Title Page

Protocol Title: A Randomized, Multicenter, Evaluator-blind, Controlled Study to Evaluate the Safety and Effectiveness of JUVÉDERM VOLITE™ XC Injectable Gel for the Improvement in Cheek Skin Smoothness

Protocol Number: 1867-701-008 Amendment 3

Brief Protocol Title: JUVÉDERM VOLITE™ XC for cheek skin smoothness

Product: JUVÉDERM VOLITE™ XC injectable gel

Development Phase: IDE

Sponsor Name and Legal Registered Address:

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Irvine, CA 92612

Manufacturer: Allergan

Regulatory Agency Identifying Number(s): IDE G180064

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

Sponsor Signatory and Investigator Signatory:

Sponsor signature is provided on the last page of the protocol. The investigator signature page will be provided as a stand-alone document. The investigator is to retain the original in the site study files and return a copy to the sponsor for archiving in the trial master file.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	see last page for approval date
Amendment 2	3-July-2019
Amendment 1	28-February-2019
Original Protocol	19-September-2018

Amendment 3 (November 2019)

Overall Rationale for the Amendment:

To allow for more complete follow-up of ISRs and SAEs.

Section No. and Name	Description of Change	Brief Rationale
8.1 Withdrawal from the Study, 9.4 Safety Assessments	Added that ongoing ISRs will be followed until resolved or follow-up is no longer possible	To better characterize safety profile
9.5 Adverse Events	Clarified that SAEs be followed until follow-up is no longer possible	To better characterize safety profile

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1. Synopsis

Protocol Title and Number: 1867-701-008 Amendment 3: A Randomized, Multicenter, Evaluator-blind, Controlled Study to Evaluate the Safety and Effectiveness of JUVÉDERM VOLITE™ XC Injectable Gel for the Improvement in Cheek Skin Smoothness
STUDY PHASE: IDE
STUDY SITES: Up to 20 US centers
NUMBER OF SUBJECTS: Up to 263 subjects will be enrolled, and approximately 210 subjects will be randomized at a 2:1 ratio to treatment group and control group
TEST PRODUCT, DEVICE VOLUME, AND MODE OF ADMINISTRATION: JUVÉDERM VOLITE XC injectable gel will be administered using a 32 G 1/2" or a 32 G 3/16" needle in multiple microdepot injections across both cheeks. At initial and repeat (if performed) treatments, volume is not to exceed a total of 4 mL for both cheeks. At optional touch-up procedure, volume is not to exceed 2 mL for both cheeks. Needle length selection, total injection volume, and injection spacing will be determined by the TI.
DURATION OF STUDY: Treatment group: up to 1 month for screening, up to 1 month for treatment, 6 months of follow-up, and 4 months of follow-up after optional repeat treatment. **Control group**: up to 1 month for screening and 1 month of follow-up; up to 1 month for treatment and 6 months of follow-up after optional treatment.
OBJECTIVES: The objective of this study is to evaluate the safety and effectiveness of JUVÉDERM VOLITE XC injectable gel for the improvement in cheek skin smoothness.
KEY ENDPOINTS: • Primary: ACSS responder status at Month 1 • Secondary: Change from baseline to Month 1 on FACE-Q Satisfaction with Skin questionnaire • Secondary: AFLS responder status at Month 1 • Safety: FACE-Q Recovery Early Life Impact questionnaire, procedural pain, ISRs from 30-day e-diaries, AEs, Snellen visual acuity, confrontation visual fields, and ocular motility
OVERALL STUDY DESIGN: • Randomized, controlled, parallel-design • Single-blind: EIs are blinded; TIs and subjects are not blinded • Treatment group subjects receive initial treatment and optional touch-up treatment at 30 days if needed to achieve optimal correction. Follow-up visits are 3 days after each treatment (safety only) and at Months 1, 2, 4, and 6 after last treatment. Subjects exit the study at Month 6 or receive repeat treatment and are followed at Day 3 and Months 1 and 4 after repeat treatment. • Control group subjects are followed for 1 month after randomization (no-treatment control period) and then either exit the study or receive optional treatment (initial and touch-up, if needed) in the delayed treatment period. Follow-up visits are 3 days after each treatment (safety only) and at Months 1, 2, 4, and 6 after last treatment. Subjects exit the study at Month 6.

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION:

Adults seeking improvement in cheek skin smoothness

INCLUSION:

1. Age 22 or over and in good general health
2. Has an ACSS score of 2 for both cheeks or 3 for both cheeks on the 5-point Allergan cheek smoothness photonumeric scale (range: 0 to 4), as judged live by the EI
   OR
   has Fitzpatrick skin phototype V or VI and has an ACSS score of 1, 2, or 3 on both cheeks (the cheeks do not need to have the same score), as judged live by the EI (Fitzpatrick V/VI safety cohort)
3. Has a FACE-Q Satisfaction with Skin Questionnaire sum score of 39 or less (sum score of 39 is equivalent to Rasch-transformed score of 69) unless enrolled as part of the Fitzpatrick V/VI safety cohort
4. Ability to follow study instructions and likely to complete all required visits
5. Written informed consent and data privacy consent have been obtained

EXCLUSION:

1. Requires more than 6 mL of product for optimal correction of both cheeks based on the TI's clinical judgment
2. Has undergone tissue augmentation with dermal fillers including HA, calcium hydroxylapatite, autologous fat, mesotherapy, or other cosmetic procedures (eg, face-lift, laser, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, or other ablative procedures) in the face within 12 months before screening or is planning to undergo any such treatment during the study
3. Has received any crosslinked HA filler in any anatomic area within 12 months of screening
4. Has undergone treatment with botulinum toxin in the cheek area (including crow's feet) within 6 months of screening or is planning to undergo such treatment during the study
5. Has ever received semipermanent fillers or permanent facial implants (eg, poly-L-lactic acid, polymethylmethacrylate, silicone, expanded polytetrafluoroethylene) anywhere in the face or is planning to be implanted with any of these products at any time during the study
6. Has facial tattoos, piercings, pigmentation, hair (ie, beard, mustache), or past trauma that would interfere with the visualization of the face for the effectiveness assessments
7. Has undergone a dental procedure within 6 weeks before treatment or plans to undergo a dental procedure (other than prophylaxis or dental fillings) during the course of the study
8. Has a tendency to develop hypertrophic scarring
9. Has a history of allergy to lidocaine, HA products, and/or to gram-positive bacterial proteins as HA is produced by *Streptococcus*-type bacteria, or is planning to undergo desensitization therapy during the term of the study
10. Has a history of anaphylactic shock
11. Has current cutaneous inflammatory or infectious processes (eg, acne, herpes), abscess, an unhealed wound, or a cancerous or precancerous lesion on the face (injection may be delayed to allow subjects with a history of recurrent oral herpes to take prophylactic antiviral/herpes medication for 2 days)
12. Is on an ongoing regimen of anticoagulation therapy (eg, warfarin) or is known to have a coagulation disorder
13. Is on an ongoing regimen of medications (eg, aspirin, ibuprofen) or other substances (eg, herbal supplements with garlic, ginkgo biloba, or ginseng) known to increase coagulation time within 10 days of undergoing study device injection (study device injection may be delayed as necessary to accommodate this 10-day washout period)
14. Has active autoimmune disease
15. Has received any investigational product within 30 days before enrollment or is planning to participate in another investigation during the course of this study
16. Has begun using any over-the-counter or prescription, oral or topical, anti-wrinkle products on the face 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)

17. Females who are pregnant, nursing, or planning a pregnancy during the study
18. Is an employee (or a relative of an employee) of the PI/TI/EI/site, Allergan, or representative of Allergan
19. 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

STATISTICAL METHODS:

Sample Size Calculation:

A sample size of 112 subjects in the treatment group and 56 subjects in the control group will provide 99.9% power to detect a difference of at least 40% in the responder rates on ACSS between the groups, based on a 2-sided Fisher's exact test at the 5% level. The treatment group is assumed to have at least an 80% responder rate at Month 1, and the control group is assumed to have at most a 40% responder rate. The assumptions of responder rates are estimated from Allergan study V12-001.

At least 135 subjects with a baseline AFLS score of 2 on both cheeks or 3 on both cheeks are expected to enroll. The number of subjects with baseline AFLS score of 0, 1, or 4 on either cheek, or 2 on one cheek and 3 on the other cheek is not expected to exceed 75. Assuming at least 65% of subjects will have baseline AFLS score of 2 on both cheeks or 3 on both cheeks, 72 subjects in treatment group and 36 subjects in control group will provide 94.4% power to detect a difference of at least 35% in the responder rates on AFLS between the treatment groups, based on a 2-sided Fisher's exact test at the 5% level. The treatment group is assumed to have at least an 80% responder rate at Month 1, and the control group is assumed to have at most a 45% responder rate. The assumptions of responder rates are estimated from Allergan study V12-001.

Accounting for subject attrition of 20% during the study, 210 subjects will be randomized at a 2:1 ratio to treatment group and control group. Randomization will be within each study site.

Assuming 119 subjects from the treatment group and 28 subjects from the control group will be treated, a total of 147 treated subjects will provide 95% power to detect an AE related to treatment with an incidence rate of 2% in the population using a 1-sided exact binomial test at the 2.5% level. The safety calculation used an inequality test for 1 proportion.

Effectiveness:

The primary effectiveness measure is the EI's assessment of cheek skin smoothness using the ACSS. The primary effectiveness analysis is the ACSS responder rate at Month 1. A responder is defined as a subject who shows at least a 1-point improvement from baseline on the ACSS on both cheeks. The responder rate and corresponding 95% confidence interval will be summarized. A 2-sided, Fisher's exact test at the 5% level will be used to test whether the ACSS responder rate at Month 1 in the treatment group is significantly greater than that in the control group at Month 1 in the control period. The primary effectiveness endpoint will be met if the responder rate for the treatment group is statistically greater than that for the control group at Month 1.

The secondary effectiveness variables are 1) subject responses on the FACE-Q Satisfaction with Skin questionnaire, and 2) EI's assessment of fine lines on the cheeks on the AFLS. The secondary effectiveness analyses include change from baseline in FACE-Q scale score at Month 1 and the AFLS responder rate at Month 1. The responses to the 12 FACE-Q items will be summed and converted to a scale score that ranges from 0 to 100 (higher score indicates more satisfaction) using the algorithm developed by the FACE-Q scale developers. An AFLS responder is defined as a subject who shows at least a 1-point improvement from baseline on the AFLS scale on both cheeks. The AFLS responder rate will be analyzed in the same manner as the ACSS responder rate. Only subjects with baseline AFLS score of 2 on both cheeks or 3 on both cheeks will be included in the analysis.

Safety:

AEs will be summarized by primary system organ class, preferred term, and severity. Treatment-related AEs, AEs leading to discontinuation, serious adverse events, and deaths will be listed or tabulated. ISRs will be summarized using descriptive statistics, by symptom, maximum reported severity, and duration for initial,

touch-up, and repeat treatments, separately. Frequency distributions or descriptive summaries of procedural pain and results of FACE-Q Recovery Early Life Impact questionnaire will be provided. Snellen visual acuity, confrontation visual fields, and ocular motility assessments performed by the TI (or designee) will be summarized descriptively.

2. Schedule of Activities

In general, study procedures may be done in sequence as listed in the below tables, but the sequence may be modified based on each site's usual and customary clinic flow. However, there are certain procedures that must be performed before others, and that sequence cannot be altered: inclusion/exclusion criteria including ACSS and FACE-Q Satisfaction with Skin questionnaire **must be completed on the day of Randomization and must be completed before Randomization occurs**). Where possible, subject questionnaires are to be completed prior to other assessments at each visit.

Table 2-1 Screening Visit Procedures: All Subjects

Procedure	Screening
Visit Window	-30 Days
Consent/Authorization	X
Subject demographics	X
Height, weight, and vital signs[a]	X
Fitzpatrick skin phototype and sun exposure history	X
Smoking history	X
Cosmetic, medical, surgical, and dental history	X
Inclusion/Exclusion criteria (TI, EI, Subject). **Exclude ACSS assessment and FACE-Q Satisfaction with Skin assessment if Randomization does not occur during this visit**[b]	X
Urine pregnancy test[c]	X

[a] Includes blood pressure (systolic and diastolic) while subject is seated, pulse rate, and temperature.

[b] ACSS assessment by EI and FACE-Q Satisfaction with Skin assessment by Subject are to be performed only at Randomization visit. Note: it is possible the subject will subsequently be deemed ineligible for the study once these assessments are performed at the Randomization visit.

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

Table 2-2 Treatment Group Procedures

Procedure	Rand/Initial Tx[a]	Day 3 after Initial Tx	Touch-up Tx Day 30[b]	Day 3 after Touch-up Tx	Month 1	Month 2	Month 4	Month 6[c]		Day 3 after RTx	Month 1 After RTx	Month 4 After RTx/Study Exit
								Study Exit	RTx			
Visit Window (Days)		+2	-2/+7	±2	-2/+7	±7	±7	±10	±10	±2	-2/+7	±7
Urine pregnancy test[d]	X		X					X	X			X
Inclusion/Exclusion criteria (TI, EI, Subject)	X											
FACE-Q Satisfaction with Skin questionnaire (Subject)	X		X		X	X	X	X	X		X	X
FACE-Q Appraisal of Lines-Overall questionnaire (Subject)	X		X		X	X	X	X	X		X	X
ACSS (EI)	X		X		X	X	X	X	X		X	X
AFLS (EI)	X		X		X	X	X	X	X		X	X
Skin hydration (EI)	X		X		X	X	X	X	X		X	X
2D facial imaging	X	X	X		X	X	X	X	X		X	X
Randomization[e]	X											
Snellen visual acuity (TI or designee)	X[f]	X	X[f]	X	X				X[f]	X	X	
Confrontational visual fields (TI or designee)	X[f]	X	X[f]	X	X				X[f]	X	X	
Ocular motility (TI or designee)	X[f]	X	X[f]	X	X				X[f]	X	X	
Treatment procedure[g] (TI)	X		X						X			
Procedural pain (Subject)	X											
Safety e-diary[h] (Subject)	X		X						X			
FACE-Q Recovery Early Life Impact questionnaire (Subject)		X										
Natural look and feel assessment (Subject)			X		X	X	X	X	X		X	X
GAIS (Subject)			X		X	X	X	X	X		X	X
Weight measurement					X			X	X			X
Concomitant medications, procedures, treatments	Continuous Monitoring											
Adverse events	Continuous Monitoring											

[a] Randomization must occur within 30 days of screening; screening visit and randomization visit can occur on the same day if subjects do not require washout. If screening and randomization visits occur on the same day, inclusion/exclusion criteria and urine pregnancy testing need not be repeated.

[b] The TI may perform a touch-up treatment, 30 days after initial treatment, if the TI determines that optimal correction was not achieved with initial treatment. If no touch-up treatment is performed, Day 30 visit becomes Month 1 visit.

[c] Study exit visit is at Month 6 for subjects not receiving repeat treatment. If repeat treatment is performed, Month 6 will be repeat treatment visit, and exit visit will be at Month 4 after repeat treatment.

[d] For female subjects of childbearing potential; administered and confirmed negative prior to randomization/treatment. A female subject is not considered of childbearing potential if she has been postmenopausal for at least 1 year or does not have a uterus at the time of study entry.

[e] Randomization and initial treatment for the treatment group must occur on the same day.

[f] On treatment days, vision assessments will be performed before treatment and approximately 30 minutes after treatment.

[g] The treatment procedure is to be performed after all effectiveness assessments and 2D facial imaging.

[h] The 30-day daily safety e-diaries are to be completed following each treatment starting on the day of treatment and are considered complete if all days are completed until the Day 30/Month 1 visit.

Table 2-3 Control Group Procedures (No-Treatment Period)

Procedure	Randomization[a]	Month 1 Study Exit visit
Visit Window (Days)		-2/+7
Urine pregnancy test[b]	X	
Inclusion/Exclusion criteria (TI, EI, Subject)	X	
FACE-Q Satisfaction with Skin questionnaire (Subject)	X	X
FACE-Q Appraisal of Lines-Overall questionnaire (Subject)	X	X
ACSS (EI)	X	X
AFLS (EI)	X	X
Skin hydration (EI)	X	X
2D facial imaging	X	X
Randomization	X	
Weight measurement		X
Concomitant medications, procedures, treatments	Continuous Monitoring	
Adverse events	Continuous Monitoring	

[a] Randomization must occur within 30 days of screening; screening visit and randomization visit can occur on the same day if subjects do not require washout. If screening and randomization visits occur on the same day, inclusion/exclusion criteria and urine pregnancy testing need not be repeated.

[b] For female subjects of childbearing potential; administered and confirmed negative prior to randomization. A female subject is not considered of childbearing potential if she has been postmenopausal for at least 1 year or does not have a uterus at the time of study entry.

Table 2-4 Control Group Procedures (Delayed Treatment Period)

Procedure	Initial Tx[a]	Day 3 after Initial Tx	Touch-up Tx Day 30[b]	Day 3 after Touch-up Tx	Month 1	Month 2	Month 4	Month 6 Study Exit Visit
Visit Window (Days)	+7	+2	-2/+7	± 2	-2/+7	±7	±7	±7
Urine pregnancy test[c]	X		X					X
Snellen visual acuity (TI or designee)	X[d]	X	X[d]	X	X			
Confrontational visual fields (TI or designee)	X[d]	X	X[d]	X	X			
Ocular motility (TI or designee)	X[d]	X	X[d]	X	X			
Treatment procedure[e]	X		X					
Procedural pain	X							
Safety e-diary[f] (Subject)	X		X					
FACE-Q Recovery Early Life Impact questionnaire (Subject)		X						
2D facial imaging		X	X		X	X	X	X
FACE-Q Satisfaction with Skin questionnaire (Subject)			X		X	X	X	X
FACE-Q Appraisal of Lines-Overall questionnaire (Subject)			X		X	X	X	X
Natural look and feel assessment (Subject)			X		X	X	X	X
GAIS (Subject)			X		X	X	X	X
ACSS (EI)			X		X	X	X	X
AFLS (EI)			X		X	X	X	X
Skin hydration (EI)			X		X	X	X	X
Weight measurement								X
Concomitant medications, procedures, treatments		Continuous Monitoring						
Adverse events		Continuous Monitoring						

[a] Initial treatment for the control group is offered only after completion of 1 month of no-treatment control period.

[b] The TI may perform a touch-up treatment, 30 days after initial treatment, if the TI determines that optimal correction was not achieved with initial treatment. If no touch-up treatment is performed, Day 30 visit becomes Month 1 visit.

[c] For female subjects of childbearing potential; administered and confirmed negative prior to treatment. A female subject is not considered of childbearing potential if she has been postmenopausal for at least 1 year or does not have a uterus at the time of study entry.

[d] On treatment days, vision assessments will be performed before treatment and approximately 30 minutes after treatment.

[e] The treatment procedure is to be performed after all effectiveness assessments and 2D facial imaging.

[f] The 30-day daily safety e-diaries are to be completed following each treatment starting on the day of treatment and are considered complete if all days are completed until the Day 30/Month 1 visit.

3. Introduction

JUVÉDERM VOLITE™ XC (with lidocaine) is an HA-based injectable gel dermal filler for improvement in facial skin smoothness to meet an unmet need for this indication.

3.1 Study Rationale

JUVÉDERM VOLITE without lidocaine was CE-marked in 2015, and the product with lidocaine was CE-marked in 2016. An open-label European study (V12-001) of JUVÉDERM VOLITE without lidocaine provided evidence of the product's safety and effectiveness in improving facial skin smoothness, and it serves as a feasibility study. This protocol is designed as a pivotal study to collect safety and effectiveness data on JUVÉDERM VOLITE XC for improvement in facial skin smoothness in order to support FDA product approval.

3.2 Background

JUVÉDERM VOLITE XC (HA concentration 12 mg/mL) is the newest member of the VYCROSS® technology platform, which includes JUVÉDERM VOLBELLA® XC (15 mg/mL, FDA-approved in 2016), JUVÉDERM VOLLURE™ XC (17.5 mg/mL, FDA-approved in 2017), and JUVÉDERM VOLUMA® XC (20 mg/mL, FDA-approved in 2013). Each VYCROSS product is specifically tailored for its relative clinical use (lift capacity and spreadability), with JUVÉDERM VOLITE XC having the lowest HA concentration to serve the unmet need of a filler for fine lines. JUVÉDERM VOLITE XC also contains 0.3% lidocaine (w/w gel) to reduce injection pain and uncrosslinked HA to ease filler extrusion, which is the same amount of lidocaine and uncrosslinked HA included in VOLBELLA and VOLLURE.

The safety of JUVÉDERM VOLITE XC is supported by preclinical biocompatibility data, which show that it is nontoxic, noncytotoxic, nongenotoxic, nonirritant, nonsensitizing, noncarcinogenic, and nonpyrogenic.

A prospective, single-arm European postapproval study (V12-001) was conducted at a single center (6 injecting physicians from 6 countries) to assess the safety and effectiveness of JUVÉDERM VOLITE without lidocaine in treating fine lines and skin roughness in the face and neck. Treatment was administered on both sides of the face (cheek and forehead) and neck (if desired) for fine lines and the improvement in skin roughness. For 131 treated subjects, a total of 261 cheeks, 120 foreheads, and 96 necks were treated. Touch-up treatments were provided for 31 subjects (23.7%) and 46 cheeks (17.6%), and repeat treatments at 9 months were provided for 62 subjects (47.3%) and 124 cheeks (47.5%). The responder rate on the ACSS (formerly known as the Allergan Skin Roughness Scale) was 96.2% at Month 1, 76.3% at Month 4, 34.9% at Month 6, 15.8% at Month 9, and 87.1% at 1 month after repeat treatment. Among treated cheeks with scores of moderate or severe at baseline on the AFLS, the AFLS responder rate was 89.4% at Month 1, 66.7% at Month 4, 40.5% at Month 6, 15.6% at Month 9, and 94.3% at 1 month after repeat treatment. A statistically significant improvement ($p < 0.001$) in subject satisfaction with

skin based on the FACE-Q Satisfaction with Skin questionnaire was observed at all timepoints. The V12-001 study served as the basis for the present study's sample size calculations (see Section 10.1) and injection volumes and treatment characteristics (see Section 5.5) as well as a study follow-up duration of 6 months based on the product's observed clinical duration.

3.3 Device Description

JUVÉDERM VOLITE XC is a sterile, biodegradable, nonpyrogenic, viscoelastic, clear, colorless, homogeneous, HA gel implant (dermal filler). It consists of crosslinked HA produced by the *Streptococcus* species of bacteria, formulated to a concentration of 12 mg/mL and 0.3% lidocaine in a physiological buffer. The gel is provided in a plastic syringe, which is packaged with two 32 G 1/2" needles, and 32 G 3/16" needles are provided separately.

3.4 Benefit/Risk Assessment

A risk analysis linked to the manufacturing, biocompatibility, and usage of JUVÉDERM VOLITE XC was conducted according to ISO 14971:2007/EN ISO 14971:2012 and is detailed in the risk management file.

The injection procedure, anesthetic agents, or JUVÉDERM VOLITE XC may cause some of the risks and/or discomforts listed below. 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.

As with any skin injection, risks can be posed by the injection procedure itself, the anesthetic agent, and injection of JUVÉDERM VOLITE XC injectable gel. Risks related to the injection procedure include redness, itching, pain, tenderness, swelling, bruising, and lumps and bumps, which are common to dermal filler injection procedures in general. The use of a small gauge needle to deliver JUVÉDERM VOLITE XC used in this study is intended to minimize tissue trauma. The inclusion of 0.3% lidocaine in the formulation is meant to reduce pain during the injection, and this needs to be taken into account when administering concomitant additional anesthetics as well as in relation to subjects' medical history (ie, allergy to lidocaine). Risks associated with the anesthetic agent include allergic reactions that may manifest as an anaphylactic reaction, skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient loss of skin color.

Prior to administering any topical pretreatment anesthesia, the TI will thoroughly review the subject's history to confirm the suitability of the planned anesthetic agent. Additionally, the investigational DFU must be carefully reviewed, and each individual subject's medical history must be carefully considered, when evaluating a potential subject's candidacy for study enrollment.

The benefit of using HA dermal fillers in facial aesthetics has been documented in the published literature showing the safety and effectiveness of HA dermal fillers. It is anticipated that the safety and effectiveness of treatment to improve facial skin smoothness are similar to those identified in studies of JUVÉDERM products for equivalent indications such as perioral lines. The physicochemical properties of JUVÉDERM VOLITE XC potentially provide the benefit of use of HA dermal fillers for improvement in facial skin smoothness.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of JUVÉDERM VOLITE XC are provided in the investigational DFU.

4. Objectives and Endpoints

4.1 Study Objectives and Endpoints

The objective of this study is to evaluate the safety and effectiveness of JUVÉDERM VOLITE XC in subjects seeking improvement in cheek skin smoothness.

Objectives	Endpoints/Measures
Effectiveness To evaluate the effectiveness of JUVÉDERM VOLITE XC in adult subjects seeking improvement in cheek skin smoothness	• Primary: ACSS responder status at Month 1
	• Secondary: Change from baseline to Month 1 on FACE-Q Satisfaction with Skin questionnaire
	• Secondary: AFLS responder status at Month 1
	• Other: Primary and secondary endpoints at other applicable timepoints
	• Other: Change from baseline on FACE-Q Appraisal of Lines Overall questionnaire
	• Other: Natural look and feel of the skin
	• Other: Global aesthetic improvement on GAIS
	• Other: Change from baseline in cheek skin hydration measured by MoistureMeter® D instrument
	• Exploratory: Composite responder status on ACSS and FACE-Q Satisfaction with Skin questionnaire
Safety To evaluate the safety of JUVÉDERM VOLITE XC in adult subjects seeking improvement in cheek skin smoothness	• FACE-Q Recovery Early Life Impact questionnaire • Procedural pain • ISRs • AEs • Snellen visual acuity, confrontational visual fields, ocular motility

4.2 Clinical Hypotheses

The clinical hypothesis is that the percentage of subjects with a clinically significant change (defined as at least a 1-point improvement on the ACSS as assessed by the EI) in cheek skin smoothness from baseline to Month 1 for both cheeks) will be significantly greater in the JUVÉDERM VOLITE XC treatment group than in the untreated control group.

5. Study Design

5.1 Overall Design

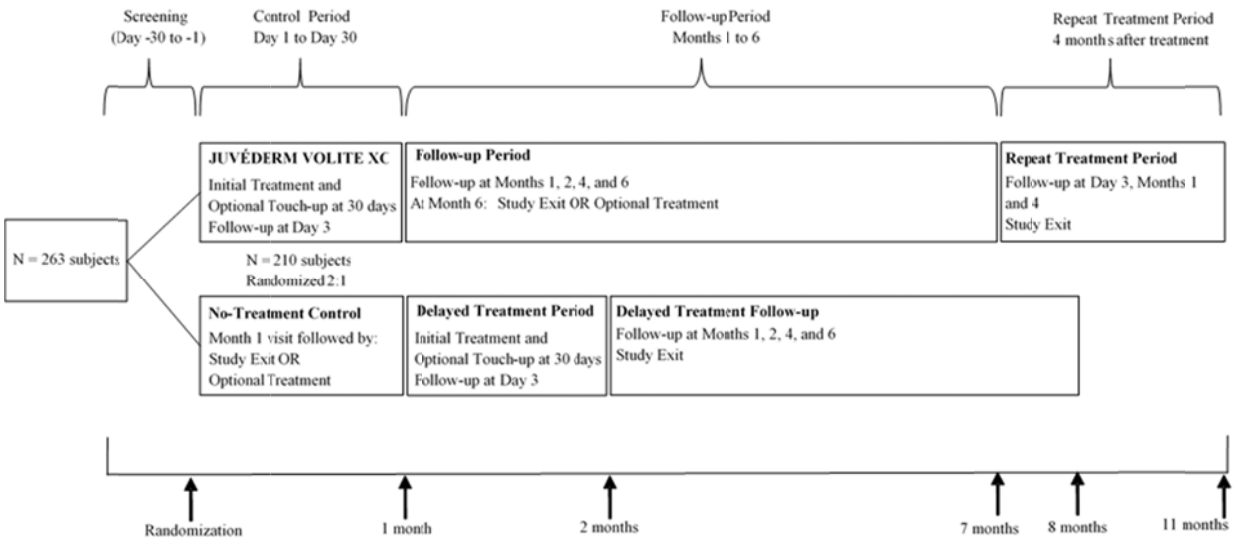
This is a multicenter, evaluator-blind, controlled, parallel-design, prospective study of adults seeking improvement in cheek skin smoothness. Up to 20 investigational sites will enroll and follow subjects who meet the study criteria according to the study design in Figure 5-1. Each site will have a PI who is responsible for the overall conduct of the study at that site and may also be the TI. The TI performs all study treatments, and the blinded EI evaluates ACSS, AFLS, and skin hydration measurements.

The study will span a total of approximately 20 months: an estimated 9 months for recruitment and 11 months for follow-up. For the treatment group, each subject's participation will encompass up to 30 days of treatment and up to 10 months of follow-up (6 months for those choosing not to receive repeat treatment at Month 6). For the control group, each subject's participation will encompass 1 month; for control subjects who opt to receive treatment, the treatment period will be up to 30 days, and the follow-up period will be up to 6 months.

Treatment group subjects receive initial treatment and optional touch-up treatment at 30 days if needed to achieve optimal correction. Follow-up visits are 3 days after each treatment (safety only) and at Months 1, 2, 4, and 6 after last treatment. Subjects exit the study at Month 6 or receive repeat treatment and are followed at Day 3 and Months 1 and 4 after repeat treatment. Control group subjects are followed for 1 month after randomization (no-treatment control period) and then either exit the study or receive optional treatment (initial and touch-up, if needed) in the delayed treatment period. Post-treatment follow-up visits are 3 days after each treatment and at Months 1, 2, 4, and 6 after last treatment.

To ensure adequate enrollment of subjects with Fitzpatrick skin phototype V and VI, up to 10 subjects may be enrolled in the Fitzpatrick V/VI safety cohort with less stringent inclusion criteria (see Section 6.1) and followed for safety only.

Figure 5-1 Study Design



5.2 Subject and Study Completion

A maximum of 263 subjects will be enrolled at up to 20 US sites in order to have 210 subjects randomized and 112 treatment group subjects and 56 control group subjects complete the study based on an anticipated dropout rate of 20%. A maximum of 20% of the study population may be enrolled at any 1 investigational site. See Section 10.1 for explanation of sample size determination.

5.3 End of Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study.

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit. Treatment group subjects who elect not to receive repeat treatment are considered completers if they complete the Month 6 visit. Control group subjects who elect not to receive treatment are considered completers if they complete the Month 1 visit.

5.4 Scientific Rationale for Study Design

This pivotal study was designed with a no-treatment control because there are no FDA-approved dermal fillers for improving cheek skin smoothness to use as a comparator.

5.5 Justification for Device Volume and/or Treatment Administration

In the V12-001 study of JUVÉDERM VOLITE, subjects could receive up to 7 mL in the face and neck. Within this limitation, the maximum volume injected in the cheeks was 2.5 mL total at

initial treatment and 2 mL at touch-up treatment. To ensure that optimal correction can be obtained, the maximum allowable injection volume for this study in the cheeks was set at 4 mL for initial treatment and 2 mL for touch-up treatment. An additional 4 mL is allowed for repeat treatment at Month 6. Consistent with the product attributes and V12-001 study methods, treatment is to be performed in multiple microdepot intradermal injections via 32 G 1/2" or 32 G 3/16" needles, as described in the investigational IFU provided in the Site Study Binder.

6. Study Population

Adults seeking improvement in cheek skin smoothness. The randomization target is a minimum of 20 subjects of Fitzpatrick skin phototypes I/II, 20 of phototypes III/IV, and 20 of phototypes V/VI (up to 10 of whom may be enrolled in the Fitzpatrick V/VI safety cohort).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Age 22 or over and in good general health
2. Has an ACSS score of 2 for both cheeks or 3 for both cheeks on the 5-point Allergan Cheek Smoothness photonumeric scale (range: 0 to 4), as judged live by the EI
   OR
   has Fitzpatrick skin phototype V or VI and has an ACSS score of 1, 2, or 3 on both cheeks (the cheeks do not need to have the same score), as judged live by the EI (Fitzpatrick V/VI safety cohort)
3. Has a FACE-Q Satisfaction with Skin Questionnaire sum score of 39 or less (sum score of 39 is equivalent to Rasch-transformed score of 69) unless enrolled as part of the Fitzpatrick V/VI safety cohort
4. Ability to follow study instructions and likely to complete all required visits
5. Written informed consent and data privacy consent have been obtained

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Requires more than 6 mL of product for optimal correction of both cheeks based on the EI's clinical judgment
2. Has undergone tissue augmentation with dermal fillers including HA, calcium hydroxylapatite, autologous fat, mesotherapy, or other cosmetic procedures (eg, face-lift, laser, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, or other ablative procedures) in the face within 12 months before screening or is planning to undergo any such treatment during the study

3. Has received any crosslinked HA filler in any anatomic area within 12 months of screening
4. Has undergone treatment with botulinum toxin in the cheek area (including crow's feet) within 6 months of screening or is planning to undergo such treatment during the study
5. Has ever received semipermanent fillers or permanent facial implants (eg, poly-L-lactic acid, polymethylmethacrylate, silicone, expanded polytetrafluoroethylene) anywhere in the face or is planning to be implanted with any of these products at any time during the study
6. Has facial tattoos, piercings, pigmentation, hair (ie, beard, mustache), or past trauma that would interfere with the visualization of the face for the effectiveness assessments
7. Has undergone a dental procedure within 6 weeks before treatment or plans to undergo a dental procedure (other than prophylaxis or dental fillings) during the course of the study
8. Has a tendency to develop hypertrophic scarring
9. Has a history of allergy to lidocaine, HA products, and/or to gram-positive bacterial proteins as HA is produced by *Streptococcus*-type bacteria, or is planning to undergo desensitization therapy during the term of the study
10. Has a history of anaphylactic shock
11. Has current cutaneous inflammatory or infectious processes (eg, acne, herpes), abscess, an unhealed wound, or a cancerous or precancerous lesion on the face (injection may be delayed to allow subjects with a history of recurrent oral herpes to take prophylactic antiviral/herpes medication for 2 days)
12. Is on an ongoing regimen of anticoagulation therapy (eg, warfarin) or is known to have a coagulation disorder
13. Is on an ongoing regimen of medications (eg, aspirin, ibuprofen) or other substances (eg, herbal supplements with garlic, ginkgo biloba, or ginseng) known to increase coagulation time within 10 days of undergoing study device injection (study device injection may be delayed as necessary to accommodate this 10-day washout period)
14. Has active autoimmune disease
15. Has received any investigational product within 30 days before enrollment or is planning to participate in another investigation during the course of this study
16. Has begun using any over-the-counter or prescription, oral or topical, anti-wrinkle products on the face 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)
17. Females who are pregnant, nursing, or planning a pregnancy during the study
18. Is an employee (or a relative of an employee) of the PI/EI/TI/site, Allergan, or representative of Allergan
19. 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

6.3 Lifestyle Restrictions

Within the first 12 hours after treatment, it is recommended that subjects not apply make-up to the treatment area. Within the first 24 hours after treatment, it is recommended that subjects avoid shaving in the treatment area, strenuous exercise, extensive sun or heat exposure, and consumption of alcoholic beverages. Subjects will be advised not to enter a hot spring or sauna, or receive excessive exposure to the sun or temperatures below 0°C for 2 weeks following any study treatment (initial, touch-up, or repeat treatments). Exposure to any of these may cause temporary redness, swelling, and/or itching at the injection sites.

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized/treated. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, including reason for screen failure, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened except for those eligible for the Fitzpatrick V/VI safety cohort. Additional information on subject discontinuation/withdrawal criteria is provided in Section 8.

7. Treatments

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

7.1 Treatments Administered

Study Treatment Name	JUVÉDERM VOLITE™ XC
Formulation	Injectable gel
Concentration	12 mg/mL HA + 0.3% lidocaine (w/w gel)
Route of Administration	Intradermal, 32 G 1/2" or 32 G 3/16" needle in multiple microdepot injections across both cheeks
Packaging and Labeling	JUVÉDERM VOLITE XC will be provided sterile in plastic syringes. Each kit will contain 1 or more blisters, each containing 1 syringe prefilled to 1.0 mL and 2 single-use sterile needles (32 G 1/2"), specifically intended for injecting JUVÉDERM VOLITE XC. The 32 G 3/16" needles will be supplied separately. An investigational caution label, such as the following, will appear on the individual syringe package and the outer box: Protocol 1867-701-008 Kit# VVVV Lot# VVVV CAUTION - Investigational Device. Limited by Federal (or United States) law to Investigational Use Use as directed per protocol
Manufacturer	Allergan Industrie, SAS
Number and Timing of Treatments	• Initial treatment • Day 30: optional touch-up • Month 6: optional repeat treatment (treatment group only)
Volume Per Treatment	• Initial treatment: up to 4 mL • Optional touch-up treatment: up to 2 mL • Optional repeat treatment: up to 4 mL

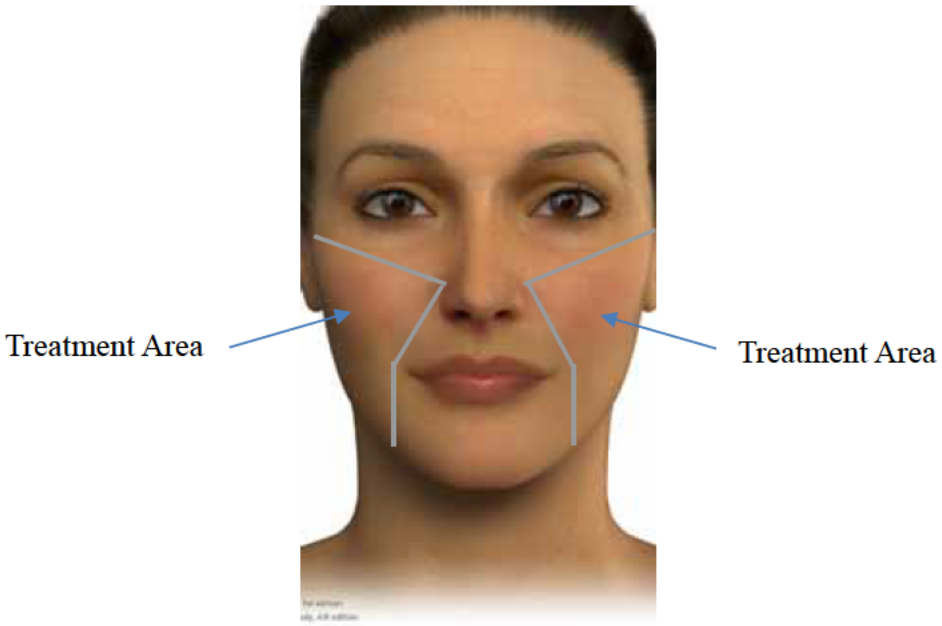
7.1.1 Instructions for Use and Administration

The TIs must be experienced in the use and administration of HA injectable gels and be practicing in the field of aesthetic medicine, dermatology, or plastic/cosmetic/reconstructive surgery. Before the study begins, the TIs will receive training in the administration of JUVÉDERM VOLITE XC according to the technique specified for this study. This injection technique is multiple microdepot intradermal injections to the cheeks, from the zygomatic arch to the edge of the jaw, lateral from the nasolabial fold and oral commissures to the preauricular cheek (see allowable treatment area in Figure 7-1). Needle length selection, total injection volume, and injection spacing will be determined by the TI in accordance with the maximum volume restrictions of 4 mL for initial and repeat treatments and 2 mL for touch-up treatment. Topical anesthesia and/or ice may be applied prior to injection to reduce pain as directed by the TI. After ensuring that the subject has thoroughly washed the treatment area with soap and water,

the area must be prepped with alcohol or other antiseptic. The detailed injection technique guidelines are provided in the investigational DFU included in the Site Study Binder.

During each study visit, subjects will be required to remove all make-up, and male subjects must be clean-shaven in the treatment area to avoid interference with effectiveness assessments.

Figure 7-1 Allowable Treatment Area



7.1.2 Washout Intervals

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

7.1.3 Run-In Medications and Administration

Run-in Intervals	Medication
2 days before treatment 30 days before enrollment	• Prophylactic herpes treatment for subjects with a history of recurrent oral herpes lesions • Over-the-counter or prescription, oral or topical, anti-wrinkle products on the face for subjects who will use such products during the study

7.1.4 Study Supplies

The sponsor will provide product kits, 32 G 3/16" needles, digital imaging equipment, mirrors for subject assessments, subject e-diaries, and subject questionnaires. The investigational site is responsible for routine supplies related to device administration and follow-up visits (eg, antiseptics, drapes, gloves, gauze, anesthesia, ice packs, urine pregnancy test kits (with sensitivity of at least 50 mIU/mL for human chorionic gonadotropin), blood pressure cuff, scale, and internet connection for IWRS and eCRF completion.

7.2 Treatment Modification

Retreatment Criteria

A subject may receive touch-up treatment if optimal correction has not been achieved at Day 30 in the opinion of the TI and is agreed upon by both subject and TI. The TI will have access to the EI-rated ACSS scores to assist in making the determination of whether optimal correction has been achieved. All treatment group subjects are eligible to receive repeat treatment at Month 6 if desired.

7.3 Concomitant Therapy

The use of concomitant medication, prescription or over-the-counter, as well as concomitant procedures or therapies is to be recorded on the subject's eCRF at each visit along with the reason for the treatment.

7.3.1 Prohibited Treatments

During the course of the study, subjects must not:

- Receive injectable anesthesia during study treatment
- Undergo tissue augmentation with dermal fillers including HA, calcium hydroxylapatite, autologous fat, mesotherapy, or other cosmetic procedures (eg, face-lift, laser,

photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, or other ablative procedures) in the face

- Undergo treatment with botulinum toxin in the cheek area (including crow's feet)
- Undergo treatment with semipermanent fillers or permanent facial implants (eg, poly-L-lactic acid, polymethylmethacrylate, silicone, expanded polytetrafluoroethylene) anywhere in the face
- Undergo a dental procedure (other than prophylaxis or dental fillings)
- Be on a regimen of medications (eg, aspirin, ibuprofen) or other substances (eg, herbal supplements with garlic, ginkgo biloba, or ginseng) known to increase coagulation time for 3 days after each study treatment
- Receive any other investigational product
- Use any over-the-counter or prescription, oral or topical, anti-wrinkle products on the face that were not a stable regimen for at least 30 days prior to study enrollment
- The use of hyaluronidase for aesthetic purposes is not permitted. If hyaluronidase is used, the subject will be followed for safety only from that point on.

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

7.3.2 Permitted Treatments

Any medication/treatment or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the subject's welfare may be given at the discretion of the TI.

It is recommended that the sponsor (or designee) be contacted if there are any questions regarding concomitant or prior therapy or the permissibility of a specific medication/treatment.

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

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

7.4 Method of Treatment Assignment and Allocation Ratio

Prior to initiation of study treatment, each consented subject will be assigned a subject number that will be recorded on the appropriate eCRF. At the time of randomization (ie, at the Randomization/Initial Treatment visit), eligible subjects will be randomly assigned at a 2:1 ratio to treatment group or control group. Randomization will be within each study site. All subjects will be centrally randomized using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. If subjects are withdrawn, they will not be replaced.

7.5 Blinding/Masking

The EIs will be blinded to treatment and will not be present during the injection procedures.

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

7.6 Preparation/Handling/Storage/Accountability

1. The PI or designee must confirm appropriate temperature conditions have been maintained during transit and pre-treatment storage for all study treatment and ensure any discrepancies are reported and resolved before use of the study treatment.

2. Only subjects enrolled in the study may receive study treatment, and only the TI may administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (automated) area in accordance with the labeled storage conditions with access limited to the PI/TI and authorized site staff.

3. The PI (or a delegated designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Include subject ID number, device serial or lot number, and date of treatment.

4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Site Binder.

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

8. Discontinuation/Withdrawal Criteria

Notification of early subject discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

Reasons for discontinuation from the study treatment and/or the study may include the following:

- AE
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject

8.1 Withdrawal from the Study

If a subject has a positive urine pregnancy test prior to initial treatment, the subject will be exited from the study. If the test is positive at the touch-up treatment visit, no touch-up treatment will be performed, but the subject will continue to be followed in the study and will be exited at Month 6. If the test is positive at the repeat treatment visit, no repeat treatment will be performed, and the subject will be exited from the study. Pregnancies for treated subjects will be followed as described in Section 9.5.6.

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

- Receives any dermal filler or fat injection to the cheeks
- Receives cosmetic procedures (eg, face-lift, laser, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, or other ablative procedures) in the face

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the PI/TI for safety, behavioral, or administrative reasons.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the PI (or a delegated designee) must document this in the site study records.

See the schedule of activities (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

For any subject who withdraws from the study, the date and reason for withdrawal will be recorded on the eCRF. If an ISR or treatment-related AE is ongoing at the time of withdrawal, the TI will attempt to follow the subject until the ISR or AE has been resolved or follow-up is no longer possible. The PI/TI shall ask for the subject's permission to follow his/her status/condition outside the study.

If a subject fails to return for 1 or more scheduled study visits, the PI/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.

8.2 Lost to Follow-Up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or will continue in the study.

- Before a subject is deemed lost to follow-up, the PI/TI (or designee) must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts will be documented in the subject's medical record.

- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

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

- An unscheduled visit may occur for safety purposes (eg, evaluation of AEs or ISRs as requested by the subject and/or TI) or photographic reshoots. Applicable procedures will be performed and recorded on the eCRF.

- Throughout the study, to the extent possible, it is recommended that treatment and safety assessments for a particular subject be performed by the same TI, and effectiveness assessments (ACSS, AFLS, and hydration measurements) 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.

- Where possible, subject questionnaires are to be completed prior to other assessments at each follow-up visit, with the FACE-Q questionnaires completed first.

- Safety e-diaries will ensure that subjects complete diaries on a daily basis by locking entry for prior days once they have passed.

- Study procedures and their timing are summarized in the schedule of activities (Section 2).

- Protocol waivers or exemptions are not allowed.

- Immediate safety concerns must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject will continue or discontinue study treatment.

- Adherence to the study design requirements, including those specified in the schedule of activities (Section 2), is essential and required for study conduct.

- Inclusion/Exclusion criteria including ACSS and FACE-Q Satisfaction with Skin Questionnaire must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. If Screening and Randomization are at separate visits, ACSS and FACE-Q Satisfaction with Skin Questionnaire are only completed on the day of randomization. The PI will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the subject's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of activities (Section 2).

9.1 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics to be collected at screening include sex, age, race, height, weight, Fitzpatrick skin phototype, sun exposure, smoking history, medical/surgical/cosmetic/dental procedure history, and prior medications. Two-dimensional facial imaging is captured at randomization and all follow-up visits to provide visual evidence of safety and effectiveness. Height and weight will be collected at screening, and weight will also be collected at Month 1, Month 6, and study exit due to its potential influence on effectiveness measures.

Vital sign measurements, including blood pressure (systolic and diastolic, while subject is seated), pulse rate, and temperature, and a urine pregnancy test for women of childbearing potential will also be performed. If the test is positive, the subject will be exited from the study. Females who are postmenopausal for at least 1 year or have no uterus are considered not of childbearing potential.

9.2 Treatment Administration Assessments

Characteristics of treatment administration will be collected and evaluated for anesthesia usage (topical or ice), needle length (32 G 1/2" or 32 G 3/16") injection volume, injection spacing (≤ 5 mm, > 5 mm to 1 cm, > 1cm), and injection plane (intradermal or other).

9.3 Effectiveness Assessments

9.3.1 Primary Effectiveness Measure

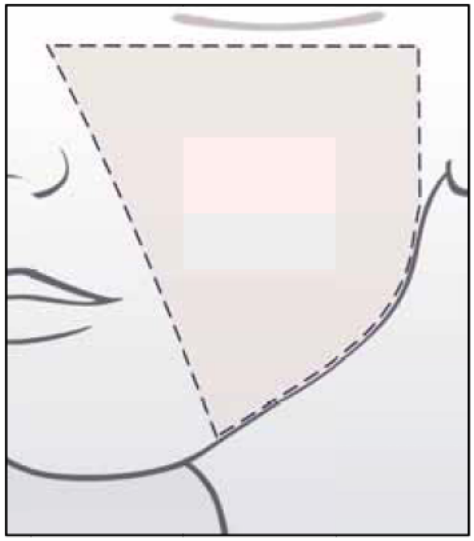
The primary effectiveness measure is the EI's assessment of cheek skin smoothness using the ACSS scale described in Table 9-1. The anatomic area to be rated for skin smoothness is defined as from the oral commissure to the preauricular cheek and from the zygomatic arch to the mandible (Figure 9-1).

The ACSS is a validated 5-point ordinal scale developed by Allergan to grade the severity of skin smoothness on the cheeks. The ACSS contains a morphed subject photograph showing all 5 severities of cheek smoothness as well as photographic images of subjects representing different Fitzpatrick skin types, race categories, both sexes, and all severities of skin smoothness. Prior to initiating enrollment at their site, all investigators (TIs and EIs) will be trained in the use of the ACSS and demonstrate substantial inter- and intra-rater agreement.

Table 9-1 Allergan Cheek Smoothness Scale

Score	Grade	Description
0	None	Smooth visual skin texture
1	Minimal	Slightly coarse and uneven visual skin texture
2	Moderate	Moderately coarse and uneven visual skin texture; may have early elastosis
3	Severe	Severely coarse visual skin texture, crosshatched fine lines; may have some elastosis
4	Extreme	Extremely coarse visual skin texture, crosshatched deep creases; extreme elastosis

Figure 9-1 Assessment Area for the Allergan Cheek Smoothness Scale



9.3.2 Secondary Effectiveness Measures

The first secondary effectiveness measure is subject responses on the FACE-Q Satisfaction with Skin questionnaire, which was designed and validated to assess the impact of treatment from the subject's perspective, targeting satisfaction with skin (Klassen 2016). Although the questionnaire is not specific to fine lines on the cheeks, it is anticipated that JUVÉDERM VOLITE XC treatment will improve satisfaction with skin. In accordance with FDA guidance on developing patient-reported outcome measures, all FACE-Q questionnaires were developed for use in clinical studies to support approval and labeling claims and, thus, are robust, validated measures

(FDA Guidance on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009). The responses to the 12 items will be summed and converted to a scale score that ranges from 0 to 100 (higher score indicates increased satisfaction) using the algorithm developed by the FACE-Q scale developers.

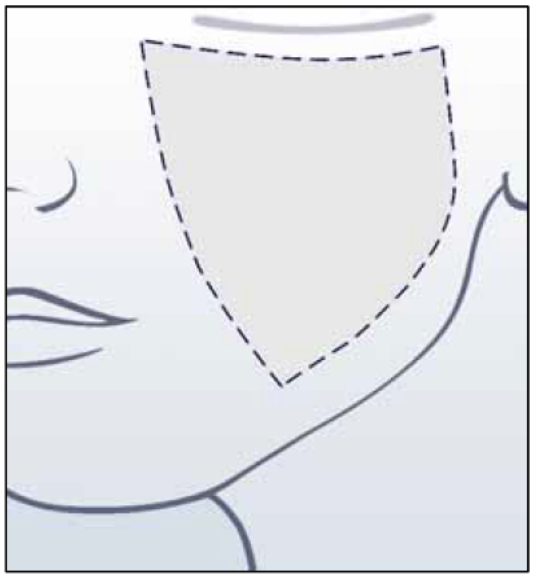
The other secondary effectiveness measure is the EI's assessment of fine lines on the cheeks using the AFLS scale described in Table 9-2. The anatomic area to be rated is defined as 1 cm lateral from the nasolabial fold to the preauricular cheek and from the inferior orbital rim to 1 cm above the mandible; this does not include nasolabial lines or crow's feet lines (Figure 9-2).

The AFLS is a validated 5-point ordinal scale developed by Allergan to grade the severity of fine lines on the cheeks. The AFLS contains photographic images of subjects representing different Fitzpatrick skin types, race categories, and severities of fine lines. Prior to initiating enrollment at their site, all investigators (TIs and EIs) will be trained in the use of the AFLS and demonstrate substantial inter- and intra-rater agreement.

Table 9-2 Allergan Fine Lines Scale

Score	Grade	Description
0	None	No fine lines
1	Minimal	1-2 superficial lines
2	Moderate	3-5 superficial lines
3	Severe	Greater than 5 superficial lines; no crosshatching
4	Diffuse	Diffuse superficial lines; crosshatching

Figure 9-2 Assessment Area for the Allergan Fine Lines Scale



9.3.3 Other Effectiveness Measures

Other effectiveness measures include:

- Subject responses on the validated FACE-Q Appraisal of Lines-Overall questionnaire (Klassen 2016; 10 items scored in the same manner as the first secondary effectiveness measure)
- Subject assessment of the natural look of the cheek skin on an 11-point scale ranging from 0 (unnatural looking) to 10 (natural looking)
- Subject assessment of the natural feel of the cheek skin on an 11-point scale ranging from 0 (unnatural feeling) to 10 (natural feeling)
- Subject assessment of the global aesthetic improvement of the cheek skin on the 5-point GAIS (Table 9-3)

Table 9-3 Global Aesthetic Improvement Scale

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

- Skin hydration measured by MoistureMeter® D instrument (Delfin Technologies) on the zygoma at the upper cheek, at the point where a vertical line from the lateral canthus intersects with the most prominent portion of the zygoma

MoistureMeter® D instrument generates a high-frequency electromagnetic wave that penetrates perpendicularly into the skin. The resulting reflected wave is recorded, and the dielectric constant obtained is proportional to the quantity of fluids in the cutaneous area studied. Depending on the captor chosen, it is thus possible to measure the water content at different depths of the dermis and hypodermis. In this study, we will use the XS5 probe (depth of effective measurement: 0.5 mm) to measure the water content in the dermis. Prior to initiating enrollment, the EIs will be trained in the use of the MoistureMeter® D.

9.4 Safety Assessments

Safety measures include:

- Subject responses on the validated FACE-Q Recovery Early Life Impact questionnaire (Klassen 2015; 12 items scored in the same manner as the first secondary effectiveness measure)
- Subject assessment of procedural pain at initial treatment on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable)
- Subject assessment of the presence and severity of ISRs, recorded in the subject's daily e-diary for each cheek for up to 30 days after treatment (initial, touch-up, and repeat) starting on the day of treatment
- AEs from TI observation and inquiry at scheduled follow-up visits
- Monitoring of concomitant medications and concurrent procedures
- Snellen visual acuity assessed by the TI (or designee)
- Confrontational visual fields assessed by the TI (or designee)
- Ocular motility assessments assessed by the TI (or designee)

The subject's daily safety e-diary will list the following ISRs that have been reported previously with HA dermal filler injections and will include space to include other symptoms:

- Redness
- Pain after injection
- Tenderness to touch
- Firmness
- Swelling
- Lumps/bumps
- Bruising
- Itching
- Discoloration (not redness or bruising)

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

None	None or not applicable.
Mild	Symptoms causing little, if any, discomfort leading to little, if any, effect on daily activities.
Moderate	Symptoms causing some discomfort leading to some effect on daily activities.
Severe	Symptoms causing great discomfort leading to compromised performance of daily activities.

Subjects are to bring the e-diaries to their Day 3 and Day 30/Month 1 visits for review by the TI, and the TI will determine if the ISR qualifies as an AE. ISRs that are ongoing at the end of the diary will be reported on the ongoing ISR eCRF and tracked to resolution or until follow-up is no longer possible. Subjects who did not record the e-diaries for the entire diary period are to enter the responses on the Day 30/Month 1 visits to ensure a consistent recording between eCRF and e-diaries.

9.5 Adverse Events

AEs will be monitored throughout the study beginning with signing of the ICF. At each post-baseline visit, the TI 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?" Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate eCRF.

The definitions of an AE/ADE/AESI or SAE/SADE are provided in Appendix 12.3.

The PI/TI and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE/ADE/AESI or SAE/SADE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study (see Section 8).

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

The PI/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. Additional information is available in the investigational DFU. 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, the subject condition is considered stable by the PI/TI, or follow-up is no longer

possible. After the final visit, the subject will resume receiving the standard medical care according to the standard care of the clinic.

The following is a list of known potential AEs:

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

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

9.5.1 Time Period and Frequency for Collecting AE/ADE and SAE/SADE Information

All SAEs/SADEs from the signing of the ICF until the last follow-up visit will be collected at the timepoints specified in the schedule of activities (Section 2), and as observed or reported spontaneously by study subjects.

All AEs/ADEs from the signing of the ICF until the last follow-up visit will be collected at the timepoints specified in the schedule of activities (Section 2), and as observed or reported spontaneously by study subjects.

Medical occurrences that begin before the start of study treatment but after obtaining IC will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs/SADEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 12.3. The PI/TI will submit any updated SAE data to the sponsor within 24 hours of it being available.

PIs/TIs are not obligated to actively seek AE or SAE information in former study subjects. However, if the PI/TI learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the PI/TI must promptly notify the sponsor.

Safety data collection and reporting guidelines are summarized in Table 9-4. The method of recording, evaluating, and assessing causality of AEs/ADEs and SAEs/SADEs and the procedures for completing and transmitting SAE/SADE reports are provided in Appendix 12.3.

Table 9-4 Safety Data Collecting and Reporting Guidelines

AE Type	Reporting to Sponsor (upon awareness)	Start Collection	End Collection
AE, ADE	Record on AE eCRF for review by the Monitor	Immediately after ICF signed	Last subject visit
AESI	Record on appropriate eCRF & report via fax/email to sponsor within 24 hours of awareness	Immediately after ICF signed	Last subject visit
SAE, SADE	Record on SAE form & report via fax/email to sponsor within 24 hours of awareness	Immediately after ICF signed	Last subject visit
Medical device incident	Record on the appropriate form & report via fax/email to sponsor within 24 hours of awareness	Immediately after ICF signed	Last subject visit
Device deficiency	Record on the appropriate form & report via fax/email to sponsor within 24 hours of awareness	Immediately after ICF signed	Last subject visit

9.5.2 Method of Detecting AEs/ADEs and SAEs/SADEs

Care will be taken not to introduce bias when detecting AEs/ADEs and/or SAEs/SADEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

9.5.3 Follow-up of AEs/ADEs and SAEs/SADEs

After the initial report, the PI/TI is required to proactively follow each subject at subsequent visits/contacts. All AEs/ADEs/SAEs/SADEs and AESIs as defined in Section 9.5.5 will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.2). For subjects who complete the study with an ongoing treatment-related AE or withdraw from the study with an ongoing treatment-related AE, the PI/TI will attempt to follow the subject until the AE has been resolved or follow-up is no longer possible. The PI/TI will ask for the subject's permission to follow his/her status/condition outside the study.

The PI/TI is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Allergan Medical Safety Physician to elucidate the nature and/or causality of the AE/ADE or SAE/SADE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study, the PI/TI will provide the Allergan Medical Safety Physician with a copy of any postmortem findings including histopathology.

New or updated information will be recorded on the originally completed eCRF.

The PI/TI will submit any updated SAE/SADE data to the sponsor within 24 hours of receipt of the information.

9.5.4 Regulatory Reporting Requirements for SAEs and SADEs

- Prompt notification by the PI to the sponsor of an SAE/SADE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and PIs.
- A PI who receives an investigator safety report describing a SAE/SADE or other specific safety information (eg, summary or listing of SAEs/SADEs) from the sponsor will review and then file it and will notify the IRB, if appropriate according to local requirements.

9.5.5 Adverse Events of Special Interest

An AESI is defined as any vision-related AE. See Section 9.5.1 for procedures for reporting an AESI.

9.5.6 Pregnancy

If a female becomes pregnant during the study, the PI/TI (or designee) will notify the sponsor immediately after the pregnancy is confirmed. The PI/TI 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 Appendix 12.3.

9.5.7 Medical Device Incidents (Including Malfunctions)

Incidents fulfilling the definition of an AE/ADE/SAE/SADE will follow the processes outlined in Section 9.5.3 and Appendix 12.3.

In order to fulfill regulatory reporting obligations worldwide, the PI is responsible for the detection and documentation of events meeting the definitions of incident, malfunction, or deficiency that occur during the study with such devices.

The definition of a medical device incident and a device deficiency can be found in Appendix 12.4.

9.5.7.1 Time Period for Detecting Medical Device Incidents

- Medical device incidents, deficiencies, or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the PI (or designee) learns of any incident at any time after a subject has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the PI (or designee) will promptly notify the sponsor.
- The method of documenting medical device incidents is provided in Appendix 12.4, and reporting information is provided in Section 9.5.7.3.

9.5.7.2 Follow-up of Medical Device Incidents

- All medical device incidents involving an AE/SAE will be followed and reported in the same manner as other AEs (see Section 9.5.3). This applies to all subjects, including those who discontinue study treatment or the study.
- The PI is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the PI.

9.5.7.3 Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the PI (or designee) determines that the event meets the protocol definition of a medical device incident.
- The medical device incident will be reported to the sponsor by email. If email is unavailable, then fax will be utilized. The email address and fax number are on the front page of the protocol.
- The same individual will be the contact for the receipt of medical device reports and SAEs.

9.5.7.4 Regulatory Reporting Requirements for Medical Device Incidents

- The PI (or designee) will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The PI, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB.

9.6 Laboratory Testing

At screening, before each study treatment (initial, touch-up, and repeat), and at study exit, a trained research staff member will perform pregnancy testing on urine samples of female subjects of childbearing potential. It is recommended that the test have a sensitivity of at least 50 mIU/mL for human chorionic gonadotropin. Urine samples will be disposed of after testing.

10. Statistical Considerations

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% confidence intervals for population mean, or population proportion, will be provided as part of the descriptive summary.

10.1 Sample Size Determination

The sample size assumptions and estimate are summarized as follows:

A sample size of 112 subjects in the treatment group and 56 subjects in the control group will provide 99.9% power to detect a difference of at least 40% in the responder rates on the ACSS between the groups, based on a 2-sided Fisher's exact test at the 5% level. The treatment group is assumed to have at least an 80% responder rate at Month 1, and the control group is assumed to have at most a 40% responder rate. The assumptions of responder rates are estimated from Allergan study V12-001.

At least 135 subjects with a baseline AFLS score of 2 on both cheeks or 3 on both cheeks are expected to enroll. The number of subjects with baseline AFLS score of 0, 1, or 4 on either cheek, or 2 on one cheek and 3 on the other cheek is not expected to exceed 75. Assuming at least 65% of subjects will have baseline AFLS score of 2 on both cheeks or 3 on both cheeks, 72 subjects in treatment group and 36 subjects in control group will provide 94.4% power to detect a difference of at least 35% in the responder rates on AFLS between the treatment groups, based on a 2-sided Fisher's exact test at the 5% level. The treatment group is assumed to have at least an 80% responder rate at Month 1, and the control group is assumed to have at most a 45% responder rate. The assumptions of responder rates are estimated from Allergan study V12-001.

Accounting for subject attrition of 20% during the study, 210 subjects will be randomized at a 2:1 ratio to treatment group and control group. Randomization will be within each study site.

Assuming 119 subjects from the treatment group and 28 subjects from the control group will be treated, a total of 147 treated subjects will provide 95% power to detect an AE related to treatment with an incidence rate of 2% in the population using a 1-sided exact binomial test at the 2.5% level. The safety calculation used an inequality test for 1 proportion.

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.

10.2 Populations for Analyses

The analysis populations will consist of subjects as defined below:

- The ITT population includes all randomized subjects. Subjects will be summarized as randomized.
- The safety population includes all subjects who are randomized to study treatment and receive at least 1 study treatment (treatment group) and subjects who are randomized to no treatment (control group). Subjects will be summarized as treated.

The Fitzpatrick V/VI safety cohort will be included in the safety population for safety analyses and excluded from the ITT population for effectiveness analyses. All data for this cohort will be listed.

10.3 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses.

10.3.1 Effectiveness Analyses

The effectiveness analyses will be based on the ITT population. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

10.3.1.1 Effectiveness Endpoints

Primary effectiveness endpoint:

- WSRCSS responder status at Month 1

Secondary effectiveness endpoints:

- Change from baseline to Month 1 in subject responses to FACE-Q Satisfaction with Skin questionnaire
- WSRAFLS responder status at Month 1 (for subjects with baseline AFLS score of 2 on both cheeks or 3 on both cheeks)

Other effectiveness endpoints:

- Primary and secondary endpoints at other applicable timepoints

- Change from baseline in subject responses to FACE-Q Appraisal of Lines-Overall questionnaire
- Subject assessment of the natural look of the cheek skin on an 11-point scale ranging from 0 (unnatural looking) to 10 (natural looking)
- Subject assessment of the natural feel of the cheek skin on an 11-point scale ranging from 0 (unnatural feeling) to 10 (natural feeling)
- Subject assessment of the global aesthetic improvement of the cheek skin on the 5-point GAIS
- Change from baseline in cheek skin hydration measurements obtained via the MoistureMeter® D instrument

Exploratory effectiveness endpoint:

- Composite responder status responder status on ACSS and FACE-Q Satisfaction with Skin questionnaire

Effectiveness analyses other than those for primary and secondary endpoints will be defined in the SAP.

10.3.1.2 Primary Endpoint Analysis

The primary effectiveness variable is the EI's assessment of cheek skin smoothness on the ACSS. The primary effectiveness analysis is the ACSS responder rate at Month 1. A responder is defined as a subject who shows at least a 1-point improvement from baseline on the ACSS scale on both cheeks. The responder rate and corresponding 95% confidence interval will be summarized. A 2-sided, Fisher's exact test at the 5% level will be used to test whether the ACSS responder rate at Month 1 in the treatment group is significantly greater than that in the control group at Month 1 in the control period.

The primary effectiveness analysis will test for superiority of JUVÉDERM VOLITE XC treatment group over no treatment in the difference in ACSS responder rate based on the EI's assessment at Month 1. Month 1 refers to 1 month after the last treatment (initial or touch-up) for subjects in the JUVÉDERM VOLITE XC treatment group and 1 month after randomization for subjects in the no-treatment control group.

The null hypothesis is that the responder rate for the JUVÉDERM VOLITE XC treatment group is equal to the responder rate for the no-treatment control group. The alternative hypothesis is that the responder rates are not equal for the treatment group and the no-treatment control group. These hypotheses are stated as:

$$H_o: P_v - P_c = 0$$
$$Ha: P_v - P_c > 0 \text{ or } P_v - P_c < 0$$

where Pv and Pc denote the responder rates for the JUVÉDERM VOLITE XC group at Month 1 after last treatment (initial or touch-up) and for the no-treatment control group at Month 1 after randomization, respectively. Two-sided Fisher's exact test with 5% significance level will be used to compare treatment effects between JUVÉDERM VOLITE XC and the no-treatment control group. If the 2-sided p-value is less than 0.05 and the responder rate is greater for JUVÉDERM VOLITE XC than for the no-treatment control group, then JUVÉDERM VOLITE XC will be considered superior to the no-treatment control group.

For primary analysis, subjects with missing data at the primary timepoint (ie, Month 1) will be analyzed as non-responders. Details will be described in the SAP.

10.3.1.3 Secondary Endpoint Analysis

The first secondary effectiveness variable is subject responses on the FACE-Q Satisfaction with Skin questionnaire. The responses to the 12 items will be summed and converted to a scale score that ranges from 0 to 100 (higher score indicates more satisfaction) using the algorithm developed by the FACE-Q scale developers. The secondary effectiveness analysis is mean change from baseline in FACE-Q scale score at Month 1.

The other secondary effectiveness variable is the EI's assessment of fine lines on the cheeks on the AFLS. The AFLS responder rate at Month 1 will be analyzed in the same manner as the ACSS responder rate. Only subjects with baseline AFLS score of 2 on both cheeks or 3 on both cheeks will be included in the analysis.

10.3.2 Safety Analyses

The following safety categories will be summarized as appropriate for the safety population and will be fully defined in the SAP.

- FACE-Q Recovery Early Life Impact questionnaire
- Subject assessment of procedural pain
- ISRs
- AEs

- Snellen visual acuity, confrontational visual fields, and ocular motility assessments

FACE-Q Recovery Early Life Impact questionnaire and procedural pain will be summarized by frequency distributions or descriptive statistics.

ISRs reported by subjects will be summarized using descriptive statistics, by symptom, maximum reported severity, and duration for initial, touch-up, and repeat treatments, separately.

Incidence of AEs will be summarized by primary system organ class, preferred term, and severity. Additionally, a summary will be tabulated by onset, duration, severity, action taken, relationship to treatment, and outcome. The summary will include incidence rate as well as total number of events.

Treatment-related AEs, SAEs, AEs leading to study discontinuations, and deaths will be listed or tabulated. All pre-treatment AEs will be listed but not summarized.

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

10.3.3 Other Analyses

10.3.3.1 Demographics and Baseline Characteristics Analyses

Subject demographics, baseline characteristics, and height and weight will be summarized with descriptive statistics. Urine pregnancy test results and vital signs will be listed but not summarized.

10.3.3.2 Treatment Administration Analyses

Treatment characteristics will be summarized with descriptive statistics for anesthesia usage, needle length, injection volume, injection spacing, and injection plane.

10.3.3.3 Subgroup Analyses

Analysis of the primary effectiveness endpoint, ACSS responder status at Month 1, will be done descriptively for the following subgroups:

- Baseline ACSS score: 2 versus 3
- Fitzpatrick skin phototype: I/II, III/IV, and V/VI
- Volume injected: < median versus > median

The median total volume injected (initial plus touch-up) for both cheeks is used for this analysis.

10.3.4 Interim Analyses

No interim analysis is planned for this study. After the first 30 treated subjects complete 1-month follow-up, a safety update including descriptions of AEs and associated treatment parameters for these subjects will be provided to the FDA. An analysis of the primary and secondary endpoints may be conducted once all subjects have passed the primary timepoint (Month 1). If such an analysis is conducted, the details of the analysis will be described a priori in other study documents.

11. References

Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, December 2009. https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf. Accessed January 30, 2018.

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Klassen AF, Cano SJ, Schwitzer JA, Scott AM, Pusic AL. FACE-Q scales for health-related quality of life, early life impact, satisfaction with outcomes, and decision to have treatment: development and validation. Plast. Reconstr. Surg. 2015;135:375-386.

12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Term/Abbreviation	Definition
2D	2-dimensional
ACSS	Allergan Cheek Smoothness Scale
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AFLS	Allergan Fine Lines Scale
CDISC	Clinical Data Interchange Standards Consortium
DFU	directions for use
eCRF	electronic case report form
EI	Evaluating Investigator
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
IC	informed consent
ICF	informed consent form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	injection site response
ITT	intent-to-treat
IWRS	interactive web response system
NCI	National Cancer Institute
PI	Principal Investigator
Rand	randomization
RTx	repeat treatment
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
TI	Treating Investigator
Tx	treatment
UADE	unanticipated adverse device effect
US	United States
w/w	by weight

12.2 Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH, ISO, and GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, and other relevant documents (eg, advertisements) must be submitted to an IRB by the PI and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The PI will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, and the IRB

Financial Disclosure

PIs/TIs and EIs will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The PI or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of IC that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written IC was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the IC must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the subject.

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 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 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 PI will retain the original copy of the signed form, and the subject will receive a copy. Upon signing the IC form, the subject is considered to be enrolled in the study and receives a subject number that will be used on all documentation for the subject throughout the study. Subject numbers will be assigned in ascending order, and numbers will not be omitted or reused. The subject number is coupled with the site identification number for unique identification of each subject. The PI (or designee) is to ensure important new information is provided to new or existing subjects throughout the study.

Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Publication Policy

- The sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor 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 the sponsor.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.

- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.

- Study data will be posted on www.clinicaltrials.gov as required.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The PI is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The PI must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The PI must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the PI for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the PI's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The PI may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and must follow ALCOA (ie, records must be attributable, legible, contemporaneous, original, and accurate).

Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The PI may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or PI may include but are not limited to:

- Failure of the PI to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of subjects by the PI
- Discontinuation of further study treatment development
- 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 JUVÉDERM VOLITE 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 TI 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 ISO 14155, if a study is prematurely terminated or suspended due to safety issues, the sponsor shall inform all PIs 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 the sponsor or by the PI, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, the sponsor 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 PI or authorized designee shall promptly inform enrolled subjects, if applicable.

Compliance with Protocol

The PI is responsible for compliance with the protocol at the investigational site. A representative of the sponsor 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. The PI will enter data that may be excluded from analysis as defined by the protocol deviation specifications. All protocol deviations will be reported to the IRB according to the IRB's reporting requirements.

12.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

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.

Adverse Device Effect

An 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.

AE of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's study device, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESI has been identified for the study treatment in this protocol: vision-related AE.

AESIs must be reported to the sponsor within 24 hours of awareness of the event by completing the appropriate eCRF and notifying Allergan study management personnel and the Medical Safety Physician by fax or email. Allergan will notify the FDA of any AESI within 10 days of Allergan's awareness of the event.

Events Meeting the AE/ADE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the PI (ie, not related to progression of underlying disease)

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.
- Lack of effectiveness or failure of expected medical device results per se will not be reported as an AE or SAE. Such instances will be captured in the effectiveness assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events Not Meeting the AE/ADE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

SAE Definition

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.

All cancers that occur during a study are considered SAEs and will be documented and reported per Appendix 12.3.

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."

Unanticipated Adverse Device Effect

A 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."

Assessment of 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	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE/SADE, NOT when it is rated as severe.

Relationship to Treatment

Relationship to 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 PI determines that there is a reasonable possibility that the AE may have been caused by the device or is associated with

the procedure, such as an event that can be attributed to other products, surgical techniques, or medications required specifically for the procedure. Relationship to the device or procedure must be determined by the PI and cannot be delegated to other study staff.

- **Recording AEs/ADEs and/or SAEs/SADEs** When an AE/ADE or SAE/SADE occurs, it is the responsibility of the PI to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The PI will then record all relevant AE/ADE or SAE/SADE information in the CRF.

- It is **not** acceptable for the PI to send photocopies of the subject's medical records to the Allergan Medical Safety Physician in lieu of completion of the AE/ADE/SAE/SADE eCRF page.

- There may be instances when copies of medical records for certain cases are requested by the Allergan Medical Safety Physician. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Allergan Medical Safety Physician.

- The PI will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the event.

Procedures for Reporting an AE or ADE

All AEs/ADEs occurring during the study period (beginning with signing ICF) are to be recorded on the appropriate CRF. For any treatment-related AE/ADE that is ongoing at the exit, the PI/TI will attempt to follow the subject until the AE/ADE has been resolved or follow-up is no longer possible.

AEs/ADEs that start after the study follow-up period has ended will be considered outside the scope of the study but will be captured.

Procedures for Reporting an SAE or SADE

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

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

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

- 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.

- Provide the sponsor 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.

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

12.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 7.1 for the list of sponsor medical devices).

Medical Device Incident Definition
A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health. Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened

AND

- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents
• A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A subject's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A subject's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 12.3. • The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

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 PI/TI or designee will notify the sponsor 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 the sponsor. The sponsor 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.

12.5 Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [Modified from ICH E2A] Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Death	The absence of life or state of being dead (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a study
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by subject	An indication that a study subject has removed itself from the study (NCI)

12.6 Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Study information	Study Title	A Randomized, Multicenter, Evaluator-blind, Controlled Study to Evaluate the Safety and Effectiveness of JUVÉDERM VOLITE™ XC Injectable Gel for the Improvement in Cheek Skin Smoothness
	Clinical Study Sponsor	Allergan
	Study Phase Classification	IDE
	Study Indication	Cheek skin smoothness
	Study Indication Type	Treatment
	Study Type	Effectiveness Safety
	Study Length	20 months
	Planned Country of Investigational Sites	US
	Planned Number of Subjects	263
	FDA-Regulated Device Study Indicator	Yes
	FDA-Regulated Drug Study Indicator	No
	Pediatric Study Indicator	No
Subject information	Diagnosis Group	Cheek skin smoothness
	Healthy Subject Indicator	N/A
	Planned Minimum Age of Subjects	22
	Planned Maximum Age of Subjects	None
	Sex of Subjects	Both
	Stable Disease Minimum Duration	N/A

Treatments	Investigational Therapy or Treatment	JUVÉDERM VOLITE™ XC Injectable Gel
	Intervention Type	Device
	Pharmacological Class of Invest. Therapy	N/A
	Dose per Administration	Up to 4 mL (initial and repeat); up to 2 mL (touch-up)
	Dose Units	mL
	Treatment Frequency	Initial, touch-up, and repeat (treatment group only) treatments
	Route of Administration	Injection
	Current Therapy or Treatment	N/A
	Added on to Existing Treatments	No
	Control Type	No-treatment control
	Comparative Treatment Name	None
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Study is Randomized	Yes
	Randomization Quotient	2:1
	Study Blinding/Masking Schema	Single blind
	Stratification Factor	None
	Adaptive Design	No
	Study Stop Rules	Yes

12.7 Appendix 7: Protocol Amendment History

The protocol amendment summary of change table for the current amendment is located directly before the table of contents.

Amendment 2 (3 July 2019)

Overall Rationale for the Amendment:

Allow for enrollment of a Fitzpatrick skin phototype V/VI safety cohort.

Section No. and Name	Description of Change	Brief Rationale
Synopsis and 6.1 Inclusion Criteria	Revised inclusion criteria 2 and 3 to allow less stringent criteria for the Fitzpatrick V/VI safety cohort	To ensure adequate enrollment of subjects with Fitzpatrick skin phototypes V and VI
5.1 Overall Design	Added a sentence stating that up to 10 subjects may be enrolled in the Fitzpatrick V/VI safety cohort and followed for safety only	To ensure adequate enrollment of subjects with Fitzpatrick skin phototypes V and VI
6. Study Population	Specified that up to 10 subjects may be enrolled in the Fitzpatrick V/VI safety cohort and followed for safety only	To ensure adequate enrollment of subjects with Fitzpatrick skin phototypes V and VI
6.4 Screen Failures	Specified that screen failures may be rescreened if they are eligible for the Fitzpatrick V/VI safety cohort	To ensure adequate enrollment of subjects with Fitzpatrick skin phototypes V and VI
10.2 Populations for Analyses	Specified that the Fitzpatrick V/VI safety cohort will be included in the safety population for safety analyses and excluded from the ITT population for effectiveness analyses	To specify statistical reporting for the new Fitzpatrick V/VI safety cohort

Amendment 1 (28 February 2019)

Overall Rationale for the Amendment:

Clarifications to assist sites with study execution.

Section No. and Name	Description of Change	Brief Rationale
Title Page	Added IDE number	To include Regulatory Agency identifying number
Section 1 and Table 2-1 Screening Visit Procedures	Clarified that ACSS and FACE-Q are only to be performed on day of randomization if randomization occurs on a different day than screening	To clarify procedures
Table 2-2 Treatment Group Procedures	Clarified the order of procedures	To clarify the order and timing of procedures
Table 2-3 Control Group	Clarified the order of procedures	To clarify the order and

Procedures		timing of procedures
Table 2-4 Control Group Procedures	Clarified the order of procedures and removed skin hydration assessment at initial treatment for control group since it is already assessed at Month 1 in no-treatment period	To clarify the order and timing of procedures and remove redundant assessment
9. Study Assessments and Procedures	Clarified that ACSS and FACE-Q are only to be performed on day of randomization if randomization occurs on a different day than screening	To clarify procedures
9.3.1 Primary Effectiveness Measure	Added detail about ACSS features	To better describe the primary effectiveness measure
9.5.1 Time Period and Frequency for Collecting AE/ADE and SAE/SADE Information	Revised 1 sentence to align with current protocol template	To align with current protocol template
12.3 Appendix 3: Adverse Events	Deleted 1 sentence to align with current protocol template	To align with current protocol template