigued and aged appearance to the face (Hirmand 2010). An aged appearance is often caused by a infraorbital hollowing, which is characterized as a sunken appearance of the eye that results in the casting of a dark shadow over the nasal lower eyelid, giving a fatigued appearance despite adequate rest, and is refractory to attempts at cosmetic concealment (Sadick 2007, Sharad 2012). However, infraorbital hollowing is not exclusively associated with age. Mild hollowing has been observed in younger individuals (Hirmand 2010, Huber-Vorlander 2015). The presence of infraorbital hollowing in younger subjects without pseudoherniated lower lid fat or midface ptosis could be explained by tethering of the orbitomalar ligament to the overlying orbicularis oculi and its adherent overlying skin to the inferior orbital rim (Kane 2005).

There are various treatment options for correcting the infraorbital volume loss, both surgically invasive and noninvasive. The use of HA dermal fillers to treat infraorbital hollowing has an advantage over other filler options in that unevenness or overcorrection may be addressed with light massage (Bosniak 2008). Lambros (2007) reported a high degree of subject satisfaction with the use of HA in the treatment of tear troughs. He also reported that most complications were self-limiting and could be treated by massage. The largest disadvantage of HA in the infraorbital area is its temporary volume augmentation. Although treatment can have a long-lasting effect of 1 year or more, its effect is not permanent (Lambros 2007).

VOLBELLA® XC, included in the JUVÉDERM range of products, is a malleable gel that meets the physical constraints that would be experienced with injection and volume expansion. VOLBELLA XC is formulated using a combination of high and low molecular weight HA, which reduces the concentration of crosslinking reagent needed while increasing overall crosslinking efficiency. The final formulation includes a small quantity of noncross-linked HA to decrease extrusion force during injection, and lidocaine (0.3% w/w) to increase patient comfort. In a postmarketing study, VOLBELLA without Lidocaine (CE marked in 2007) was demonstrated to be safe and effective in providing smooth and natural improvement in a variety of facial aesthetic indications (Eccleston 2012), including lip and perioral enhancement (Philipp-Dormston 2014, Raspaldo 2105, Raspaldo 2105a, Taylor 2016). VOLBELLA XC represents an improvement with the addition of 0.3% (w/w) lidocaine hydrochloride to reduce procedural pain.

2.2 Risk and Benefit

As with any skin injection, risks can be posed by the injection procedure itself, the anesthetic agent, and injection of VOLBELLA XC. Unforeseeable risks or results are also a possibility. Risks related to the injection procedure include redness, itching, pain, tenderness, swelling, bruising, and lumps and bumps, which are common to dermal filler injection procedures, in general. The use of a small gauge needle or cannula to deliver VOLBELLA XC used in this study is intended to minimize tissue trauma. Risks associated with the anesthetic agent include allergic reactions that may manifest as an anaphylactic reaction, skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient loss of skin color. The inclusion of 0.3% lidocaine in the formulation is meant to reduce pain during the injection and this should be taken into account when administering concomitant additional anesthetics. Risks associated with treatment to the infraorbital area include injury to the surrounding anatomical structures. There are many superficial arteries of the periorbital area that are distal branches of the ophthalmic artery. In addition, the retinal artery is the proximal branch of the ophthalmic artery. Therefore, arterial occlusion of the retinal artery by direct injection or direct injury to the vessels is a rare but serious risk in this anatomic area (Hirsch 2007). Several dermal fillers, including VOLBELLA XC, have been clinically evaluated to determine their safety and effectiveness in treating infraorbital hollowing. The available data suggest that the injection of HA dermal fillers into the infraorbital area is a safe procedure when administered by trained and experienced practitioners.

Treatment using VOLBELLA XC as an alternative to treatment options for correcting infraorbital volume loss has many benefits. VOLBELLA XC is less invasive, has much lower

rates of infection, has little or no risk of scarring, has no risk of surgery or general anesthesia, and has much shorter recovery times. Furthermore, as an HA-based filler, VOLBELLA XC is much safer than fat injections or particulate fillers. It is anticipated that the safety and effectiveness of treatment to the infraorbital area are similar to those identified in studies of JUVÉDERM products for similar indications.

2.3 Clinical Rationale

VOLBELLA XC was designed specifically for volumizing and has demonstrated safety and effectiveness as a dermal filler for lip and perioral enhancement (Philipp-Dormston 2014, Raspaldo 2105, Raspaldo 2105a, Taylor 2016). The protocol is designed as a pivotal study to collect safety and effectiveness data associated with the use of VOLBELLA XC for correction of infraorbital hollowing in adults.

3. Study Objectives and Clinical Hypotheses

3.1 Study Objectives

The objective of this study is to evaluate the safety and effectiveness of VOLBELLA XC in adult subjects seeking correction of infraorbital hollowing.

3.2 Clinical Hypotheses

The responder rate at Month 3 in the treatment period will be significantly greater than that in the control group at Month 3 in the control period, and the majority of subjects will have clinically significant improvement in infraorbital hollowing at Month 3.

4. Study Design

4.1 Structure

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

4.2 Duration

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

Participation for each subject in the control group will encompass up to 1 month for screening, 3 months for the no-treatment control period, up to 1 month for optional treatment, and 9 months of follow-up after the last treatment (initial or touch-up).

4.3 Treatment Groups and Treatment Regimen

4.3.1 Study Treatment

VOLBELLA XC injectable gel

4.3.2 Control Treatment

No treatment

4.3.3 Methods for Blinding

The Evaluating Investigator (EI) and the image analysis technician will be blinded to treatment. The EI will not be present during the injection procedures. As the image files will be accessed by the blinded image analysis technician, the image files will not reveal subject treatment randomization or the timepoint at which the image was captured.

The Treating Investigators (TIs), study coordinators, and subjects will not be blinded to treatment, but they will secure the randomization and other records (eg, records of study treatments and 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 touch-up treatment is recommended 30 days after the initial treatment (ie, at the Month 1 follow-up visit) [redacted] and both the subject and TI agree that optimal correction has not been achieved. The total injection volume for an individual subject for the initial and touch-up treatments combined is not to exceed 2.2 mL per side.

Treatment group subjects will be offered a repeat treatment after completion of the Month 12 visit. The total injection volume for repeat treatment is not to exceed 2.2 mL per side.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

All medications and treatments are permitted with the exception of the restricted medications and treatments described in Section 4.4.2.

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

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

4.4.2 Prohibited Medications/Treatments

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

During the course of the study, subjects must not:

- be enrolled in another study and may not receive another investigational product in the 30 days prior to study enrollment
- receive permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face
- receive facial tissue augmentation with fat injections above the subnasale; semi-permanent dermal fillers (eg, calcium hydroxyapatite, poly-L-lactic acid) in the temple or midface; or dermal filler injections
- receive botulinum toxin injections above the subnasale
- undergo mesotherapy or receive cosmetic facial procedures (eg, face-lift, brow lift, facial reconstructive surgery, laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) anywhere in the face
- undergo allergen desensitization therapy
- undergo any piercing or tattooing procedures above the subnasale

The use of hyaluronidase for aesthetic purposes (eg, to reverse overcorrection) is not permitted.

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

4.4.3 Special Diet or Activities

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

For 2 days after treatment, it is recommended that subjects avoid unnecessary external compression of the treatment site that could cause displacement or indentation where the product has been placed.

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

For 3 months after treatment, it is recommended that subjects not wear tight-fitting swim goggles.

4.5 Treatment Allocation Ratio

Subjects are randomized at an allocation ratio of 3:1 to treatment with VOLBELLA XC or no treatment control group.

5. Study Population

5.1 Number of Subjects

Up to 175 subjects will be enrolled at up to 15 sites in order to randomize 140 subjects and have an estimated 112 subjects complete the study based on an anticipated 20% screen fail rate and dropout rate of 20% during the study.

5.2 Study Population Characteristics

Adult subjects with infraorbital hollowing who are seeking restoration will be recruited. The randomization target is a minimum of 18 subjects of Fitzpatrick skin phototypes I/II, 18 of phototypes III/IV, and 18 of phototypes V/VI.

5.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Age 22 or over and in good general health
2. Has "Moderate" or "Severe" infraorbital hollowing (grade 2 or 3 on the AIHS) for each eye as assessed by the EI (ie, both eyes must qualify but do not need to have the same score)
3. TI considers the subject's anatomy to be amenable to improvement to an AIHS grade of 0 or 1 (None or Minimal)
4. Is able to complete effectiveness self-assessments without the use of glasses (contact lens use is acceptable if they will be used for all subject self-assessments)
5. Ability to follow study instructions and likely to complete all required visits
6. Written informed consent has been obtained

5.4 Exclusion Criteria

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

1. Has atrophic skin in the tear trough region as determined by the TI
2. Has large lower lid fat pads that would mask improvement, as determined by the TI
3. Has hyperpigmentation in the infraorbital area (does not include dark circles under the eyes not due to hyperpigmentation)
4. Has significant volume loss in the midface
5. Has a cornea that projects farther forward than the most anteriorly projected part of the cheek
6. 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
7. Has ever undergone fat injections above the subnasale or is planning to undergo this procedure during the study
8. Has tattoos, piercings, facial hair (ie, beard, mustache), or scars that would interfere with visual assessment of the infraorbital hollows

9. Has undergone volume augmentation with semipermanent dermal fillers (eg, calcium hydroxyapatite, poly-L-lactic acid) or temporary dermal fillers in the malar area, temples, or around the eyes within 12 months before enrollment or is planning to undergo such treatment during the study
10. Has active or recurrent inflammation or infection in either eye
11. Has ever received a blepharoplasty, facelift, browlift, or is planning to during the study
12. 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
13. Has experienced trauma to the infraorbital area within 6 months before enrollment or has residual deficiencies, deformities, or scarring in the periorbital or cheek areas
14. Has a tendency to develop hypertrophic scarring
15. 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
16. Has active autoimmune disease
17. 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
18. Has received any investigational product within 30 days prior to study enrollment or is planning to participate in another investigation during the course of this study
19. Has begun using any new over-the-counter or prescription oral or topical, anti-wrinkle products within 30 days before enrollment or is planning to begin using such products during the study (subjects who have been on a regimen of such products for at least 30 days are eligible for the study if they intend to continue their regimen throughout the study)
20. Females who are pregnant, nursing, or planning a pregnancy
21. Is an employee (or a relative of an employee) of the TI, EI, or Allergan, or a representative of Allergan
22. Has a condition or is in a situation which in the TI'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

6. Procedures

6.1 Washout or Run-In Intervals

6.1.1 Washout Intervals

Washout Intervals	Medication or Procedure
10 days before treatment	• Ongoing regimen of medications and/or substances known to increase coagulation time (eg, aspirin, ibuprofen, or herbal supplements) NOTE: The 10-day washout period for anticoagulants must continue for 3 days after treatment (initial, touch-up, and repeat) is administered
30 days before enrollment	• Any investigational product

6.1.2 Run-in Intervals

Run-in Intervals	Medication or Procedure
30 days before enrollment	• Over-the-counter or prescription, oral or topical, anti-wrinkle products above the subnasale for subjects who will use such products during the study

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 AIHS prior to initiating enrollment.

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 (AIHS 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 adverse events (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?” Directed questioning and examination will then be done as appropriate and may include referral to a retinal specialist.

Any subject with any ophthalmic signs and symptoms or vision loss will be referred immediately to a retinal specialist for an examination. All reported AEs will be documented.

6.2.1 Screening Visit

At the screening visit, the TI (or designee) will discuss routine alternative treatments that may be available with any subject who is interested in participating in the study. The available alternative treatments include plastic surgery, autologous fat injection, etc; he/she will counsel the subject regarding his/her treatment goals, and the potential benefit and limitations of study treatment. After counseling, if the subject's expectations are not realistic, the TI (or designee) will not proceed with obtaining the subject's signature on the Informed Consent Form (ICF) and will discontinue the subject from the study.

A subject is considered enrolled when he/she has signed the 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 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, 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 EI will evaluate the subject's infraorbital hollowing for each side using the AIHS. Subjects who have an AIHS score of "Moderate" or "Severe" for each infraorbital hollowing will be eligible for the study. Although both infraorbital hollows must qualify, each infraorbital hollow can have a different score (eg, 1 eye can be "Moderate" and the other "Severe").

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 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. Before randomization, subjects will undergo [redacted] imaging. [redacted] 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.

Subjects will be randomized in a 3:1 ratio to the treatment group or to the control group and 1:1 to receive the first treatment in the right or left side. The same order must be used for all treatments. Subjects randomized to the treatment group will complete the validated FACE-Q Appraisal of Lower Eyelids questionnaire and have vision safety assessments performed by the TI. Subjects randomized to the control group will have no additional required procedures for the randomization visit.

6.2.3 Treatment Group

The treatment group will receive treatment at the start of the study and an optional touch-up treatment 1 month later. They will be followed for safety and effectiveness for 12 months with the option for a repeat treatment and an additional month of follow-up at Month 12.

6.2.3.1 Initial Treatment, Touch-up Treatment, and Follow-up

If the subject is randomized to the treatment group, initial treatment should be performed on the same day as randomization. In addition, vision assessments (Snellen visual acuity, confrontational visual fields, and ocular motility) will be performed before treatment. 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 both the right and left treatment area according to the investigational directions for use (IDFU) and Section 9.1.2 of this protocol. The TI will determine the appropriate volume to inject to achieve optimal correction based on clinical experience.

Approximately 30 minutes after treatment, the TI (or designee) will perform vision assessments. The TI will also evaluate treatment characteristics, including injection ease and product moldability, and will record any AEs.

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 3 days after treatment. If any change to vision is reported during a telephone follow-up or unscheduled phone call, the subject will be asked to come in immediately or will be referred to a retinal specialist for further evaluation. Subjects will return for an office visit 14 days after treatment to undergo [redacted] imaging, and the TI (or designee) will perform vision assessments. The subject will not see the blinded EI at the Day 14 visit.

Thirty days after treatment, the subject and the TI will discuss the results of the initial treatment, [redacted], a touch-up may be performed if agreed upon by the subject and TI. The procedures performed after touch-up treatment are the same as those after initial treatment.

For initial treatment and touch-up treatment, details regarding anesthesia use, volume injected, kit numbers, whether needle or cannula was used, characteristics of the procedure (eg, subject assessment of procedural pain), and characteristics of the product (eg, TI evaluation of injection ease and moldability) will be recorded on the eCRF.

Concomitant medications, concurrent 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.

For treatment group subjects, routine follow-up visits for safety and effectiveness will occur at Months 1, 3, 6, 9, and 12 after the last treatment (initial or touch-up). The procedures and evaluations for the follow-up period are listed by visit in Table 2.

6.2.3.2 Repeat Treatment and Follow-up

Repeat treatment is offered to treatment group subjects who complete the Month 12 visit. If accepted, they will return for repeat treatment within 14 days after the Month 12 follow-up visit.

The order in which the infraorbital hollows 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.

Subjects will be followed for 1 month after 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.

6.2.4 Control Group

6.2.4.1 Control Period

Subjects randomized to the control group will complete a 3-month no-treatment control period with office visits at Months 1 and 3. The procedures and evaluations for the control group during the control period are listed by visit in Table 4.

At the Month 3 visit, subjects will be offered an optional treatment after completion of the Month 3 visit. Control group female subjects of childbearing potential who accept optional treatment will take a urine pregnancy test; if the test is positive, the subject will not receive treatment and will be exited from the study. In addition, the TI (or designee) will perform vision assessments. Control group subjects who decline optional treatment will complete the study after the Month 3 visit. The control period concludes after completion of the Month 3 procedures.

6.2.4.2 Optional Treatment, Touch-up, and Follow-up

Control group subjects who have optional treatment will be followed for safety only; no effectiveness assessments will be performed.

Female subjects of childbearing potential who accept optional treatment will take a urine pregnancy test; if the test is positive, the subject will not receive treatment and will be exited from the study. In addition, the TI (or designee) will perform vision assessments.

The optional treatment can occur on the same day as the Month 3 visit, after all visit procedures are complete. 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.

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. Routine follow-up visits for safety will occur at Months 1, 3, 6, and 9 after the last treatment (initial or touch-up). The procedures and evaluations for the optional treatment and follow-up of the control group are listed by visit in Table 5.

6.3 Instructions for the Subjects

During each study visit, subjects will be required to remove all jewelry, make-up, and lipstick, to avoid interference with the digital photographs.

For 10 days before and 3 days after study treatment administration, subjects should avoid using a regimen of anti-coagulation, antiplatelet, or thrombolytic medications; nonsteroidal anti-inflammatory drugs; supplements of Vitamin C or E, garlic, gingko biloba, or ginseng; or other supplements known to increase coagulation time. These precautions are recommended to reduce the risk of posttreatment bleeding or bruising.

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

For 2 days after treatment, it is recommended that subjects avoid unnecessary external compression of the treatment site that could cause displacement or indentation where the product has been placed.

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

For 3 months after treatment, it is recommended that subjects not wear tight-fitting swim goggles.

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

6.4 Unscheduled Visits

An unscheduled visit may occur for safety purposes (eg, if the subject needs to obtain information regarding adverse events or ISRs). An unscheduled visit may also occur to repeat facial digital images if those obtained at the scheduled visit are poor quality images. Applicable procedures will be performed and recorded on the eCRF.

6.5 Early Discontinuation of Subjects

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

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

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

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

6.6 Withdrawal Criteria

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

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

7. Response Measures and Summary of Data Collection Methods

7.1 Effectiveness Measures

7.1.1 Primary Effectiveness Measure

The primary effectiveness measure is the EI assessment of infraorbital hollowing using the AIHS. Separate AIHS scores will be provided for each infraorbital hollow.

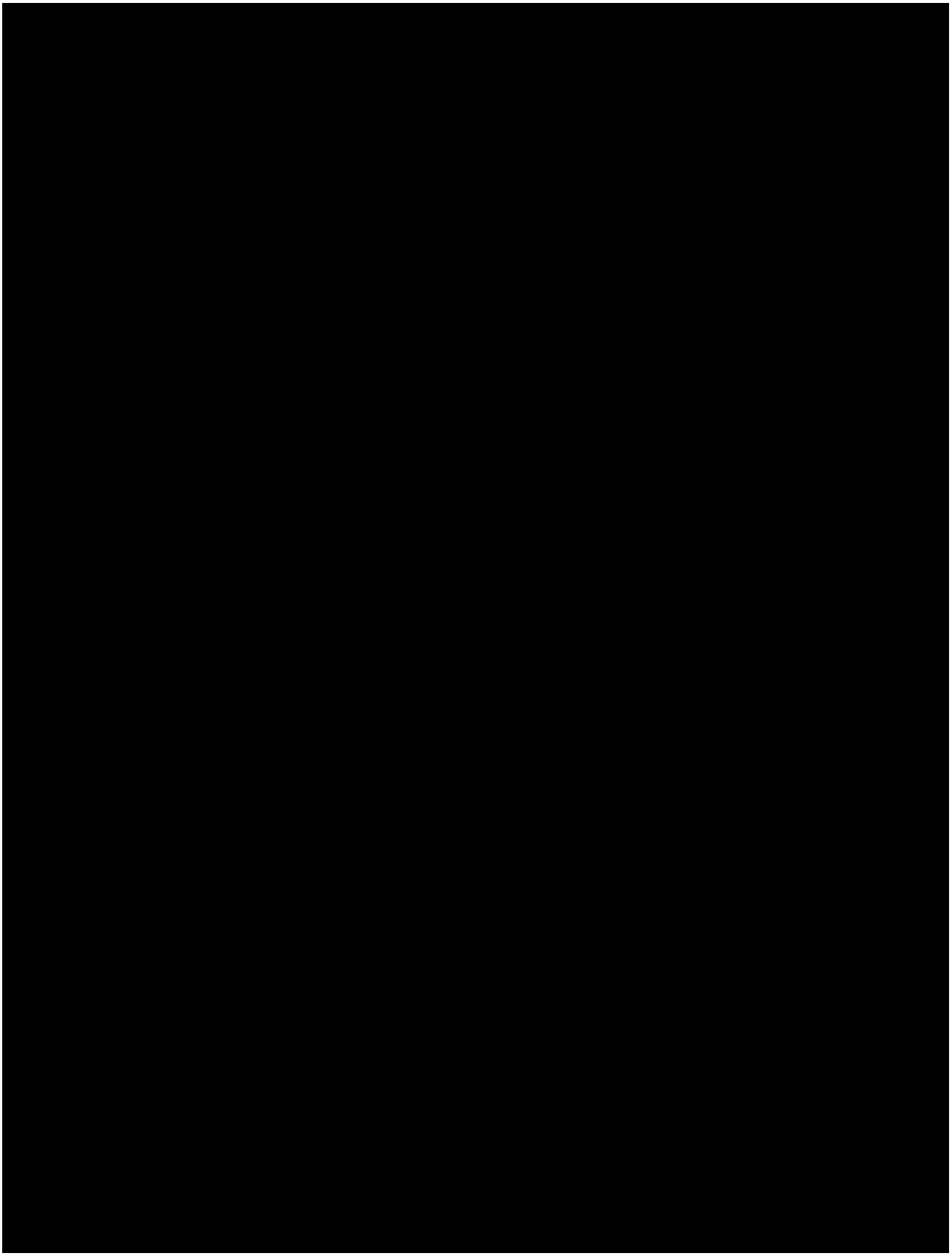
7.1.2 Secondary Effectiveness Measures

Secondary effectiveness measures include independent, noncollaborative assessments by both the EI and the subject of global aesthetic improvement in the infraorbital area using the 5-point GAIS (Table 6) and subject responses on the validated FACE-Q Appraisal of Lower Eyelids questionnaire. For GAIS and FACE-Q questionnaires, 1 overall assessment will be provided to encompass both sides. The GAIS assessment will be completed by comparing the live subject with their photo taken at baseline.

Table 6 5-Point Global Aesthetic Improvement Scale

Score	Grade
2	Much Improved
1	Improved
0	No Change
-1	Worse
-2	Much Worse

[redacted]



7.3 Demographics and Baseline Characteristics

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

7.4 Treatment Characteristics

Treatment characteristics will be evaluated by collecting information on anesthesia usage injection volume, and product moldability (11-point scale where 0 = stiff and 10 = moldable).

7.5 Summary of Methods of Data Collection

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

Subjects will complete the ISR diaries electronically. Sites will save photographs onto supplied electronic media and send the storage device to Canfield Scientific. Alternatively, files containing the facial digital photographs may be directly uploaded to Canfield Scientific from the Canfield Scientific equipment.

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. One database lock is planned after all subjects exit the study.

Descriptive statistics will be presented for key outcome measures. Categorical variables will be summarized with frequency and relative frequency. Continuous variables will be summarized by number of subjects, mean, median, standard deviation, 1st and 3rd quartiles, minimum, and maximum. Where appropriate, 2-sided 95% CIs for population mean, or population proportion, will be provided as part of the descriptive summary.

Every attempt will be made to collect complete data and limit the occurrence of missing data. Imputation of missing data may be used for sensitivity analysis of the primary effectiveness endpoint. 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), receive at least 1 study device treatment, and have baseline and at least 1 post-treatment assessment of the primary effectiveness variable, and subjects who are randomized to the control group and have baseline and at least 1 follow-up assessment of the primary effectiveness variable
- safety population: all treated subjects

Unless specified otherwise, all effectiveness analyses will be performed on the mITT population using the "as-randomized" assignment for each subject (ie, if a subject randomized to the control group is treated inadvertently at the start of the study, the assessments for that subject will nonetheless be included in the control group analysis). All safety analyses will be conducted using the safety population.

8.2 Collection/Derivation of Primary and Secondary Effectiveness Assessments

8.2.1 Primary Effectiveness Variable

The primary effectiveness variable is the responder rate at Month 3 after the last treatment. A responder is defined as subjects who show at least 1-point improvement from baseline on the AIHS in both infraorbital areas based on EI assessment. Baseline is defined as the EI assessment at screening.

8.2.2 Secondary Effectiveness Variables

The secondary effectiveness variables include EI and subject assessed GAIS responder rates, and subject mean overall satisfaction score on the validated FACE-Q Appraisal of Lower Eyelids questionnaire at Month 3 after the last treatment.

8.3 Hypothesis and Methods of Analysis

8.3.1 Primary Effectiveness Analyses

For the primary effectiveness analysis, a 2-sided, Fisher's exact test at the 5% level will be used to test whether the responder rate at Month 3 in the treatment period is significantly greater than that in the control group at Month 3 in the control period.

8.3.2 Secondary Effectiveness Analyses

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

- responder rates with 95% CI for the treatment group based separately on the EI and subject assessments of GAIS, where a "responder" is a subject who shows improvement in the overall aesthetic assessment in the infraorbital area (Improved or Much Improved on GAIS) at the Month 3 visit,

- descriptive summary of the change from baseline to Month 3 visit in the overall scores of Appraisal of Lower Eyelids module of the validated FACE-Q questionnaire; a 2-sided paired t-test at the 5% level to demonstrate that the mean overall satisfaction score at Month 3 visit is statistically greater than that at baseline for the treatment group.

No multiplicity adjustment will be made for the 2 GAIS responder rates, since these endpoints are descriptive in nature.

[redacted]

8.4 Subgroup Analyses

The primary effectiveness endpoint will be summarized by baseline AIHS score, volume injected, investigational site, and injection by needle/cannula use. Details will be provided in the statistical analysis plan.

8.5 Sample Size Calculation

[redacted].

8.6 Interim Analyses

No interim analysis is planned.

9. Materials

9.1 Study Treatment

9.1.1 Product Description

VOLBELLA XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous, gel implant (dermal filler). It consists of cross-linked HA produced by *Streptococcus* species of bacteria, formulated to a concentration of 15 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

9.1.2 Instructions for Use and Administration

For investigational use in this clinical study, VOLBELLA XC dermal filler will be injected to the infraorbital and adjacent area using the supplied needles (32 G ½ inch) or 27 G 1½ inch cannulas and aseptic injection technique to inject VOLBELLA XC submuscularly/ supraperiostially. [redacted] The TI should inject the treatment slowly using gentle, even pressure on the syringe in accordance with the randomization scheme and the DFU, which will be provided to the TI.

TIs must be experienced in the use and administration of HA implants and be practicing in the field of aesthetic medicine, plastic/cosmetic/reconstructive surgery, or dermatology.

9.1.3 Treatment Regimen Adjustments

The TI will determine the appropriate volume of VOLBELLA XC to inject based on his/her clinical experience, but the maximum volume is not to exceed 2.2 mL per side for initial and touch-up treatments combined, and not to exceed a maximum total volume of 2.2 mL per side for repeat treatment.

9.2 Other Study Supplies

Allergan will provide logarithmic eye charts for testing visual acuity, digital imaging equipment, and other supplies specific to this study (eg, 32 G ½ inch needles and 27 G 1½ inch cannulas). The investigational site is responsible for urine pregnancy tests, routine supplies related to device administration and follow-up visits (eg, antiseptics, drapes, gloves, gauze, anesthesia, ice packs, blood pressure cuff, internet connection for IWRS and eCRF completion).

10. Study Administration Procedures

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

10.1 Subject Entry Procedures

10.1.1 Overview of Entry Procedures

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

- collection of demographic information
- collection of height, weight, and vital signs
- collection of Fitzpatrick skin phototype and history of sun exposure
- collection of smoking history
- collection of medical/surgical/cosmetic/dental procedures history
- administration of urine pregnancy test to female subjects of childbearing potential
- evaluation by the EI of infraorbital hollowing using the AIHS
- evaluation of inclusion/exclusion criteria

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

10.1.2 Informed Consent and Subject Privacy

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

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

10.1.3 Method for Assignment to Treatment Groups

At the time of randomization (ie, at or within 30 days after screening/signing of the ICF), eligible subjects will be assigned to 1 of 2 treatment groups (treatment and control) in a 3:1 ratio to receive VOLBELLA XC or to the control group. Additionally, all subjects will be randomized in a 1:1 ratio to receive the first treatment on the right or left side. The same randomization of treatment order will be used for all treatments. All randomization will be based on a central randomization schedule. Block randomization will be used and will be

stratified by investigational site. An automated IWRS will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan. Study treatments will be labeled with kit numbers. The IWRS will provide the site with the specific kit number(s) for each randomized subject at the time of randomization and at each subsequent treatment visit. Sites will dispense treatment according to the IWRS instructions provided by the system.

10.2 Compliance with Protocol

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

10.3 Pregnancy

If a female 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 11.3 and 11.4.

10.4 Study Termination

If conditions arise during the study that indicate that the study or an investigational site needs to be terminated, Allergan, the TI, monitor, IRB, and/or regulatory agencies will discuss the

situation and take appropriate action after consultation. Conditions that may warrant termination of the study or site include, but are not limited to:

- the discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- the decision on the part of Allergan to suspend or discontinue testing, evaluation, or development of the study device
- failure of the TI to comply with pertinent national or state regulations, IRB-imposed conditions, or protocol requirements
- TI submission of knowingly false information to Allergan, a study monitor, the IRB, or any regulatory agency
- If a vascular embolic AE leading to skin necrosis, vision loss, or stroke occurs, all treatments at the investigational site will be suspended while the circumstances of the event are investigated. If the event is confirmed to be a vascular embolic event and related to VOLBELLA XC treatment, Allergan will suspend any further enrollment and treatments at the investigational site while performing a root cause analysis. If the AE is a result of deviation from the injection procedure, the investigator may be retrained and allowed to continue enrolling subjects. If the event is not a result of deviation from the injection procedure, all enrollment and treatments at all investigational sites will be halted until the event can be characterized, and a strategy to avoid further AEs can be developed.

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.

Although the risk of developing a serious complication is small, the TI and the research staff will monitor each subject closely, and, if a complication occurs, they will use their medical

judgment to do whatever is necessary to treat the problem. If subjects have any ongoing treatment-related SAEs at the time of the final visit, they must continue to be followed up until resolution of these events or the subject condition is considered stable by the TI. After the final visit, the subject will resume receiving the standard medical care according to the standard care of the clinic.

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

11.1 Definitions

11.1.1 Adverse Event

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

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

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

The following is a list of known potential AEs, including those related to visual symptoms:

- Redness, swelling, or a rash, which may be associated with itching, pain on pressure, after the injection
- Pain at injection site

- Bruising
- Nodules or “lumpiness” at the injection site
- Discoloration of the injection site
- Rare cases of allergy, severe sensitivity, localized inflammation and abscesses
- Very occasionally, delayed side effects can occur many months after the treatment. These side effects may appear as red lumps showing up underneath the skin, or intermittent episodes of swelling.
- In rare circumstances, facial fillers have been injected into blood vessels causing blockage and embolization which can result in skin necrosis, ulceration, or vision changes. Risks to vision include complete blindness, partial blindness, blurred vision, double vision, loss of peripheral vision, loss of a portion of the visual field or anterior segment ischemia (characterized by decreased vision and pain). These effects can be temporary or permanent but are rare.
- Swelling or edema around the eye following an injection can result in a temporary decrease of vision.
- In rare circumstances, facial fillers have been associated with granulomas, which are small inflammatory nodules under the skin.

Unforeseeable risks or results are also a possibility. The risk of developing a serious complication is small. If a complication occurs, subjects will be advised to contact the TI who will use his/her medical judgment to do whatever is necessary to treat the subject. In the event of visual disturbance, the subject must also be referred to a retinal specialist for evaluation and for appropriate care.

11.1.2 Adverse Event of Special Interest

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

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

See Section 11.4 for procedures for reporting an SAE/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 adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.

See Section 11.3 for procedures for reporting an ADE.

11.1.5 Serious Adverse Device Effect

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

See Section 11.4 for procedures for reporting a SADE.

11.1.6 Unanticipated Adverse Device Effect

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

11.1.7 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 adverse event. The severity assessment for a clinical adverse event 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
AESI	Record on AE eCRF and fax/email to Allergan within 24 hours of awareness	Signing ICF	Last subject visit
SAEs, SADEs	Record on SAE Form and fax/email to Allergan within 24 hours of awareness	Signing ICF	Last subject visit

11.3 Procedures for Reporting an AE or ADE

All AEs or ADEs occurring during the study period (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 AESI 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 fax or email. Allergan will notify FDA of any AESI 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 the fax number/email 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 device-related. For other SAEs, notify the governing IRB as required by the IRB, local regulations, and the governing health authorities.

12. Administrative Issues

12.1 Protection of Human Subjects

12.1.1 Compliance with Informed Consent Regulations

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

12.1.2 Compliance with IRB Regulations

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

12.1.3 Compliance with Good Clinical Practice

This protocol is to be conducted in compliance with GCP guidelines, and with ethical principles for clinical research.

12.1.4 Financial Disclosure/Certification Form

In accordance with 21 CFR 54.4, the Investigator and any 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, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information [HIPAA]).

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

12.4 Documentation

12.4.1 Source Documents

Source documents may include a subject's medical records, hospital charts, laboratory notes, device accountability records, investigator assessments of infraorbital hollowing using the AIHS, investigator and subject assessments of global aesthetic improvement in the infraorbital area using the GAIS, subject questionnaires and diaries, photographic negatives or digital images, clinic charts, the TI's subject study files, results of pregnancy tests, and results of any other diagnostic tests such as X-rays, laboratory tests, and magnetic resonance imaging. The SAE Form and Pregnancy Surveillance Form are also considered source documents. The TI's copies of the eCRFs serve as part of the TI's record of a subject's study-related data.

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

- Subject's name
- Subject's contact information
- Date that the subject entered the study and subject number assigned from IWRS
- Study title and/or the protocol number and study Sponsor
- A statement that IC was obtained, including the date and a statement that HIPAA Authorization or other country and local subject privacy required documentation for this study has been obtained, including the date
- Details of the injection procedure including anesthetic used, volume injected, ease of injection, details regarding molding and massage, kit numbers of study device injected, subject's assessment of procedural pain
- Dates of all subject visits

- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications are to be recorded.)
- Occurrence and status of any AEs
- Date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation
- Results of laboratory tests performed by the site (eg, urine pregnancy tests)

12.4.2 Case Report Form Completion

The TI is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. 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 International Conference on Harmonisation (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

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

Protocol 1932-701-008
Kit# VVVVV
Lot# CSVVVV
CAUTION - Investigational Device.
Limited by Federal (or United States) law to Investigational Use

Use as directed by protocol

Each kit of VOLBELLA XC contains 2 blisters, each containing 1 syringe prefilled to 0.55 mL and 2 single-use sterile needles (32G ½ inch) specifically intended for injecting VOLBELLA XC.

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.

VOLBELLA XC must be stored at room temperature (up to 25°C) 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 identification number, device serial/lot number, date of implantation, and date of explantation if applicable. Study device accountability will be performed within IWRS according to the instructions provided by the system. The study product must be dispensed to study subjects by an appropriately qualified person and is to be used in accordance with the protocol under the direct supervision of a study TI.

12.5.4 Return of Study Devices

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

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

12.6 Monitoring by Allergan

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

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

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

12.7 Testing of Biological Specimens

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

12.8 Publications

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

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14. Protocol Amendment Summary

Version Date/ Amend. No.	Changes to Protocol
dd Oct 2017/1	• Header – added "Amendment 1" throughout • Title page - added Amendment 1 to the study number • Investigator Signature page - added Amendment 1 to the study number • Synopsis (STUDY DESIGN) and throughout - corrected the scale name (Allergan Infraorbital Hollows Scale) • Synopsis (STUDY DESIGN) – clarified that all subjects will be randomized 1:1 to receive the first treatment on the right or left side; deleted assessment of "transient puffiness" after treatment • Synopsis (STUDY DESIGN) – clarified that GAIS is at Months 1 and 3 only for control subjects • Table of Contents – updated to include Section 14 [redacted] • Section 1 – Abbreviations and Terms – corrected the scale name (Allergan Infraorbital Hollows Scale) • Section 5.2 - clarified that the randomization targets for different Fitzpatrick skintypes are a minimum of 18 • Section 7.1.2 – added "The GAIS assessment will be completed by comparing the live subject with their photo taken at baseline". • Section 8 – added that continuous variables will be summarized by 1st and 3rd quartiles • Section 8.1 – clarified that the mITT had at least 1 follow-up assessment of the primary effectiveness variable • Section 8.3.4 – clarified that AEs that occur before initial treatment will be listed, but not summarized • Section 10.1.3 – clarified that "all" subjects will be randomized in a 1:1 ratio to receive the first treatment on the right or left side. • Section 14 – added protocol amendment summary

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Protocol 1932-701-008_Amd 1

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Approval Date: 10-Oct-2017