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Study Title:	A multicenter, evaluator-blinded, randomized, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUX™ XC injectable gel for restoring jawline definition
Protocol Number:	V25L-002 Amendment 2
Product Name:	JUVÉDERM VOLUX™ XC injectable gel
Development Phase:	Pivotal
Sponsor:	Allergan Sales LLC 2525 Dupont Drive Irvine, CA 92612
Manufacturer:	Allergan
Safety reporting:	Fax: +1-877-605-4524 or +1-714-796-9567 Email: DL-LC-Global_Safety_Reporting@Allergan.com

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

INVESTIGATOR SIGNATURE PAGE

NAME of INVESTIGATOR:
PROTOCOL NUMBER: V25L-002
AMENDMENT NUMBER: 2

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices, and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

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

Investigator Printed Name	Signature	Date

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Synopsis

NUMBER AND TITLE OF STUDY:
V25L-002: A multicenter, evaluator-blinded, randomized, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUX™ XC injectable gel for restoring jawline definition

DEVELOPMENT PHASE: Pivotal

STUDY CENTERS: Up to 20 centers in the United States

NUMBER OF SUBJECTS: Up to 280 subjects will be enrolled and up to 216 subjects will be randomized.

OBJECTIVES: The objectives of this study are to evaluate the safety and effectiveness of JUVÉDERM VOLUX™ XC (hereafter, VOLUX XC) injectable gel in adults seeking to restore jawline definition.

Study design:

This is a multicenter, evaluator-blinded, randomized, parallel-group, controlled study of the safety and effectiveness of VOLUX XC hyaluronic acid (HA) injectable gel to restore a loss of jawline definition. Successfully screened subjects will be randomized to either a treatment or control group (3:1 ratio, respectively).

Subjects randomized to the treatment group will receive treatment on Day 1. After treatment completion (initial and touch-up if touch-up administered), they will be followed for safety and effectiveness for 12 months, with an optional maintenance treatment at Month 12 and additional 3 months of follow-up for safety and effectiveness.

Subjects randomized to the control group will complete a 6-month no-treatment control period. After control period completion, they will have the option to exit the study or receive a delayed-treatment. After treatment completion (initial and touch-up if touch-up administered), subjects will be followed for effectiveness for 6 months and for safety for 12 months without optional maintenance treatment. After follow-up completion (12 months), they will exit the study.

At the Screening visit, after written informed consent (IC) has been given, the Treating Investigator (TI, or a designee) will document the subject's demographics, height, weight, vital signs, Fitzpatrick skin phototype, race, and history of sun exposure, smoking and tobacco use, and medical, surgical, dental, and cosmetic procedures. Female subjects of childbearing potential will undergo urine pregnancy testing. Subjects will undergo 3-dimensional (3D) facial digital images. The Evaluating Investigator (EI) will rate the subject on the 5-grade photonumeric Allergan Loss of Jawline Definition Scale (ALJDS) to determine eligibility for the study. The TI will ensure the subject's anatomy is amenable to at least 1-grade improvement on the ALJDS.

Treatment group:
Before treatment on Day 1, for subjects randomized to the treatment group, the following activities will be performed:

- Subject assessments:
  - FACE-Q Satisfaction with Lower Face and Jawline questionnaire
  - FACE-Q Appraisal of Lines: Marionette questionnaire
  - Jaw Functional Limitation Scale
- EI assessment of facial sensation
- Recording of subject pronunciation video
- TI (or designee) assessment of vision (Snellen visual acuity, confrontational visual fields, and ocular motility)

The TI will use supplied 27 G 1/2" needles and/or 25 G 1 1/2" cannulas to inject VOLUX XC to the pre- and post-jowl sulci, chin, marionette lines, and angle of the mandible to restore jawline definition, provide a smooth contour, and achieve an aesthetically pleasing result. Topical or local anesthesia or ice will be applied as necessary. Injectable anesthesia may also be used but must be limited to the treatment area and cannula insertion site.

On the day of treatment, after injection, the following activities will be performed:

- TI assessments
  - product moldability
  - adverse events (AEs)

- recording of concomitant medications and procedures
- TI (or designee) assessments
  - Vision (Snellen visual acuity, confrontational visual fields, and ocular motility) approximately 30 minutes after treatment
- Subject assessments
  - procedural pain on an 11-point scale
  - daily safety e-diary to record the presence and severity of injection site responses (ISRs) for up to 30 consecutive days after treatment starting on the day of treatment.

Subjects will receive a safety follow-up telephone call at Day 3. If any change to vision is reported during a telephone follow-up or unscheduled phone call, the subject will be asked to come in to the investigational site immediately or will be instructed to receive appropriate care, which may include referral to a retinal specialist. Subjects will return for an office visit at Day 14 to undergo 3D facial digital imaging and complete the Jaw Functional Limitation questionnaire; at that visit, the TI will also perform all safety assessments and the TI (or designee) will perform vision assessments. The subject will not be assessed by the EI at the Day 14 Visit.

At Day 30, if the TI judges that an ALJDS score improvement of at least 1 grade has not been achieved on each side, a touch-up treatment is recommended. If the TI judges that an ALJDS score improvement of at least 1 grade has been achieved on each side, a touch-up may be performed if agreed upon by the subject and the 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.

Follow-up visits for safety and effectiveness will occur at 1, 3, 6, 9, and 12 months after initial and touch-up, if applicable, are complete. At each visit, the following activities will be performed:

- 3D facial digital imaging
- Recording of pronunciation video
- EI effectiveness assessments
  - ALJDS
  - improvement in jawline area using the Global Aesthetic Improvement Scale (GAIS)
- EI safety assessments
  - facial sensation
- TI safety assessments
  - AEs
  - recording of concomitant medications and procedures
- Subject assessments
  - FACE-Q Satisfaction with Lower Face and Jawline questionnaire
  - Subject's Satisfaction with Treatment
  - Natural Look and Natural Feel of the treatment area
  - Subject's willingness to recommend the treatment (Month 6 and Month 12 visits only after initial treatment, and Month 3 after optional maintenance treatment)
  - FACE-Q Appraisal of Lines: Marionette
  - Jaw Functional Limitation Scale questionnaire
  - improvement in jawline area using the GAIS

After completion of the Month 12 Visit, subjects will be offered an optional maintenance treatment. Subjects who decline maintenance treatment will exit the study. Subjects who agree to receive maintenance treatment will be followed for 3 additional months and then exit the study. The procedures and assessments to be performed at maintenance treatment and at the 4 follow-up visits (Day 3, Day 14, and Months 1 and 3) after maintenance treatment are identical to those after the initial treatment, with the exception that no touch-up will be offered and the product characteristics won't be recorded.

Subjects who are randomized to the treatment group and decide to exit the study at any point before the Month 12 Visit must complete the Early Exit Visit procedures in addition to all applicable visit procedures.

Control group: Subjects randomized to the control group will complete a 6-month no-treatment control period following randomization with office visits at Months 1, 3, and 6. At each of these office visits, the following activities will be performed:

- 3D facial digital imaging

- Recording of pronunciation video
- EI effectiveness assessments
  - ALJDS
  - improvement in the jawline definition using the GAIS
- EI safety assessment of facial sensation
- TI safety assessments
  - AEs
  - recording of concomitant medications and procedures

Subjects in the control period who decide to exit the study at any point before the Month 6 Visit must complete the Early Exit Visit procedures in addition to all applicable visit procedures.

After the Month 6 procedures are complete, subjects will be offered to enter the delayed-treatment period. During this part of the study they will receive treatment (initial with optional touch-up) after which they will be followed for safety and effectiveness for 6 months:

- 3D facial digital imaging
- Recording of pronunciation video
- TI safety assessments
  - AEs
  - recording of concomitant medications and procedures
- TI (or designee) safety assessments
  - Vision (Snellen visual acuity, confrontational visual fields, and ocular motility [before and approximately 30 minutes after treatment, and Day 14 after treatment])
- EI effectiveness assessment
  - ALJDS
  - improvement in jawline area using the GAIS
- EI safety assessment of facial sensation
- Subject assessments
  - procedural pain on an 11-point scale
  - daily safety e-diary to record the presence and severity of ISRs for up to 30 consecutive days after treatment starting on the day of treatment.
  - Jaw Functional Limitation Scale questionnaire
  - FACE-Q Satisfaction with Lower Face and Jawline questionnaire
  - improvement in jawline area using the GAIS

Control subjects who receive optional treatment will also complete safety phone calls at 9 and 12 months.

Control subjects in the delayed-treatment period who decide to exit the study at any point before the Month 6 Visit must complete the Early Exit Visit procedures in addition to all applicable visit procedures.

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION:

Adults seeking treatment to restore jawline definition.

INCLUSION:

1. Age 22 or over and in good general health
2. Has "Moderate" or "Severe" loss of jawline definition as determined by the EI using the ALJDs (Grade 2 or 3 on the ALJDS) on both sides. The grade does not have to be the same on both sides, but must be Grade 2 or 3
3. TI considers the subject's jaw amenable to an improvement of at least 1 grade on the scale for the jawline definition
4. Ability to follow study instructions and likely to complete all required visits
5. Written IC has been obtained

EXCLUSION:

1. Has ever received permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study
2. Has ever undergone fat injections in the malar, chin or jawline area or is planning to undergo this procedure during the study
3. Has facial tattoos, piercings, hair (ie, beard, mustache), or scars below the subnasale that would interfere with visual assessment of the chin or jaw area
4. Has undergone semipermanent dermal filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) below the subnasale within 36 months before enrollment or is planning to undergo such treatment during the study
5. Has undergone dermal filler injections in the malar, chin or jawline area within 12 months before enrollment or is planning to undergo this procedure during the study
6. 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 in the chin, masseter, perioral area, or platysmal bands within 6 months before enrollment or is planning to undergo any of these procedures during the study
7. Has received deoxycholic acid treatment in the submental region in the last 6 months.
8. Has severe midface volume deficit such that restoration of the lower face volume would have an aesthetically unpleasant outcome, as determined by the TI
9. Has severe submental fat, as determined by TI
10. Has severe skin laxity that can interfere with visual assessment of the chin or jaw area, as determined by TI
11. Has a significant facial asymmetry, including but not limited to asymmetry due to trauma, as determined by TI
12. Has experienced trauma to the chin and jaw area within 6 months before enrolment or has residual deficiencies, deformities, or scarring, as determined by TI
13. Has a tendency to develop hypertrophic scarring
14. Has active autoimmune disease
15. Has current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, in chin or masseter
16. Has a history of severe reactions (anaphylaxis) or allergy to lidocaine, HA products, or *Streptococcal* protein
17. Is on a regimen of anti-coagulation therapy (eg, warfarin, clopidogrel)
18. Is on a regimen of medications (eg, aspirin or ibuprofen) or other substances known to increase coagulation time (eg, herbal supplements with garlic or gingko biloba) within 10 days of undergoing study device injection (study device injection may be delayed as necessary to accommodate this 10-day washout period)
19. 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
20. Has begun using any new over-the-counter or prescription oral or topical, anti-wrinkle products below the subnasale 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)
21. Is planning to undergo orthodontic treatment (eg, removal of braces, jaw surgery, headgear) during the study, with the exclusion of prophylaxis and dental filling. Dentures are acceptable if stable.
22. Females who are pregnant, nursing, or planning a pregnancy during the course of the study.
23. Is an employee (or a relative of an employee) of the TI, EI, Allergan, or a representative of Allergan
24. 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:
VOLUX XC injectable gel with lidocaine will be administered via supplied needles (27 G 1/2") or cannula (25 G 1 1/2") to the pre- and post-jowl area, chin, marionette lines, and angle of the mandible. Appropriate injection volume for the jawline will be determined by the TI but must not exceed a maximum total volume of 8.0 mL for initial and touch-up treatments combined. Injection volume for maintenance treatment must not exceed 8.0 mL.

DURATION OF STUDY: Study duration will be 12 to 17 months for the treatment group and 6 to 20 months for the control group. **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), an option for maintenance treatment at Month 12, and an additional 3 months of follow-up after maintenance treatment. **Control group**: up to 1 month for screening, a 6-month no-treatment control period, after which they have the option to exit the study or receive treatment, and if treated, 1 month for treatment and 12 months for follow-up after the last treatment (initial or touch-up).

RESPONSE MEASURES:

Effectiveness:

The primary effectiveness measure is the EI assessment of loss of jawline definition using the ALJDS. Each side of the jawline (left and right) will be assessed independently. [redacted]

Secondary effectiveness measures include independent, noncollaborative assessments by both the EI and the subject of global aesthetic improvement in jawline area using the 5-point GAIS and subject responses on the validated FACE-Q Satisfaction with Lower Face and Jawline questionnaire. For GAIS and FACE-Q questionnaires, 1 overall assessment will be provided to encompass both sides.

Other effectiveness measures include:

- [redacted]

Safety: Safety measures include:

- Subject assessment of procedural pain during treatment on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable)
- Subject assessment of jaw function using the 20-item Jaw Functional Limitation Scale questionnaire
- Presence, severity (mild, moderate, or severe), and days with ISRs recorded by subjects in daily safety diaries for 30 days after any treatment (initial, touch-up, and maintenance)
- EI assessment of facial sensation
- Pronunciation video recording
- AEs observed by the TI or reported to the TI by the subject
- Snellen visual acuity, confrontational visual fields, and ocular motility assessed by TI (or designee)
- Monitoring of concomitant medications and concurrent procedures

Vital sign measurements, including blood pressure (systolic and diastolic), temperature, pulse, and respiratory rate, and a urine pregnancy test for female subjects of childbearing potential will also be performed.

STATISTICAL METHODS:

Sample Size Calculation: A sample size of 120 subjects in the treatment group and 40 subjects in the control group will provide > 99% power to detect a difference of at least 40% in the responder rates between the groups. This calculation is based on a 1-sided Fisher's exact test at the 2.5% level. The treatment group is assumed to have at least 80% responder rate and the control group will have at most 40% responder rate. Assuming a screen fail rate of 25% and a drop-out rate of 15% between randomization and the Month 6 visit, up to 280 subjects will be enrolled, with at least 144 subjects and at most 162 subjects randomized to the treatment group and at least 48 subjects and at most 54 subjects randomized to the control group (3:1 ratio).

This sample size is considered to be adequate to determine the safety profile of the product in the jawline area. Assuming a screen fail rate of 25%, a 5% drop-out rate between randomization and initial treatment for the treatment group, and a 15% drop-out rate between randomization and optional treatment for the control group, it is estimated that at least 176 subjects will be treated in the study. With 176 treated subjects, there is at least 92% power to detect an AE related to treatment with an incidence rate of 1.5% in the population using a 1-sided exact binomial test at the 2.5% level.

Effectiveness:

The primary effectiveness endpoint is the responder rate at Month 6. A responder is defined as a subject who shows at least a 1-point improvement on the ALJDS from baseline based on EI assessment on both sides of the jaw. Baseline is defined as the last assessment by EI prior to randomization.

One-sided Fisher´s exact test with 2.5% significance level will be used to compare responder rates between the treatment and control groups. If the 1-sided p-value is < 0.025 and the responder rate for the treatment group is statistically greater than 50%, then the primary effectiveness endpoint will be considered met. The primary effectiveness analysis will be performed on the intent-to-treat (ITT) population, which includes all randomized subjects.

Secondary effectiveness endpoints include EI and subject assessed GAIS responder rates, where a "responder" is a subject who shows improvement in the overall aesthetic assessment in jawline area (Improved or Much Improved on GAIS) at the Month 6 Visit, and subject mean overall satisfaction on the validated FACE-Q Satisfaction with Lower Face questionnaire at Month 6.

Secondary efficacy analyses will include:

- 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 jawline area (Improved or Much Improved on GAIS) at the Month 6 visit.
- Descriptive summary of the change in overall score of subject's satisfaction with lower face and jawline since baseline at the Month 6 visit based on the treatment group subjects' responses on the validated FACE-Q Satisfaction with Lower Face and Jawline questionnaire; a 2-sided paired t-test at the 5% level to demonstrate that the mean overall satisfaction score at Month 6 is statistically greater than that at baseline. This test is only performed if the primary endpoint is met.

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

Safety:

Subject assessment of procedural pain score, and of jaw function using the 20-item Jaw Functional Limitation Scale questionnaire will be summarized descriptively. Assessments from the pronunciation recordings and facial sensation assessment will be summarized descriptively. Snellen visual acuity, confrontation visual fields, and ocular motility assessments assessed by the TI (or designee) will be summarized descriptively. ISRs will be summarized by maximum severity and ISR days for initial, touch up, and maintenance treatments, separately. Summaries will include the incidence rate for each ISR. Treatment-emergent AEs and treatment-related AEs (ie, device- or procedure-related) will be summarized by System Organ Class and preferred term, and severity. In addition, treatment-related AEs will also be tabulated by duration, severity, causality, action taken, and outcome. The safety analyses will be performed on the safety population.

Table of Contents

List of Tables

Table 1 Screening Visit Procedures: All Subjects

Study Period	Screening
Visit Window	30 days
Written informed consent	X
Demographics	X
Height, weight, and vital signs[a]	X
Fitzpatrick skin phototype and sun exposure	X
Smoking and tobacco use history	X
Medical/surgical/cosmetic/dental procedures history	X
ALJDS (EI)[b]	X
Inclusion/Exclusion criteria	X
3D facial digital imaging	X
Urine pregnancy test[c]	X

3D = 3-dimensional; ALJDS = Allergan Loss of Jawline Definition Scale; EI = Evaluating Investigator

[a] Vital signs include blood pressure (systolic and diastolic, while seated), temperature, pulse, and respiratory rate.

[b] [redacted]

[c] For female subjects of childbearing potential. A female subject is not considered of childbearing potential if she has been menopausal for at least 1 year or does not have a uterus at the time of study entry.

Table 2 Schedule of Visits and Procedures: Treatment Group (Treatment Period)

Study Period	Day 1 Rand[a] / ITx	Day 3 After ITx	Day 14 After ITx	Day 30 Optional TTx[b]	Day 3 After Optional TTx	Day 14 After Optional TTx	Early exit visit[c]
Visit Window		-1/+2 Days	± 3 Days	-2/+10 Days	-1/+2 Days	± 3 Days	
Inclusion/Exclusion criteria[d]	X						
Urine pregnancy test[e]	X			X			X
3D facial digital imaging			X	X[f]		X	
Pronunciation video recording	X[f]			X[f]			
Randomization (IWRS)	X						
FACE-Q Satisfaction with Lower Face and Jawline (subject)	X[f]						
FACE-Q Appraisal Lines: Marionette	X[f]						
Jaw Functional Limitation Scale (subject)	X[f]		X	X[f]		X	
Facial sensation assessment (EI)	X[f]			X[f]			
Snellen visual acuity (TI or designee)	X[g]		X	X[g]		X	
Confrontational visual fields (TI or designee)	X[g]		X	X[g]		X	
Ocular motility (TI or designee)	X[g]		X	X[g]		X	
Pretreatment anesthesia	X			X			
Treatment (TI)	X			X			
Injection ease and product moldability (TI)	X			X			
Procedural pain (subject)	X			X			
ALJDS (EI)[h]				X			
Safety telephone call		X			X		
Weight							X
Subject safety e-diary[i]	Continuous			Continuous			
Concomitant Medications, Procedures, Therapies	Continuous						X
Adverse Events	Continuous						X

[redacted].

3D = 3-dimensional; ALJDS = Allergan Loss of Jawline Definition Scale; EI = Evaluating Investigator; GAIS = Global Aesthetic Improvement Scale; ITx = initial treatment; IWRS = interactive web response system; Rand = Randomization; TI = Treating Investigator; TTx = touch-up treatment

[a] Randomization must occur within 30 days of screening.

[b] A touch-up treatment is recommended on Day 30 if the TI determines that the subject has not achieved at least a 1-grade improvement on ALJDS on each side. If the TI judges that an ALJDS score improvement of at least 1 grade has been achieved on each side, a touch-up may be performed if agreed upon by the subject and the TI. If a touch-up treatment is not performed, then complete Month 1 visit procedures (Table 3) instead of the Day 30 visit procedures.

[c] Subjects who discontinue early are to complete applicable study visit procedures and Early Exit Visit procedures.

[d] Inclusion criteria 2 and 3 are not repeated.

[e] For female subjects of childbearing potential; must be confirmed negative prior to injection.

[f] Done before study treatment.

[g] On initial and touch-up treatment days, vision assessments performed before treatment and approximately 30 minutes after treatment.

[h] [redacted]

[i] The subject safety e-diaries are to be completed following each injection starting on the date of treatment. The diary is to be completed consecutively on a daily basis, until the subject returns for a touch-up/Month 1 Visit (as appropriate) or for 30 consecutive days, whichever is shorter.

Table 3 Schedule of Visits and Procedures: Treatment Group (Follow-up/Maintenance Treatment Period)

Study Period[a]	Month 1	Month 3	Month 6	Month 9	Month 12 / Study Exit Visit[b]	MTx	Day 3 After MTx	Day 14 After MTx	Month 1 After MTx	Month 3 After MTx/Study Exit Visit	Early Exit Visit[c]
Visit Window	-2/+10 Days	± 10 Days	±10 Days	±10 Days	±10 Days	Month 12 Visit +14 Days[d]	-1/+2 Days	±3 Days	-2/+10 Days	±10 Days	
ALJDS (EI)[e]	X	X	X	X	X				X	X	
3D facial digital imaging	X	X	X	X	X			X	X	X	
Pronunciation video recording	X	X	X	X	X	X[f]			X	X	
FACE-Q Satisfaction with Lower Face and Jawline (subject)	X	X	X	X	X				X	X	
Satisfaction with treatment (subject)	X	X	X	X	X				X	X	
Natural look and Natural Feel (subject)	X	X	X	X	X				X	X	
FACE-Q Appraisal of Lines: Marionette (subject)	X	X	X	X	X				X	X	
Jaw Functional Limitation Scale (subject)	X	X	X	X	X			X	X	X	
GAIS (EI)	X	X	X	X	X				X	X	
GAIS (subject)	X	X	X	X	X				X	X	
Facial sensation assessment (EI)	X	X	X	X	X	X[f]			X	X	
Weight			X		X						X
Recommendation to a friend (subject)			X		X					X	
Urine pregnancy test[g]					X	X				X	X
Snellen visual acuity (TI or designee)						X[h]		X			
Confrontational visual fields (TI or designee)						X[h]		X			
Ocular motility (TI or designee)						X[h]		X			
Pretreatment anesthesia						X					
Treatment injections (TI)						X					
Procedural pain (subject)						X					

Study Period[a]	Month 1	Month 3	Month 6	Month 9	Month 12 / Study Exit Visit[b]	MTx	Day 3 After MTx	Day 14 After MTx	Month 1 After MTx	Month 3 After MTx/Study Exit Visit	Early Exit Visit[c]
Visit Window	-2/+10 Days	± 10 Days	±10 Days	±10 Days	±10 Days	Month 12 Visit +14 Days[d]	-1/+2 Days	±3 Days	-2/+10 Days	±10 Days	
Reason for not receiving maintenance treatment					X						
Safety telephone call							X				
Subject safety e-diary[i]						Continuous					
Concomitant Medications, Procedures, Therapies	Continuous Monitoring										X
Adverse Events	Continuous Monitoring										X

[redacted]

3D = 3-dimensional; ALJDS = Allergan Loss of Jawline Definition Scale; EI = Evaluating Investigator; GAIS = Global Aesthetic Improvement Scale; MTx = maintenance treatment; TI = Treating Investigator

[a] The follow-up visit schedule is based on the date of the treatment completion (ie, if no touch-up treatment is performed, the Month 1 visit occurs 30 days after initial treatment; if touch-up treatment is performed, the Month 1 visit occurs 30 days after touch-up treatment).

[b] For subjects not receiving maintenance treatment.

[c] Subjects who discontinue early are to complete applicable study visit procedures and Early Exit Visit procedures.

[d] The 14-day window for MTx begins on the date of the Month 12 visit.

[e] [redacted]

[f] Duplicate procedures do not need to be completed. If MTx occurs on the same day as Month 12, all Month 12 procedures should be completed before beginning MTx.

[g] For female subjects of childbearing potential; must be confirmed negative prior to injection.

[h] Vision assessments performed before treatment and approximately 30 minutes after treatment.

[i] The subject safety e-diaries are to be completed following each injection starting on the date of treatment. The diary is to be completed consecutively on a daily basis, until the subject returns for a touch-up/Month 1 Visit (as appropriate) or for 30 consecutive days, whichever is shorter.

Table 4 Schedule of Visits and Procedures: Control Group (No-treatment Period)

Study Period	Rand[a]	Month 1	Month 3	Month 6/ Exit Visit	Early Exit Visit[b]
Visit Window		-2/+10 Days	± 10 Days	± 10 Days	
Inclusion/Exclusion criteria	X				
Urine pregnancy test[c]	X			X	X
Randomization (IWRS)	X				
Pronunciation video recording	X	X	X	X	
Facial sensation assessment (EI)	X	X	X	X	
3D facial digital imaging		X	X	X	
ALJDS (EI)[d]		X	X	X	
GAIS (EI)		X	X	X	
Weight				X	X
Concomitant Medications, Procedures, Therapies	Continuous Monitoring				X
Adverse Events	Continuous Monitoring				X

[redacted]

Control subjects who complete Month 6 procedures, but choose not to have optional treatment, will be considered to have completed the study.

3D = 3 dimensional; ALJDS = Allergan Loss of Jawline Definition Scale; EI = Evaluating Investigator; GAIS = Global Aesthetic Improvement Scale; IWRS = interactive web response system; Rand = randomization

[a] Randomization must occur within 30 days of screening.

[b] Subjects who discontinue early, ie, before the Month 6 Visit, are to complete applicable study visit procedures and Early Exit Visit procedures.

[c] For female subjects of childbearing potential, must be confirmed negative before randomization.

[d] [redacted]

Table 5 Schedule of Visits and Procedures: Control Group (Delayed-Treatment Period)

Study Period	Day 1 Opt ITx[a]	Day 3 After Opt ITx	Day 14 After Opt ITx	Day 30/ Opt TTx[b]	Day 3 After Opt TTx	Day 14 After Opt TTx	Month 1	Month 3	Month 6	Month 9	Month 12/ Study Exit	Early Exit Visit[c]
Visit Window	Month 6 Visit +14 Days	-1/+2 Days	±3 Days	-2/+10 Days	-1/+2 Days	±3 Days	-2/+10 Days	±10 Days	±10 Days	±10 Days		
Urine pregnancy test[d]	X			X					X			X
Snellen visual acuity (TI or designee)	X[e]		X	X[e]		X						
Confrontational visual fields (TI or designee)	X[e]		X	X[e]		X						
Ocular motility (TI or designee)	X[e]		X	X[e]		X						
Pretreatment anesthesia	X			X								
Treatment injections (TI)	X			X								
Procedural pain (subject)	X			X								
Jaw Functional Limitation Scale (subject)	X[f]		X	X[f]		X	X	X	X			
FACE-Q Satisfaction with Lower Face and Jawline (subject)	X[f]						X	X	X			
3D facial digital imaging	X			X[f]			X	X	X			
Pronunciation video recording	X[f]			X[f]			X	X	X			
GAIS (subject)							X	X	X			
ALJDS (EI)[g]							X	X	X			
Facial sensation assessment (EI)	X[f]			X[f]			X	X	X			
GAIS (EI)							X	X	X			
Weight									X			
Safety telephone call		X			X					X		
Subject safety e-diary[h]	Continuous			Continuous								
Concomitant medications, procedures, therapies	Continuous Monitoring											X
Adverse Events	Continuous Monitoring											X

[redacted]

EI = Evaluating Investigator; GAIS = Global Aesthetic Improvement Scale; ITx = initial treatment; Opt = optional; TI = Treating Investigator; TTx = touch-up treatment

[a] Optional initial treatment can occur same day or within 14 days after the Month 6 Visit. If optional initial treatment occurs on the same day as the Month 6 Visit, duplicate assessments do not have to be repeated.

[b] Subjects may undergo a touch-up treatment on Day 30 if the TI and subject determine that improvement was not achieved with the initial treatment. If a touch-up treatment is not performed, then Day 30 visit will be the Month 1 visit.

[c] Subjects who discontinue before the Month 6 Visit are to complete applicable study visit procedures and Early Exit Visit procedures.

[d] For female subjects of childbearing potential; must be confirmed negative prior to injection.

[e] Vision assessments performed before treatment and approximately 30 minutes after treatment.

[f] Done before treatment.

[g] [redacted]

[h] The subject safety e-diaries are to be completed following each injection starting on the date of treatment. The diary is to be completed consecutively on a daily basis, until the subject returns for a touch-up/Month 1 Visit (as appropriate) or for 30 consecutive days, whichever is shorter.

1. Abbreviations and Terms

Term/Abbreviation	Definition
2D	2-dimensional
3D	3-dimensional
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALJDS	Allergan Loss of Jawline Definition Scale
CFR	US Code of Federal Regulations
eCRF	electronic case report form
EI	Evaluating Investigator
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 for Harmonisation
IDFU	investigational directions for use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	injection site response
ITT	Intent-to-Treat
IWRS	interactive web response system
NLF	nasolabial folds
PI	Principal Investigator
SADE	serious adverse device effect
SAE	serious adverse event
TI	Treating Investigator
Tx	treatment
UADE	unanticipated adverse device effect
US	United States

2. Background, Risk and Benefit, and Clinical Rationale

2.1 Background

The defining feature of the lower face is the jawline, or mandible (Shire 2008). The mandible is divided into the ascending branch, horizontal branch, and chin, which is the most prominent portion containing overlying soft tissue. Its shape affects the mouth, chin, and neck. Factors affecting the straight jawline are jowling, and the development of the prejowl notch or sulcus, and the associated marionette lines (Shire 2008). The chin is also important to overall facial appearance. If the chin is of less than ideal size, it will cause other areas of the face to appear too large or too small. If the chin projection or width is inadequate, the adjacent neck and jowl soft tissues appear prematurely aged (Sykes 2016).

As an individual ages, the reduction in skeletal support of this region makes soft tissue atrophy prominent, exaggerating jowls, decreasing chin protrusion, and making the jawline appear weak (Romo 2005). Signs of aging that are clearly visible in the lower third of the face include the loss of elasticity and descent of fat in the jowl region; laxity of the neck skin, muscle, and fat; development of perioral rhytids, deep nasolabial folds (NLFs), and marionette lines; and loss of definition of the lips (Agarwal 2005). As in other areas of the face, changes in the jawline are products of soft tissue and bony changes (Bass 2015). Because the jawline and chin play a strong role in the facial profile, there has been an increasing desire for safe and effective tools that can contour the area nonsurgically.

The hyaluronic acid (HA) injectable gels have become a primary treatment for facial rejuvenation, with an established record of safety and effectiveness (Jones 2010). A number of HA injectable gels are available for correction of wrinkles and folds. However, the paradigm for achieving a more youthful looking face has moved away from the approach of treating discrete wrinkles and folds to one focused on panfacial volumizing. The HA product, JUVÉDERM VOLUMA® with Lidocaine, was specifically designed for volumizing as it has improved qualities of lift and projection compared with HA gels designed for correction of wrinkles and folds, and has demonstrated effectiveness in improving facial volume (eg, restoring age-related mid-face volume deficit [Jones 2013]; prejowl sulci, marionette regions, and nasolabial groups [Goodman 2015]; glabella, malar eminences, and chin [Bae 2013]; malar and chin areas [Fischer 2010]; malar area, NLFs, chin, temporal region, and other [Carruthers 2010]; malar area, NLFs, chin, temples, and other [Hoffmann 2009]; and mid-face, hollow temporal areas, eyebrows, scar depressions, and/or nose [Raspaldo 2008]).

Other areas of the face where lift and projection are important aspects of volumizing are the chin and jaw area and VOLUMA has been increasingly utilized for structural support of the chin and for the angle of the jaw and jawline, prejowl and marionette areas in the aging patient (Goodman 2015).

JUVÉDERM VOLUX™ XC (hereafter, VOLUX XC) is a temporary HA dermal filler that is a structural gel manufactured specifically to provide a safe, minimally invasive method to restore and create facial volume. VOLUX XC is similar to JUVÉDERM VOLUMA with Lidocaine. The primary difference between the products is the concentration of HA, which is 20 mg/mL in JUVÉDERM VOLUMA with Lidocaine and 25 mg/mL in VOLUX XC. The higher concentration of HA in VOLUX XC is expected to provide improved volumizing and lift properties. VOLUX XC is designed for injection into the subcutaneous and/or supraperiosteal space, and because it is moldable after injection, VOLUX XC permits sculpting, contouring, and shaping across the injected areas. As the chin and jaw are high mobility areas, they represent an excellent target for testing the volumizing and lift capabilities of VOLUX XC, as well as its durability.

2.2 Risk and Benefit

HA skin injection procedures carry the usual risks of erythema, pain, tenderness, swelling, itching, bleeding, bruising, lumps/bumps, firmness (induration), and skin infection. Allergic reactions to anesthetic agents are rare and may include skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient (temporary) loss of skin color.

Results of a multicenter, single-blind, randomized, controlled clinical study (V25L-001) conducted in 120 subjects demonstrated that VOLUX XC injectable gel was safe and effective in restoring and creating facial volume, and in sculpting, shaping, and contouring in the chin and jaw area. The primary effectiveness measure (glabella, subnasale, and pogonion angle measured by the blinded image-analysis technician from digital images of the subject's facial profile) showed significant improvement in projection of the chin. Procedural pain in this study was minimal. The most common injection site responses (ISRs) after initial/touch-up treatment were firmness, tenderness to touch, and swelling, and most ISRs resolved within 1 week of treatment. Prior to repeat treatment, treatment-related adverse events (AEs) were observed for 38.7% of subjects treated with VYC-25L injectable gel, with the most common being mild injection site mass (verbatim term: lumps/bumps). These are commonly reported events following treatment with HA dermal fillers. Most treatment-related AEs did not require treatment. A small percentage of treated subjects (3.4%, 4/119) after initial or touch-up treatment and 1.1% (1/89) after repeat treatment experienced

treatment-related AEs of speech disorder (investigator term: unclear pronunciation), considered to be related to the physical presence of filler in subjects' chin. The events were mild in severity, self-limiting, and resolved without sequelae within a few days. The subjects who experienced these events tended to have larger than average volumes injected into the pogonion and mentum (> 1.5 mL in each area). No deaths or treatment-related serious adverse events (SAEs) were observed.

The results of Study V25L-001 demonstrate that treatment with VOLUX XC injectable gel is an effective treatment for restoring and creating facial volume. The safety profile indicates that VOLUX XC injectable gel is safe and well tolerated by subjects in all treated areas.

2.3 Clinical Rationale

VOLUX XC is a structural gel intended as a non-surgical alternative to silicone implants for restoration and creation of facial volume in less severe patients. This protocol is designed as a pivotal study to collect safety and effectiveness data associated with restoring jawline definition 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 VOLUX XC injectable gel in adults seeking to restore jawline definition.

3.2 Clinical Hypotheses

The responder rate at Month 6 in the treatment group will be statistically significantly greater than in the control group at Month 6, and the responder rate at Month 6 for the treatment group will be statistically significantly greater than or equal to 50%. Responder rate is the percentage of subjects who show at least 1-point improvement on the Allergan Loss of Jawline Definition Scale (ALJDS) from baseline based on both sides of the jaw.

4. Study Design

4.1 Structure

This is a multicenter, evaluator-blinded, randomized, parallel-group, controlled study. Up to 20 investigational sites in the United States will enroll and follow subjects who meet the study criteria.

4.2 Duration

Study duration will be 12 to 17 months for the treatment group and 6 to 20 months for the control group.

Participation for subjects in the treatment group may include up to 1 month for screening, 1 month for treatment, 12 months of follow-up after the last treatment (initial or touch-up), an option for maintenance treatment at Month 12, and an additional 3 months of follow-up after maintenance treatment. Participation for subjects in the control group may include up to 1 month for screening, a 6-month no-treatment control period, after which they have the option to exit the study or receive treatment, and if treated, 1 month for treatment and 12 months of follow-up after the last treatment (initial or touch-up).

4.3 Treatment Groups and Treatment Regimen

4.3.1 Study Treatment

VOLUX XC injectable gel.

4.3.2 Control Treatments

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.

Prior to site activation, the sponsor will ensure that study site staff, including the investigator, are trained on the importance of maintaining EI blind.

The Treating Investigator (TI) and study coordinators will not be blinded to treatment, but 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. Subjects will not be blinded to treatment and will be instructed not to speak with the EI about treatment. The Principal Investigator (PI) maintains the study role of TI in this study.

4.3.4 Retreatment Criteria

At Day 30, if the TI judges that an ALJDS score improvement of at least 1 grade has not been achieved on each side, a touch-up treatment is recommended. If the TI judges that an ALJDS score improvement of at least 1 grade has been achieved on each side, a touch-up may be performed if agreed upon by the subject and the TI. Total injection volume for initial and touch-up treatments combined must not exceed 8.0 mL.

Treatment group subjects will be offered an optional maintenance treatment after completion of the Month 12 visit. No touch-up treatment will be offered after maintenance treatment. Injection volume for maintenance treatment must not exceed 8.0 mL.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

Topical anesthesia may be used during treatment according to routine practice, but it must be limited to the treatment areas only. Examples of permitted topical anesthesia include ice and lidocaine cream. Injectable anesthesia may also be used but must be limited to the treatment area and cannula insertion site.

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

Otherwise, 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 the sponsor.

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, herbal supplements) in the 10 days prior to undergoing study device injection and for 3 days afterwards.

During the course of the study, subjects must not:

- Be enrolled in another study and may not receive another investigational product during the course of this study
- Receive permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck
- Undergo fat injections in the malar, chin, or jawline area
- Undergo any piercing or tattooing procedures below the subnasale
- Undergo semi-permanent dermal fillers (eg, calcium hydroxyapatite, poly-L-lactic acid) below the subnasale
- Undergo dermal filler injections in the malar, chin or jawline area
- Undergo 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
- Receive botulinum toxin injections in the chin, masseter, perioral area, or platysma bands
- Receive deoxycholic acid in the chin, neck, or jawline area

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 subject as the primary consideration. When possible, Allergan is to be notified before the prohibited medication/treatment is administered.

4.4.3 Escape Medications

None.

4.4.4 Special Diet or Activities

Within the first 24 hours after treatment, subjects will be advised to 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 1 week after treatment, subjects will be advised not to have a massage, enter a hot spring or sauna, receive excessive sun exposure, or go swimming.

Subjects will be advised to maintain a consistent weight.

4.5 Treatment Allocation Ratio

Subjects will be randomized at an allocation ratio of 3:1 to treatment with VOLUX XC or no-treatment control group.

5. Study Population

5.1 Number of Subjects

Up to 280 subjects will be enrolled at up to 20 sites, with at least 144 subjects and at most 162 subjects randomized to the treatment group and at least 48 subjects and at most 54 subjects randomized to the control group. No more than 20% of all randomized subjects will be randomized at an individual site.

5.2 Study Population Characteristics

Adults seeking treatment to restore jawline definition. Subjects will represent all Fitzpatrick skin phototypes; a minimum of 20 subjects of each of phototype group I/II, III/IV, and V/VI will be randomized. At least 20 males will be randomized into the study.

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" loss of jawline definition as determined by the EI using the ALJDs (Grade 2 or 3 on the ALJDS) on both sides. The grade does not have to be the same on both sides, but must be Grade 2 or 3.
3. TI considers the subject's jaw amenable to an improvement of at least 1 grade on the scale for the jawline definition
4. Ability to follow study instructions and likely to complete all required visits
5. Written informed consent (IC) has been obtained

5.4 Exclusion Criteria

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

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

7. Has received deoxycholic acid treatment in the submental region in the last 6 months.
8. Has severe midface volume deficit such that restoration of the lower face volume would have an aesthetically unpleasant outcome, as determined by the TI
9. Has severe submental fat, as determined by TI
10. Has severe skin laxity that can interfere with visual assessment of the chin or jaw area, as determined by TI
11. Has a significant facial asymmetry, including but not limited to asymmetry due to trauma, as determined by TI
12. Has experienced trauma to the chin and jaw area within 6 months before enrolment or has residual deficiencies, deformities, or scarring, as determined by TI
13. Has a tendency to develop hypertrophic scarring
14. Has active autoimmune disease
15. Has current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes, gum disease), abscess, an unhealed wound, or a cancerous or precancerous lesion, in chin or masseter
16. Has a history of severe reactions (anaphylaxis) or allergy to lidocaine, HA products, or *Streptococcal* protein
17. Is on a regimen of anti-coagulation therapy (eg, warfarin, clopidogrel)
18. Is on a regimen of medications (eg, aspirin or ibuprofen) or other substances known to increase coagulation time (eg, herbal supplements with garlic or gingko biloba) within 10 days of undergoing study device injection (study device injection may be delayed as necessary to accommodate this 10-day washout period)
19. 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
20. Has begun using any new over-the-counter or prescription oral or topical, anti-wrinkle products below the subnasale 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)
21. Is planning to undergo orthodontic treatment (eg, removal of braces, jaw surgery, headgear) during the study, with the exclusion of prophylaxis and dental filling. Dentures are acceptable if stable.

22. Females who are pregnant, nursing, or planning a pregnancy
23. Is an employee (or a relative of an employee) of the TI, EI, Allergan, or a representative of Allergan
24. 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 maintenance treatment) 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 below 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 ALJDS prior to initiating enrollment.

Throughout the study, to the extent possible, it is recommended that all treatments and safety assessments for a particular subject be performed by the same TI (in the case of the facial sensation assessment, by the same EI), and effectiveness assessments (ALJDS 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 follow-up evaluations, the EI will use the [redacted]

EIs assessment of facial sensation will be as follows: the EI will test sensation in the chin area using a 2-point discrimination test and a light touch test. Two-point discrimination will be tested at 4 locations (anterior to the jowl and posterior to the jowl on each side of the jawline). Using the [redacted], the EI will lightly touch the set of prongs to each location on the chin, as specified by the eCRF, while the subject reports whether s/he feels "1" or "2" objects touching his/her skin. The light touch test will be performed at the same 4 locations on the jawline. The EI will press [redacted] (specified on the eCRF) against the subject's skin and record the smallest filament size that elicits a response at each assessed location.

[redacted]

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 such as, "How have you been feeling since the last visit?" In addition, the TI will ask the subject a general, non-directed question about vision symptoms, "Since your last visit, have you experienced any changes in or around either eye? For example, loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving your eyes, skin changing color around the eyes, or crusty or scabby skin around the eyes." Subjects will be informed that they are to call the site if they experience any symptoms consistent with these events. Directed questioning and examination will then be done as appropriate and may include an in person visit at the investigation site and/or referral to a retinal specialist. Any subject with any vision loss will be referred immediately to a retinal specialist for 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).

A subject is considered enrolled when he or 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 and tobacco use history, Fitzpatrick skin phototype, and sun exposure estimate. Physical measurements (height and weight) and vital signs 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. Subjects will undergo 3D facial digital imaging.

The EI will rate the subject on the 5-grade photonumeric ALJDS; the EI will use the [redacted] to determine eligibility for the study (Inclusion criterion 2). The TI will ensure the subject's anatomy is amenable to at least a 1-grade improvement on the ALJDS (Inclusion criterion 3).

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 or who withdraw consent before randomization.

The schedule of procedures to be performed at screening is provided in Table 1.

6.2.2 Day 1/Randomization Visit

The randomization visit must occur within 30 days after screening/signing of the ICF. Day 1/Randomization procedures are listed in Table 2.

Subjects will be randomized at a 3:1 ratio to the treatment group or the control group. Subjects randomized to the treatment group will proceed to treatment with VOLUX XC (Section 6.2.3) that day, after completion of all of the above procedures. Subjects randomized to the control group will finish the required procedures for the randomization visit and return for a Month 1, 3, and 6 visit during the control period (Section 6.2.4).

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 after the last treatment (initial or touch-up) with the option for maintenance treatment at Month 12 and an additional 3 months of follow-up.

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

If the subject is randomized to the treatment group, treatment will 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 of the 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 insertion site only. The TI will use aseptic skin preparation and will administer injections 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 at least a 1-grade improvement on the ALJDS 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 ISRs starting on the day of treatment and for up to 30 consecutive days after treatment. The diary is to be completed consecutively on a daily basis, until the subject returns for a touch-up/Month 1 Visit (as appropriate) or for 30 consecutive days, whichever is shorter.

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 to the investigational site immediately or will be instructed to receive appropriate care, which may include referral to a retinal specialist. Subjects will return for an office visit 14 days after treatment to undergo 3D facial digital 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 TI will discuss the results of the initial treatment. If the TI judges that an ALJDS score improvement of at least 1 grade has not been achieved on each side of the face, it is recommended that the TI perform a touch-up treatment. If the TI judges that an ALJDS score improvement of at least 1 grade has been achieved on each side, a touch-up may be performed if agreed upon by the subject and the TI.

If no touch-up is performed, the subject will exit the initial treatment period and continue with posttreatment follow-up visits and procedures (Section 6.2.3.2), and this visit becomes the Month 1 visit.

If a touch-up is performed, the touch-up treatment visits, procedures, and follow-up are identical to those of initial treatment. The subject will continue with follow-up visits after treatment, as described in Section 6.2.3.2, beginning with the Month 1 follow-up visit, approximately 30 days after touch-up treatment.

Note that before touch-up treatment, women of childbearing potential will take a urine pregnancy test. If the urine test is positive, no touch-up will be performed, and the pregnancy will be followed as described in Section 10.3.

The procedures and evaluations for the treatment period are listed by visit in Table 2.

6.2.3.2 Treatment Group: Follow-up/Maintenance Treatment Period

Follow-up visits for safety and effectiveness will occur at 1, 3, 6, 9, and 12 months after initial treatment (or touch-up, if applicable).

After completion of the Month 12 visit, subjects will be offered an optional maintenance treatment. Subjects who decline maintenance treatment will exit the study. Subjects who agree to receive maintenance treatment will be followed for 3 additional months and then exit the study.

The procedures and assessments to be performed at maintenance treatment and at the 4 follow-up visits (Day 3, Day 14, and Months 1 and 3) after maintenance treatment are identical to those after the initial treatment, with the exception that no touch-up will be offered and the product characteristics won't be recorded.

Subjects who are randomized to the treatment group and decide to exit the study at any point before the Month 12 visit must complete the Early Exit Visit procedures in addition to all applicable visit procedures.

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

6.2.4 Control Group

6.2.4.1 Control Group: No-treatment Period

Subjects randomized to the control group will complete a 6-month no-treatment control period with office visits at Months 1, 3, and 6 after randomization.

After the Month 6 procedures are complete, subjects will be offered an optional treatment (Section 6.2.4.2). 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. Control subjects who complete the Month 6 procedures, but choose not to have optional treatment, will be considered to have completed the study.

Subjects in the control period who decide to exit the study at any point before the Month 6 Visit must complete the Early Exit Visit procedures in addition to all applicable visit procedures.

The procedures and evaluations for the control group during the no-treatment period are listed by visit in Table 4.

6.2.4.2 Control Group: Delayed-Treatment Period

During the delayed-treatment period, subjects will receive optional treatment (initial with optional touch-up) after which they will be followed for effectiveness for 6 months and for safety for 12 months after the last treatment (initial or touch-up).

Control subjects who receive treatment will have the same follow-up visit schedule as the treatment group for 6 months after treatment (initial or initial with touch-up).

Control subjects in the delayed-treatment period who decide to exit the study at any point before the Month 6 Visit must complete the Early Exit Visit procedures in addition to all applicable visit procedures.

The procedures and evaluations for the control group during the delayed-treatment period are listed by visit in Table 5.

6.3 Instructions for the Subjects

During each study visit, subjects will be required to remove jewelry (on the neck and/or above the shoulders), make-up, and lipstick, and subjects must be clean-shaven below the subnasale to avoid interference with digital imaging and evaluations of the jaw area.

For 10 days before and 3 days after study treatment administration, it is recommended that subjects 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.

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 follow-up for AEs or ISRs). If an AE is reported during a safety phone call and requires evaluation by the TI in person, an unscheduled visit will be conducted. An unscheduled visit may also occur to repeat facial digital imaging if the images obtained at the scheduled visit are of poor quality. 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. Subjects who discontinue early are to complete applicable study visit procedures and Early Exit Visit procedures. 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 will 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.

If a subject has a positive urine pregnancy test at the time of the initial or maintenance treatment visit, 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 visits and non-treatment procedures. The pregnancy will be followed as described in Section 10.3.

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

- receives any dermal filler or fat injection to the chin area
- undergoes facelift or facial reconstructive surgery
- receives treatment with hyaluronidase in the chin area
- changes his/her decision about having photographs taken

A subject may also be withdrawn at the discretion of physician.

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 loss of jawline definition using the ALJDS. Each side of the jawline (left and right) will be assessed independently. [redacted]

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 jawline area using the 5-point GAIS (Table 6) and subject responses on the validated FACE-Q Satisfaction with Lower Face and Jawline questionnaire. For GAIS and FACE-Q questionnaires, 1 overall assessment will be provided to encompass both sides.

Table 6 5-Point Global Aesthetic Improvement Scale

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

7.1.3 Other Effectiveness Measures

Other effectiveness measures include:

[redacted]

[redacted]

7.2 Safety Measures

Safety measures include:

- Subject assessment of procedural pain during treatment on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable)
- Subject assessment of jaw function using the 20-item Jaw Functional Limitation Scale questionnaire
- Presence, severity (mild, moderate, or severe), and days with ISRs recorded by subjects in daily safety diaries for approximately 30 consecutive days after any treatment (initial, touch-up, and maintenance)
- AEs observed by the TI or reported to the TI by the subject
- Snellen visual acuity, confrontational visual fields, and ocular motility assessed by the TI (or designee)
- EIs assessment of facial sensation
- Pronunciation video recordings
- Monitoring of concomitant medications and concurrent procedures

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

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

The subject's daily safety diary will list the following severities for ISRs to be recorded:

None

Mild

Moderate

Severe

Subjects are to bring the e-diaries to their Day 14 and Day 30/Month 1 visits for review by the TI, and the TI will determine if the ISR qualifies as an AE.

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

Vital sign measurements, including blood pressure (systolic and diastolic, while subject is seated), temperature, pulse, and respiratory rate, and a urine pregnancy test for female subjects of childbearing potential will also be performed. Females who are postmenopausal for at least 1 year or who do not have a uterus at the time of study entry are considered not of childbearing potential.

7.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics to be collected include sex, age, race, height, weight, Fitzpatrick skin phototype and sun exposure, smoking and tobacco 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, product moldability (11-point scale where 0 = stiff and 10 = moldable), and injection ease (11-point scale where 0 = difficult and 10 = easy).

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 and attested to by the PI.

Investigators will provide access to hospital files, medical records, and other source documents containing subject clinical/medical or research study information. Source document verification will be performed by the sites' assigned monitors.

Subjects will complete the ISR diaries electronically. Sites can save photographs onto supplied electronic media and send the encrypted storage device to [redacted]. Alternatively, files containing the facial digital photographs may be directly uploaded to [redacted].

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, 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:

- Intent-to-treat (ITT) population: all randomized subjects
- Safety population: all subjects randomized to treatment group who receive at least 1 study treatment and all subjects randomized to control group

Unless specified otherwise, all effectiveness analyses will be performed on the ITT 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 6. A responder is defined as a subject who shows at least a 1-point improvement on the ALJDS from baseline based on EI assessment on both sides of the jaw. Baseline is defined as the last assessment by EI prior to randomization.

8.2.2 Secondary Effectiveness Variables

Secondary effectiveness variables include EI and subject assessed GAIS responder rates, where a "responder" is a subject who shows improvement in the overall aesthetic assessment in jawline area (Improved or Much Improved on GAIS) at the Month 6 Visit, and subject mean overall satisfaction on the validated FACE-Q Satisfaction with Lower Face questionnaire at Month 6.

8.3 Hypothesis and Methods of Analysis

8.3.1 Primary Effectiveness Analyses

The study device will be determined to be clinically effective if at least 50% of subjects in the treatment group are observed to be responders (subjects who show ≥ 1-point improvement on the ALJDS compared with pretreatment) at Month 6 and if the responder rate for treatment group is statistically superior to the responder rate for the control group at Month 6. The following hypotheses will be tested:

H_o: $P_v < 50\%$
H_a: $P_v \geq 50\%$

and

H_o: P_v £ P_c
H_a: $P_v > P_c$

where P_v and P_c denote the responder rates for the treatment group at Month 6 after last treatment and control group at Month 6 after randomization, respectively. The first

hypothesis will be tested using 2-sided 95% CI. The null hypothesis will be rejected if the lower bound of the 95% CI is greater than or equal to 50%. The second hypothesis will be tested using 1-sided Fisher´s exact test at 2.5% significance level (or 2-sided Fisher's exact test at 5% significance level) to compare responder rates between the treatment and control groups. The null hypothesis will be rejected if the 1-sided p-value is < 0.025 (or 2-sided p-value is < 0.05).

The primary effectiveness analysis will be performed on the ITT population using the last observation carried forward for any missing assessment of the primary endpoint at the Month 6 Visit. Additionally, as part of sensitivity analysis, the primary effectiveness analysis will be repeated on the ITT population using observed data as well as using multiple imputation procedure. Details of the multiple imputation procedure will be provided in the statistical analysis plan. Furthermore, additional sensitivity analyses of the primary effectiveness endpoint will be performed on the ITT population, excluding subjects who were inadvertently unblinded to the EI or who did not have a baseline ALJDS score of 2 or 3.

The impact of investigational sites on the primary effectiveness analysis at Month 6 will be evaluated by presenting the primary effectiveness analysis by each site.

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 jawline area (Improved or Much Improved on GAIS) at the Month 6 Visit.

- Descriptive summary of the change in overall score of subject's satisfaction with lower face and jawline since baseline at the Month 6 Visit based on the treatment group subjects' responses on the validated FACE-Q Satisfaction with Lower Face and Jawline questionnaire; a 2-sided paired t-test at the 5% level to demonstrate that the mean overall satisfaction score at Month 6 is statistically greater than that at baseline. This test is only performed if the primary endpoint is met.

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

8.3.3 Other Effectiveness Analyses

[redacted]

8.3.4 Safety Analyses

Subject assessment of procedural pain score and of jaw function using the 20-item Jaw Functional Limitation Scale questionnaire will be summarized descriptively. Assessments from the pronunciation recordings and facial sensation assessment will be summarized descriptively.

Snellen visual acuity, confrontational visual fields, and ocular motility assessments will be summarized descriptively.

ISRs will be summarized by maximum severity and ISR days for initial, touch-up, and maintenance treatments, separately. Summaries will include the incidence rate for each ISR.

Treatment-emergent AEs and treatment-related AEs (ie, device- or procedure-related) will be summarized by System Organ Class and Preferred Term, and severity. In addition, treatment-related AEs will also be tabulated by duration, severity, causality, action taken, and outcome. The summary will include incidence rate as well as total number of events.

AEs that occur after obtaining written IC but before treatment will be listed, but not summarized.

8.4 Subgroup Analyses

Details will be provided in the statistical analysis plan.

8.5 Sample Size Calculation

Sample size is determined to provide adequate power to demonstrate that the product is effective as well as safe. A sample size of 120 subjects in the treatment group and 40 subjects in the control group will provide > 99% power to detect a difference of at least 40% in the responder rates between the groups. This calculation is based on a 1-sided Fisher's exact test at the 2.5% level. The treatment group is assumed to have at least 80% responder rate and the control group will have at most 40% responder rate. Assuming a screen fail rate of 25% and a drop-out rate of 15% between randomization and the Month 6 visit, up to 280 subjects will be enrolled, with at least 144 subjects and at most 162 subjects randomized to the treatment group and at least 48 subjects and at most 54 subjects randomized to the control group (3:1 ratio).

This sample size is considered to be adequate to determine the safety profile of the product in the jawline area. Assuming a screen fail rate of 25%, a 5% drop-out rate between randomization and initial treatment for the treatment group, and a 15% drop-out rate between randomization and optional treatment for the control group, it is estimated that at least 176 subjects will be treated in the study. With 176 treated subjects, there is at least 92% power to detect an AE related to treatment with an incidence rate of 1.5% in the population using a 1-sided exact binomial test at the 2.5% level.

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

8.6 Interim Analyses

No interim analysis is planned. An analysis of the primary and secondary endpoints may be conducted once all subjects have passed the primary timepoint (Month 6). If such an analysis is conducted, the details of the analysis will be described *a priori* in other study documents.

9. Materials

9.1 Study Treatment

9.1.1 Product Description

VOLUX XC is a newly formulated sterile, biodegradable, nonpyrogenic, viscoelastic, clear, colorless, homogenized, HA gel implant (dermal filler). The HA is produced by *Streptococcus* species of bacteria and is mixed with phosphate buffer and crosslinked by adding a minimum amount of 1,4-Butanediol diglycidyl ether (BDDE) to form a 3D HA gel. The HA concentration is 25 mg/mL, and 0.3% weight by weight (w/w) lidocaine hydrochloride is added to enhance subject comfort.

9.1.2 Instructions for Use and Administration

For investigational use in this study, VOLUX XC injectable gel with lidocaine will be administered via the supplied needles (27 G 1/2") or cannula (25 G 1 1/2") to the pre- and post-jowl area, chin, marionette lines, and angle of the mandible to restore jawline definition, provide a smooth contour, and achieve an aesthetically pleasing result. When making an entry point for the cannula, only use the introducer needle that is co-packaged with the provided cannula.

The TI 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. Before the study begins, the TI will receive training in the administration of VOLUX XC according to the technique specified for this study.

The TI will use aseptic injection technique and inject the treatment slowly using gentle, even pressure on the syringe. The detailed recommended injection technique is provided in the VOLUX XC IDFU included in the Site Study Binder.

Note: In Study V25L-001, a small percentage of treated subjects (3.4%, 4/119) after initial or touch-up treatment and 1.1% (1/89) after repeat treatment experienced treatment-related AEs of speech disorder (investigator term: unclear pronunciation), which were considered to be related to the physical presence of filler in subjects' chin. The events were generally mild in severity, self-limiting, and resolved without sequelae within a few days. The subjects who experienced these events tended to have larger than average volumes injected into the pogonion and mentum (> 1.5 mL in each area).

9.1.3 Treatment Regimen Adjustments

Up to 2 treatment sessions 30 days apart are allowed; maintenance treatment is allowed 12 months after initial (or touch-up, if performed) treatment for the treatment group subjects. The TI will determine the appropriate volume of VOLUX XC to inject at the initial and touch-up treatments based on his/her clinical experience, but the maximum volume must not exceed 8.0 mL for initial and touch-up treatments combined. Injection volume for maintenance treatment must not exceed 8.0 mL.

9.2 Other Study Supplies

Allergan will provide digital imaging equipment and other supplies specific to this study (eg, 27 G 1/2" needles [see Section 12.5.1] and/or 25 G 1 1/2" 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, and internet connection for IWRS, eCRF completion, and for submitting digital images).

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 occurs prior to any screening procedures.

Screening procedures (Table 1) include:

- Collection of demographic information
- Collection of height, weight, and vital signs
- Evaluation of Fitzpatrick skin phototype and history of sun exposure
- Collection of smoking and tobacco history
- Collection of medical/surgical/cosmetic/dental procedures history
- Administration of urine pregnancy test for female subjects of childbearing potential

- Evaluation of inclusion/exclusion criteria
- 3D facial digital imaging
- Evaluation by the EI of jawline definition using the ALJDS

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 photographs 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 PI 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 IC. The TI will retain the original copy of the signed form, and the subject will receive a copy. Upon signing the ICF, the subject is considered enrolled in the study and receives a subject number that will be used on all documentation for the subject throughout the study. Subject numbers will be assigned in ascending order, and numbers will not be omitted or reused. The subject number is coupled with the site identification number for unique identification of each subject. The TI is to ensure important new information is provided to new or existing subjects throughout the study. For studies involving emergency treatments, when prior IC of the subject is not possible because of the subject's medical condition, the IC of the subject's legally authorized representative shall be requested. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the study and about all aspects of the study. The subject shall be asked to provide IC for continued participation as soon as his/her medical condition allows.

10.1.3 Method for Assignment to Treatment Groups

At the time of randomization (ie, at or within 30 days after screening/signing of the ICF), eligible subjects will be assigned to 1 of 2 treatment groups (treatment or control) in a 3:1 ratio to receive VOLUX XC or go to the control group based on a central randomization schedule. An automated IWRS will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan. Sites will dispense treatment according to the IWRS instructions provided by the system.

10.2 Compliance with Protocol

The PI is responsible for compliance with the protocol at the investigational site. A representative of Allergan will make frequent contact with the PI 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 PI upon identification. The use of the data collected for the subject will be discussed to determine if the data are to be included in the analysis. All protocol deviations will be reported to the IRB according to the IRB reporting requirements.

10.3 Pregnancy

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

Pregnancy by itself will not be considered an AE or 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, PI, 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 PI to comply with pertinent national or state regulations, IRB-imposed conditions, or protocol requirements
- PI submission of knowingly false information to Allergan, Monitor, 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 VOLUX 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 subject. 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 VOLUX 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 post-baseline visit, the TI (or designee) will begin querying for AEs by asking each subject a general, non-directed question such as "Have you had any changes to your condition since your last visit?" In addition, the TI will ask the subject a general, non-directed question about vision symptoms, "Since your last visit, have you experienced any changes in or around either eye? For example, loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving your eyes, skin changing color around the eyes, or crusty or scabby skin around the eyes." Subjects will be informed that they are to call the site if they experience any symptoms consistent with these events. Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate and may include an in person visit at the investigation site

and/or referral to a retinal specialist. Any subject with any vision loss will be referred immediately to a retinal specialist for examination. 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, bruising, swelling, swelling, tenderness to touch, firmness 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
- Tenderness or pain in the jaw when chewing, which can usually be treated with over-the-counter painkiller and generally resolves within a few days
- Numbness, problems with chewing and mild speech related difficulties which typically resolve without treatment within a few days
- Rare cases of allergy, severe sensitivity, localized inflammation and abscesses
- Very occasionally, delayed side effects can occur many months after the treatment. These delayed side effects may include: lumps, bumps, nodules, cysts, swelling, pain, bruising, skin tightness, and product dislocation.
- 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.
- In rare circumstances, facial fillers have been associated with granulomas, which are small inflammatory nodules under the skin.
- In rare circumstances, stroke

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 vision loss, the subject must also be referred to a retinal specialist for evaluation and 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 of 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 cancers 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 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

An 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 an 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 enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity

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.

An AE could be considered procedure-related when, in the judgement of the investigator, it is reasonable to believe that the event is associated with the procedure, regardless of the relationship to the study device. Procedure-related causes that contribute to the occurrence of the event can be attributed to other products, surgical techniques, or medications required specifically for the procedure.

Relationship to the treatment (device or procedure) must be determined by the investigator 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/e-mail to Allergan within 24 hours of awareness	Signing ICF	Last subject visit
SAEs, SADEs	Record on SAE Form and fax/e-mail Allergan within 24 hours of awareness	Signing ICF	Last subject visit

11.3 Procedures for Reporting an AE or ADE

All AEs or ADEs occurring during the study period (after signing of the ICF) are to be recorded on the appropriate eCRF.

If a treatment-related AE is ongoing at the time of exit, 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.

The TI will report AESIs 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 working 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/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/e-mail using the SAE/SADE reporting forms. For the SAE/SADE fax/e-mail number, 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 PI is not to implement any deviation from or changes to the protocol without prior review and documented approval from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (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, subject assessments and questionnaires and diaries, photographic negatives or digital images, clinic charts, the PI'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 PI's copies of the eCRFs serve as part of the PI's record of a subject's study-related data.

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

- Subject's name
- Subject's contact information
- Date that the subject entered the study, subject number, and subject randomization number
- Study title and/or the protocol number and study Sponsor
- A statement that IC was obtained, including the date and a statement that HIPAA Authorization or other country and local subject privacy required documentation for this study has been obtained, including the date
- Details of the injection procedure including anesthetic used, 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, results of urine pregnancy tests)

12.4.2 Case Report Form Completion

The PI is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. The PI 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 PI 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 PI 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 Department, 2525 Dupont Drive, Irvine, CA 92612.

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

12.5.1 Labeling/Packaging

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

Protocol V25L-002
Kit# VVVVV
Lot# VVVVV
CAUTION - Investigational Device.
Limited by Federal (or United States) law to Investigational Use

Use as directed per protocol

Each kit of VOLUX XC will contain 1 or more syringes prefilled to 1.0 mL and single-use sterile needles (27 G 1/2”) specifically intended for injecting VOLUX 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.

VOLUX XC must be stored per labeled storage conditions with a continuous temperature monitoring device which triggers an alarm if the temperature goes out of range. 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 PI (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 PI.

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 needles and cannulas will be disposed of onsite. Unused devices 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 needle or cannula) 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 remote and on-site visits to review, audit, and retrieve copies of study-related documents. It is the responsibility of the PI 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 PI(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 maintenance), 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 PIs 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

The following report is on file at Allergan.

Study Number	Study Title
V25L-001	A Multicenter, Single-blind, Randomized, Controlled Study of the Safety and Effectiveness of VYC-25L Hyaluronic Acid Injectable Gel for Restoration and Creation of Facial Volume in the Chin and Jaw. Final Report. Allergan, June 2018.

13.2 Literature References

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14. Attachments

14.1 Protocol Amendment Summary

Version Date/ Amend. No.	Changes to Protocol
1/31/19 Amendment 1	• Synopsis: sample size updated and 3D facial digital imaging added for control group • Table 3: collection of AEs and concomitant medications at Month 1 and clarification of visit window for MTx visit added • Table 5: 3D facial digital imaging and weight assessment added • Section 2.2: V25L-001 study results updated from Month 12 to final results • Section 4.4.2: deoxycholic acid added as a prohibited medication • Section 5.1 and 8.5: sample size updated • Section 5.2: phototype III/VI corrected to III/IV • Section 6.6: revised withdrawal criteria to state that subjects will not be withdrawn for positive pregnancy test at the touch-up treatment visit • Sections 7.1.3 and 8.3.3 and synopsis: units of measurement added for volume change and depth change • Section 7.2: ISR severity definitions and instructions added • Section 7.4: details of injection ease assessment added • Section 8.3.1: additional sensitivity analyses added • Section 10.3: pregnancy follow-up instructions updated • Section 12.1.2: EC deleted from section title • Section 13.1: V25L-001 study report updated from Month 12 to final • Minor formatting changes made throughout
2/28/19 Amendment 2	• Synopsis, Tables 1 to 5, Sections 6.2, 6.2.1, and 7.1.1: added clarification that the EI uses the [redacted] to perform ALJDS assessments. Eliminated ALJDS assessment for control group at Day 1 optional initial treatment since it is already performed at the Month 6 control period visit.