Title Page

Protocol Title: Multicenter, Evaluator-blinded, Randomized, Controlled Study of the Safety and Effectiveness of JUVÉDERM® VOLITE™ XC Injectable Gel for Improvement in Neck Appearance

Protocol Number: 2029-701-008

Amendment Number: 5

Compound: JUVÉDERM® VOLITE™ XC Injectable Gel

Study Phase: N/A

Short Title: JUVÉDERM® VOLITE™ XC Injectable Gel for Improvement in Neck Appearance

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NCT: NCT05316233

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Refer to the final page of this protocol for electronic signature and date of approval.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	May 2024
Amendment 4	August 2023
Amendment 3	January 2023
Amendment 2	January 2022
Amendment 1	November 2021
Original Protocol	August 2021

Amendment 5 (May 2024)

Overall Rationale for the Amendment:

To update the Statistical Analysis section based on FDA Feedback and to clarify the analysis of PRO questionnaires based on the availability of the validation data.

Section # and Name	Description of Change	Brief Rationale
9.2 Sample Size Determination	Addition of information for the blinded sample size re-estimation process	Based on FDA feedback
9.4.2.2 Main Analytical Approach	Addition of information for analytical approach if there are no ITT participants with missing primary effectiveness endpoints	Based on FDA feedback
9.4.3 Secondary Effectiveness Endpoints	Additional description of hypothesis testing and missing data imputation for secondary effectiveness endpoints Updated "overall FACE-Q score" to "Rasch-transformed FACE-Q score"	Based on FDA feedback
9.4.4 Other Effectiveness Endpoints	Clarification of analysis for ANSS and ANTOS questionnaires	Clarification for analysis based on status of the validation study results of these questionnaires.
9.4.6.1 Adverse Events	Replaced "discontinued" with "withdrawal of study treatment"	Clarification

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1. Protocol Summary

1.1. Synopsis

Protocol Title: Multicenter, Evaluator-blinded, Randomized, Controlled Study of the Safety and Effectiveness of JUVÉDERM® VOLITE™ XC Injectable Gel for Improvement in Neck Appearance

Short Title: JUVÉDERM® VOLITE™ XC Injectable Gel for Improvement in Neck Appearance

Rationale:

VOLITE without lidocaine was CE-marked in 2015, and JUVÉDERM® VOLITE XC (hereafter VOLITE XC) was CE-marked in 2016. An open-label European study (V12-001) of VOLITE without lidocaine provided evidence of the product's safety and effectiveness in the treatment of superficial cutaneous depressions such as fine lines on the face and neck and for additional improvement of skin quality attributes such as hydration and elasticity, with high levels of participant satisfaction.

This protocol is designed as a pivotal study to collect safety and effectiveness data on VOLITE XC for improvement of horizontal neck lines in order to support FDA approval for such intended use.

Objectives and Endpoints

Objectives	Endpoints/Measures	
Effectiveness		
To evaluate the effectiveness of VOLITE XC in adults seeking improvement in neck appearance	Primary	• Responder status based on EI's live assessment of transverse neck lines using the ATNLS at Month 1
	Secondary	• Responder status based on EI's assessments of global aesthetic improvement on the neck using the GAIS at Month 1 • Change from baseline to Month 1 in the Rasch-transformed scores on FACE-Q Appraisal of the Neck questionnaire • Responder status based on participant's assessments of global aesthetic improvement on the neck using the GAIS at Month 1
Safety		
To evaluate the safety of VOLITE XC in adults seeking improvement in neck appearance	• Participant assessment of procedural pain • Participant assessment of ISRs • Snellen visual acuity, confrontational visual fields, and ocular motility assessments by the TI (or designee) • AEs • Concomitant medications and procedures	

Overall Design

- Multicenter, randomized (2:1 ratio to treatment and control groups), controlled, parallel-design study in adult participants with moderate or severe transverse neck lines (ATNLS Grades 2 or 3)
- Single-blind: EIs are blinded; TIs and participants are not blinded
- VOLITE XC subdermal and/or intradermal injection using a 32 G 1/2" needle with or without a 25 G 1 1/2" cannula to the neck area for the treatment group and delayed treatment for the control group (a minimum of 40 participants will receive injections via cannula)
- Up to 3 mL for initial treatment, up to 2 mL for optional touch-up treatment, and up to 3 mL for repeat treatment (if administered)
- Up to 20 investigational sites in the United States, each with a PI who is responsible for the overall conduct of the study at that site and is the TI along with an EI
- Safety data from the first 20 treated participants for 14 days after initial treatment will be submitted to the FDA prior to proceeding with enrollment of additional participants.

Disclosure Statement: This is a parallel-design treatment study with 2 arms that is blinded to EIs.

Number of Participants:

Up to 212 participants are planned to be enrolled and screened initially to achieve 159 randomized (106 treatment group, 53 control group) and 144 evaluable participants (96 treatment group, 48 control group) at the Month 1 primary timepoint.

A blinded re-estimation will be performed when at least 50% of randomized participants have completed the Month 1 visit of CP, and additional participants may be enrolled if needed to achieve at least 80% power. No more than 200 participants will be randomized (133 treatment group, 67 control group), and no more than 267 participants will be screened.

"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. "Randomized" means a participant was randomly assigned to study intervention.

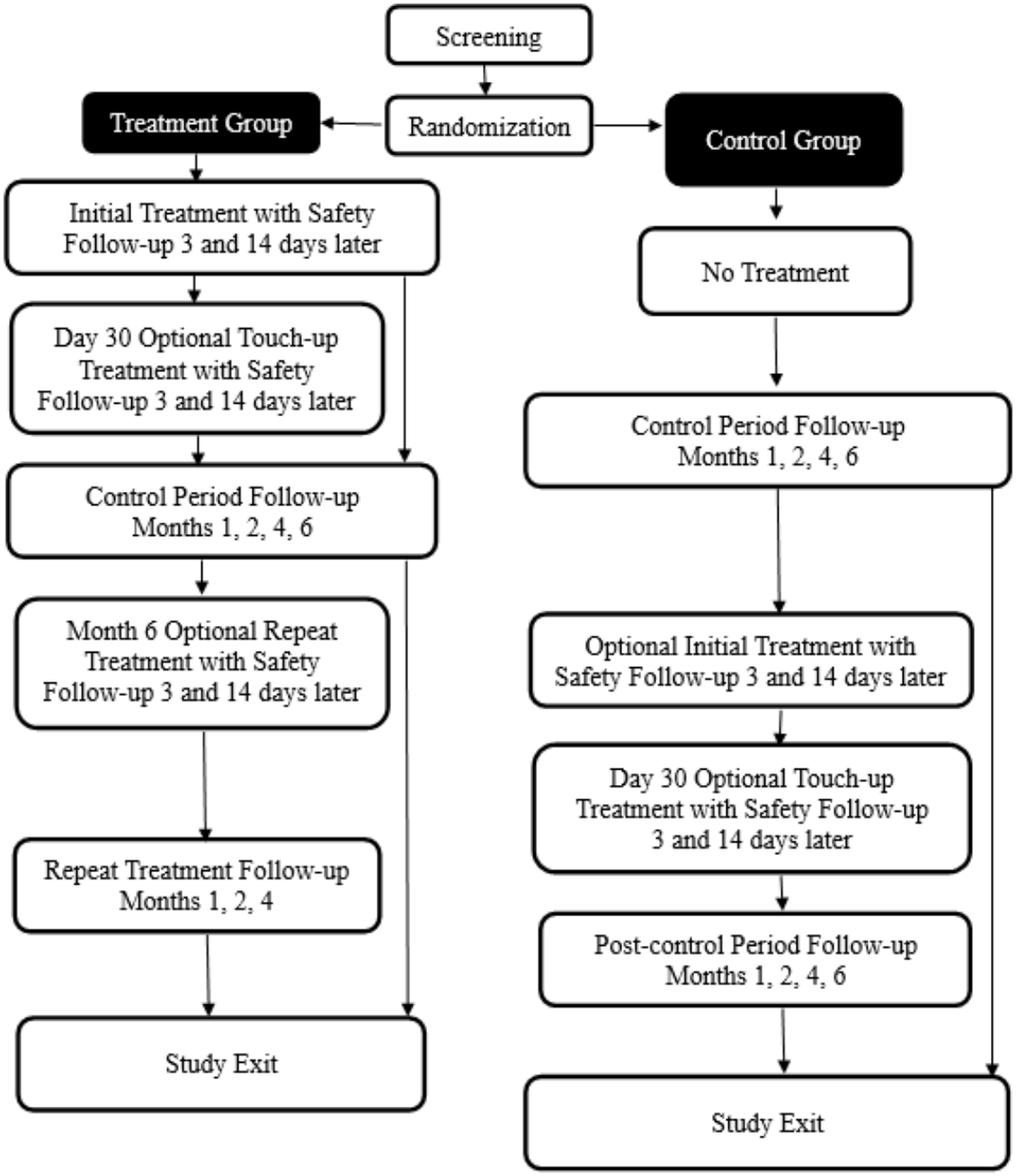
Intervention Groups and Duration:

- **Treatment group**: Participants receive initial treatment and optional touch-up treatment at 30 days if optimal correction has not been achieved and agreed upon by both the participant and TI. Follow-up visits are 3 days and 14 days after each treatment (safety telephone call only at 3 days) and at Months 1, 2, 4, and 6 after last treatment. Participants exit the study at Month 6 or receive repeat treatment and are followed at 3 days and 14 days (safety telephone call only at 3 days) and Months 1, 2, and 4 after repeat treatment.

- **Control group**: Participants are followed at Months 1, 2, 4, and 6 after randomization (control period) and then either exit the study or receive optional treatment (initial and touch-up, if needed) in the optional treatment period. Follow-up visits in the optional treatment period are 3 days and 14 days after each treatment (safety telephone call only at 3 days) and at Months 1, 2, 4, and 6 after last treatment. Participants who receive optional treatment exit the study at Month 6 after treatment.

Data Monitoring Committee: No

1.2. Schema


Screening
Randomization
Treatment Group
Control Group
Initial Treatment with Safety Follow-up 3 and 14 days later
Day 30 Optional Touch-up Treatment with Safety Follow-up 3 and 14 days later
Control Period Follow-up Months 1, 2, 4, 6
Month 6 Optional Repeat Treatment with Safety Follow-up 3 and 14 days later
Repeat Treatment Follow-up Months 1, 2, 4
Study Exit
No Treatment
Control Period Follow-up Months 1, 2, 4, 6
Optional Initial Treatment with Safety Follow-up 3 and 14 days later
Day 30 Optional Touch-up Treatment with Safety Follow-up 3 and 14 days later
Post-control Period Follow-up Months 1, 2, 4, 6
Study Exit

1.3. Schedule of Activities

Study procedures are recommended to be done in sequence as listed in the below tables, but the sequence is not mandatory except that for the Screening Visit, the consent must be obtained before any other information is collected.

If it ever becomes necessary to remain home or to shelter-in-place per local, regional, or state orders, study visits may be impacted. This may include changes such as telephone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in Section 8. Every effort is to be made to ensure the safety of participants and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic or natural disaster-related reasons, follow the modifications provided in Section 8.

Table 1-1 Screening Visit Procedures: All Participants

Procedure	Screening
Visit Window (Days)	-30
Consent/Authorization	X
Participant demographics	X
Height, weight, and vital signs[a]	X
Fitzpatrick skin phototype and sun exposure history	X
Nicotine and alcohol use history	X
Medical/surgical/cosmetic history	X
Concomitant medications and procedures	X
Urine pregnancy test[b]	X
Snellen visual acuity (TI or designee)	X
Confrontational visual fields (TI or designee)	X
Ocular motility (TI or designee)	X
Inclusion/exclusion criteria (TI/EI)[c]	X

[a] Includes blood pressure (systolic and diastolic; while participant is seated), respiratory rate, heart rate, and temperature.

[b] For female participants of childbearing potential; administered and confirmed negative prior to study intervention. A female 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.

[c] Includes EI's live preliminary assessment to determine that participant has an ATNLS grade *moderate* or *severe*. A final score will be assigned at randomization.

For the Treatment Group procedures, ALL assessments indicated with the footnote "e" MUST be done BEFORE randomization and before study intervention. RANDOMIZATION AND TREATMENT MUST OCCUR ON THE SAME DAY. For touch-up and repeat treatments, all assessments including pregnancy testing and questionnaires must be performed before treatment. The GAIS must be the last assessment performed by both the EI and participant.

Table 1-2 Treatment Group Procedures

	Control Period											Repeat Treatment Period				
Procedure	**Randomization/Initial Tx[a]**	**Day 3 After Initial Tx**	**Day 14 After Initial Tx**	**Optional Touch-up Tx Day 30[b]**	**Day 3 After Touch-up Tx**	**Day 14 After Touch-up Tx**	**Month 1**	**Month 2**	**Month 4**	**Month 6**		**Day 3 After Repeat Tx**	**Day 14 After Repeat Tx**	**Month 1 After Repeat Tx**	**Month 2 After Repeat Tx**	**Month 4 After Repeat Tx/ Study Exit**
										Study Exit[c]	**Optional Repeat Tx**					
Visit Window (Days)		+2	+2	+7	+2	+2	+7	±7	±7	±14	±14	+2	+2	+7	±7	+7
Urine pregnancy test[d]	X[e]			X[f]						X	X[g]					X
ATNLS (EI)	X[e]			X[f]			X	X	X	X	X[g]			X	X	X
Inclusion/Exclusion criteria (TI, EI)	X[e]															
FACE-Q Appraisal of the Neck (Participant)	X[e]			X[f]			X	X	X	X	X[g]			X	X	X
Participant questionnaire • ANSS—Feel • ANSS—Appearance • ANSS—Psychosocial	X[e]			X[f]			X	X	X	X	X[g]			X	X	X
2D digital imaging	X[e]			X[f]			X	X	X	X	X[g]			X	X	X
PRIMOS 3D imaging topography assessment (applicable study sites only)	X[e]			X[f]			X	X	X	X	X[g]			X	X	X
Skin hydration (EI or designee)	X[e]			X[f]			X	X	X	X	X[g]			X	X	X
Randomization	X															
Snellen visual acuity (TI or designee)	X[h]		X	X[h]		X	X				X[h]		X	X		
Confrontational visual fields (TI or designee)	X[h]		X	X[h]		X	X				X[h]		X	X		
Ocular motility (TI or designee)	X[h]		X	X[h]		X	X				X[h]		X	X		
Neurological assessment (TI or designee)	As needed															
Study intervention (TI)	X			X[b]							X					
Study intervention characteristics, injection ease, product moldability (TI)	X			X							X					
Procedural pain (Participant)	X			X							X					
Safety e-diary (Participant)[i]	X			X							X					
Safety telephone call		X			X							X				
Participant questionnaire • ANTOS—Satisfaction with Treatment • ANTOS—Recommend				X[f]			X	X	X	X	X[g]			X	X	X

	Control Period											Repeat Treatment Period				
Procedure	**Randomization/Initial Tx[a]**	**Day 3 After Initial Tx**	**Day 14 After Initial Tx**	**Optional Touch-up Tx Day 30[b]**	**Day 3 After Touch-up Tx**	**Day 14 After Touch-up Tx**	**Month 1**	**Month 2**	**Month 4**	**Month 6**		**Day 3 After Repeat Tx**	**Day 14 After Repeat Tx**	**Month 1 After Repeat Tx**	**Month 2 After Repeat Tx**	**Month 4 After Repeat Tx/ Study Exit**
										Study Exit[c]	**Optional Repeat Tx**					
Visit Window (Days)		+2	+2	+7	+2	+2	+7	±7	±7	±14	±14	+2	+2	+7	±7	+7
GAIS (Participant)				X[f]			X	X	X	X	X[g]			X	X	X
GAIS (EI)							X	X	X	X	X[g]			X	X	X
Weight measurement							X			X						X
Adverse events	Continuous Monitoring															
Concomitant medications and procedures	Continuous Monitoring															

[a] Randomization must occur within 30 days of screening; screening visit and randomization visit can occur on the same day if participants do not require washout. If screening and randomization visits occur on the same day, inclusion/exclusion criteria, urine pregnancy test, and pretreatment vision assessments need not be repeated. RANDOMIZATION AND INITIAL TREATMENT MUST OCCUR ON THE SAME DAY.

[b] The TI may perform a touch-up treatment if agreed upon by both the participant and TI. Touch-up treatment is recommended if the TI determines that optimal correction has not been achieved. If no touch-up treatment is performed, Day 30 visit becomes Month 1 visit.

[c] Study exit visit is at Month 6 for participants 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. The repeat treatment must occur no later than 14 days after the Month 6 visit. If a participant withdraws for any reason prior to the final study visit, attempts will be made to perform assessments at an exit visit.

[d] For female participants of childbearing potential; administered and confirmed negative prior to study intervention. A female 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] Done prior to randomization and study intervention.

[f] Done prior to study intervention.

[g] Done prior to repeat treatment. If repeat treatment is done on the same day as Month 6 visit, this assessment does not need to be repeated.

[h] Done prior to and approximately 30 minutes after study intervention. If there is any worsening between the pre and post vision assessments performed at the visit, complete the neurological assessment.

[i] The 30-day safety e-diaries are to be completed daily following each study intervention starting on the day of treatment and returned to the site after completion.

For the control group procedures, ALL assessments indicated with the footnote "f" MUST be done BEFORE randomization. At Month 6, participants will have all assessments performed and will then decide whether they wish to exit the study or receive optional treatment. For optional touch-up treatment, all assessments including pregnancy testing and questionnaires must be performed before treatment. The GAIS must be the last assessment performed by both the EI and participant.

Table 1-3 Control Group Procedures

	Control Period					Optional Treatment Period									
Procedure	**Randomization[a]**	**Month 1**	**Month 2**	**Month 4**	**Month 6/Study Exit[b,c]**	**Optional Tx at Month 6**	**Day 3 After Optional Initial Tx**	**Day 14 After Optional Initial Tx**	**Optional Touch-Up Tx Day 30[d]**	**Day 3 After Optional Touch-up Tx**	**Day 14 After Optional Touch-upTx**	**Month 1**	**Month 2**	**Month 4**	**Month 6/Study Exit[b]**
Visit Window (Days)		±7	±7	±7	+10	+10	+2	+2	+7	+2	+2	+7	±7	±7	±14
Urine pregnancy test[e]	X[f]					X[g]			X[g]						X
ATNLS (EI)	X[f]	X	X	X	X	X[g]			X[g]			X	X	X	X
Inclusion/Exclusion criteria (TI, EI)	X[f]														
FACE-Q Appraisal of the Neck (Participant)	X[f]	X	X	X	X	X[g]			X[g]			X	X	X	X
Participant questionnaires • ANSS—Feel • ANSS—Appearance • ANSS—Psychosocial	X[f]	X	X	X	X	X[g]			X[g]			X	X	X	X
2D digital imaging	X[f]	X	X	X	X	X[g]			X[g]			X	X	X	X
PRIMOS 3D imaging topography assessment (applicable study sites only)	X[f]	X	X	X	X	X[g]			X[g]			X	X	X	X
Skin hydration (EI or designee)	X[f]	X	X	X	X	X[g]			X[g]			X	X	X	X
Randomization	X														
Snellen visual acuity (TI or designee)						X[h]		X	X[h]		X	X			
Confrontational visual fields (TI or designee)						X[h]		X	X[h]		X	X			
Ocular motility (TI or designee)						X[h]		X	X[h]		X	X			
Neurological assessment (TI or designee)						As Needed									
Study intervention (TI)						X			X[d]						
Study intervention characteristics, injection ease, moldability						X			X						
Procedural pain (Participant)						X			X						
Safety e-diary (Participant)[i]						X			X						
Safety telephone call							X			X					

Procedure	Control Period					Optional Treatment Period								
	Randomization[a]	Month 1	Month 2	Month 4	Month 6/Study Exit[b,c]	Optional Tx at Month 6	Day 3 After Optional Initial Tx	Day 14 After Optional Initial Tx	Optional Touch-Up Tx Day 30[d]	Day 3 After Optional Touch-up Tx	Day 14 After Optional Touch-upTx	Month 1	Month 2	Month 4	Month 6/Study Exit[b]
Participant questionnaires • ANTOS—Satisfaction with Treatment • ANTOS—Recommend									X[g]			X	X	X	X
GAIS (Participant)									X[g]			X	X	X	X
GAIS (EI)		X	X	X	X	X[g]						X	X	X	X
Weight measurement		X			X										X
Adverse events	Continuous Monitoring														
Concomitant medications and procedures	Continuous Monitoring														

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

[b] If a participant withdraws for any reason prior to the final study visit, attempts will be made to perform assessments at an exit visit.

[c] At the Month 6 visit, control group participants will have the option to receive treatment. Participants who accept optional treatment will undergo the procedures specified under optional treatment at Month 6 column. Participants who do not accept optional treatment will exit the study after the Month 6 procedures are completed.

[d] The TI may perform a touch-up treatment if agreed upon by both the participant and TI. Touch-up treatment is recommended if the TI thinks that optimal correction has not been achieved. If no touch-up treatment is performed, Day 30 visit becomes Month 1 visit.

[e] For female participants of childbearing potential; administered and confirmed negative prior to study intervention. A female 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.

[f] Done prior to randomization.

[g] Done prior to study intervention.

[h] Done prior to and approximately 30 minutes after study intervention. If there is any worsening between the pre and post vision assessments performed at the visit, complete the neurological assessment.

[i] The 30-day safety e-diaries are to be completed daily following each study intervention starting on the day of treatment and returned to the site after completion.

2. Introduction

JUVÉDERM® VOLITE™ XC (hereafter, VOLITE XC) is a crosslinked HA gel implant formulated with lidocaine that was developed to provide a safe, minimally invasive method of treating fine lines and improving skin quality. VOLITE XC has an HA concentration of 12 mg/mL and has been shown to effectively and safely treat fine lines and improve skin quality in the face and neck (Niforos 2019).

2.1. Study Rationale

VOLITE without lidocaine was CE-marked in 2015, and VOLITE XC was CE-marked in 2016. An open-label European study (V12-001) of VOLITE without lidocaine provided evidence of the product's safety and effectiveness in the treatment of superficial cutaneous depressions such as fine lines on the face and neck and for additional improvement of skin quality attributes such as hydration and elasticity, with high levels of participant satisfaction (Niforos 2019; Ogilvie, Safa et al 2020).

Since its approval in Europe, European injectors have been using VOLITE XC for treatment of various anatomic areas, including the neck, and have shown that VOLITE XC can be safely and effectively used to treat horizontal neck lines. An expert panel of European physicians concluded that treatment of the neck with VOLITE XC is appropriate and may be particularly satisfying to patients as the results tend to last longer in the neck than in the face (Ogilvie, Thulesen et al 2020).

Further evidence collected under a more rigorous study design is required to fully characterize the safety and effectiveness of VOLITE XC for this indication. This protocol is designed as a pivotal study to collect safety and effectiveness data on VOLITE XC for improvement of horizontal neck lines in order to support FDA approval for such intended use.

2.2. Background

The cumulative effect of aging and environmental exposures (ie, ultraviolet, infrared, and visible light radiation and pollution) leads to wrinkles, discoloration, laxity, and roughness of sun-exposed skin. As patients achieve a younger and more refreshed appearance through facial rejuvenation procedures, the skin in the neck and décolletage does not match the facial appearance (Vanaman 2015). The neck is a frequently mentioned area by patients complaining about its crepey texture and deep lines. Horizontal neck lines are primarily associated with age, but in some cases anatomical anomalies result in visible lines developing in younger patients. Additionally, tech-neck (associated with people bending their necks to look down at telephones, tablets, etc.) is resulting in increasing horizontal neck lines being observed (Tseng 2019).

VOLITE XC (HA concentration 12 mg/mL) is a 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 VOLITE XC having the lowest HA concentration to serve the unmet need of a filler for fine lines. 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.

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 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 participants, a total of 261 cheeks, 120 foreheads, and 96 necks were treated. Touch-up treatments were provided for 31 participants (46 cheeks) and repeat treatments at 9 months were provided for 62 participants (124 cheeks, 54 foreheads, 30 necks). Among treated cheeks, the responder rate on the 5-point photonumeric Allergan Cheek Smoothness Scale (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 5-point photonumeric Allergan Fine Lines Scale, the 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 participant satisfaction with skin based on the FACE-Q Satisfaction with Skin questionnaire was observed at all timepoints. Hydration measurements with MoistureMeter® D instruments showed improvement from baseline at all timepoints in the cheeks and neck.

Biocompatibility tests have confirmed VOLITE XC to be noncytotoxic, nonirritating, nonsensitizing, nontoxic, noncarcinogenic, nonpyrogenic, and suitable for the intended purpose to be in contact with tissue/bone for more than 30 days. Based on the preclinical and clinical data, it is anticipated that VOLITE XC will be a safe and effective in treatment of transverse neck lines with VOLITE XC.

2.3. Benefit/Risk Assessment

The injection procedure, anesthetic agents, or VOLITE XC may cause some of the risks and/or discomforts listed below. Unforeseeable risks are also a possibility. If a complication occurs, participants will be advised to contact the TI who will use his/her medical judgement to do whatever is necessary to treat the participant.

As with any skin injection, risks can be posed by the injection procedure itself, the anesthetic agent, and injection of 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 soft tissue filler injection procedures in general. The use of a small gauge needle and/or cannula to deliver VOLITE XC in this study is intended to minimize tissue trauma. The inclusion of 0.3% lidocaine w/w 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 participant's 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.

There is an unlikely risk of skin necrosis from the injection into the neck area as the result of misuse of the needle or cannula. Skin necrosis is an unlikely risk due to the low risk of

intravascular injection. To decrease the risk of any intravascular injection, after insertion of the needle and just before injection, the plunger rod may be withdrawn slightly to aspirate and verify the needle is not intravascular.

Based upon the study injection technique and the anatomy of the neck's vascular supply, the risk of an intravascular injection into the major vessels of the neck is highly unlikely. In this study, injections of VOLITE XC are placed superficially, just below the skin of the neck. The common carotid artery (which gives rise to the internal and external carotid arteries) runs deep to the sternocleidomastoid muscle, lying deep below the treatment plane. Therefore, with the intended technique of injection to correct the neck lines, there is a highly unlikely risk of vascular occlusion or product embolization that could potentially lead to visual disturbances, stroke, myocardial infarction, pulmonary embolism, or pulmonary edema. However, to collect safety data and ensure participant safety, visual assessments consisting of Snellen visual acuity, confrontational visual fields, and ocular motility will be performed prior to each treatment and approximately 30 minutes after treatment and at all office visits through 1 month after each treatment. The detection of any visual disturbance symptoms that may be associated with vascular occlusion or product embolization (including, but not limited to, any loss of vision, pain in or around eye, or blind spot or shadow in the visual field) in a study participant must result in the immediate referral of the participant to an ophthalmologic retinal specialist and the event being reported as an AESI. In addition, if there are any acute cognitive changes or any change in confrontational visual fields, ocular motility, or a worsening (1-line change or more) on the Snellen visual acuity assessment, the TI or designee will perform a neurological assessment (with urgent referral to the emergency room as appropriate), and the participant will be referred to an ophthalmologist or ophthalmology subspecialist for further assessment of the visual changes.

Pneumothorax is also highly unlikely to be caused by an injection in the neck skin since the pleura and the lungs are in the thorax, not the neck. However, this could occur if the needle/cannula were misused and injected into the chest rather than the neck. If a participant displays any symptoms of pneumothorax (shortness of breath, increased respiratory rate, pain on inhalation, and increased heart rate), the TI will perform a clinical evaluation, and, if pneumothorax is suspected, urgent referral to the emergency room is required, and the event will be reported as an AESI.

The ICF and safety e-diary will inform and instruct participants to seek emergency treatment should they experience visual changes or vision loss, or symptoms of stroke, myocardial infarction, pulmonary embolism, pulmonary edema, or pneumothorax.

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

The benefit of using HA soft tissue fillers in facial aesthetics has been documented in the published literature showing the safety and effectiveness of HA fillers. It is anticipated that the safety and effectiveness of treatment to improve horizontal neck lines are similar to those identified in studies of JUVÉDERM® products for equivalent indications such as facial wrinkles

and folds. The physicochemical properties of VOLITE XC potentially provide the benefit of use of HA soft tissue fillers for improvement in transverse neck lines.

Considering a pandemic or natural disaster, the benefit and risk to participants in this study has been evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of VOLITE XC.

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

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of VOLITE XC are provided in the IDFU.

3. Objectives and Endpoints

Objectives	Endpoints/Measures	
Effectiveness		
To evaluate the effectiveness of VOLITE XC in adults seeking improvement in neck appearance	Primary	• Responder status based on EI's live assessment of transverse neck lines using the ATNLS at Month 1
	Secondary	• Responder status based on EI's assessments of global aesthetic improvement on the neck using the GAIS at Month 1 • Change from baseline to Month 1 in the Rasch-transformed scores on FACE-Q Appraisal of the Neck questionnaire • Responder status based on participant's assessments of global aesthetic improvement on the neck using the GAIS at Month 1
	Other	• Primary and secondary effectiveness measures at other applicable visits • Change from baseline in neck skin hydration measured by MoistureMeter® D instrument at each measurement visit • Participant questionnaires (ANSS—Feel, ANSS—Appearance, ANSS—Psychosocial, ANTOS—Satisfaction with Treatment, ANTOS—Recommend) at each measurement visit
	Exploratory	• Change from baseline in neck skin topography measured by PRIMOS 3D images at each measurement visit (applicable study sites only)
Safety		
To evaluate the safety of VOLITE XC in adults seeking improvement in neck appearance	• Participant assessment of procedural pain • Participant assessment of ISRs • Snellen visual acuity, confrontational visual fields, and ocular motility assessments by the TI (or designee) • AEs • Concomitant medications and procedures	

4. Study Design

4.1. Overall Design

- Multicenter, randomized (2:1 ratio to treatment and control groups), controlled, parallel-design study in adult participants with *moderate* or *severe* transverse neck lines (ATNLS Grades 2 or 3)
- Single-blind: EIs are blinded; TIs and participants are not blinded
- VOLITE XC subdermal and/or intradermal injection using a 32 G 1/2" needle with or without a 25 G 1 1/2" cannula to the neck area for the treatment group and delayed treatment for the control group (a minimum of 40 participants will receive injections via cannula)
- Up to 3 mL for initial treatment, up to 2 mL for optional touch-up treatment, and up to 3 mL for repeat treatment (if administered)
- Up to 20 investigational sites in the United States, each with a PI who is responsible for the overall conduct of the study at that site and is the TI along with an EI
- Up to 212 participants are planned to be enrolled and screened initially to achieve 159 randomized (106 treatment group, 53 control group) and 144 evaluable participants (96 treatment group, 48 control group) at the Month 1 primary timepoint. A blinded re-estimation will be performed when at least 50% of randomized participants have completed the Month 1 visit, and additional participants may be enrolled if needed to achieve at least 80% power. No more than 200 participants will be randomized (133 treatment group, 67 control group), and no more than 267 participants will be enrolled and screened.
- Safety data from the first 20 treated participants for 14 days after initial treatment will be submitted to the FDA prior to proceeding with enrollment of additional participants.
- Treatment group participants receive initial treatment and optional touch-up treatment at 30 days if optimal correction has not been achieved and is agreed upon by both the participant and TI. Follow-up visits are 3 days and 14 days after each treatment (safety telephone call only at 3 days) and at Months 1, 2, 4, and 6 after last treatment. Participants exit the study at Month 6 or receive repeat treatment and are followed at 3 days and 14 days (safety telephone call only at 3 days) and Months 1, 2, and 4 after repeat treatment. Participants who receive repeat treatment exit the study at Month 4 after repeat treatment.
- Control group participants are followed at Months 1, 2, 4, and 6 after randomization (control period) and then either exit the study or receive optional treatment (initial and touch-up, if needed) in the optional treatment period. Follow-up visits in the optional treatment period are 3 days and 14 days after each treatment (safety telephone call only at 3 days) and at Months 1, 2, 4, and 6 after last treatment. Participants who receive optional treatment exit the study at Month 6 after treatment.

During the course of the study, if it ever becomes necessary to remain home or to shelter-in-place per local, regional, or state orders, the sponsor will engage with study site staff in efforts to ensure the safety of participants, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage participant continuity of care. This may include alternative methods for assessments (eg, telephone contacts or virtual site visits) in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB. PIs are to notify the sponsor if any urgent safety measures are taken to protect the participants against any immediate hazard.

4.2. Scientific Rationale for Study Design

4.2.1. Delayed Treatment Control

The delayed treatment control was chosen primarily because no HA filler is currently FDA-approved for use in treatment of transverse neck lines; therefore, an active comparator design is not possible. A sham injection (eg, saline) was not chosen as a control because it is easily distinguished from a soft-tissue filler injection by both the injector and participant, and, therefore, does not result in any additional blinding over a delayed-treatment control. Meanwhile, a sham injection exposes control participants to the pain associated with neck injections and puts them at risk for infection or ISRs with no clinical benefit.

While surgical and other invasive options (eg, laser) to treat horizontal neck lines are available, they are not appropriate controls for a soft tissue filler injection as the mechanism of action is different and the risks associated with these surgical procedures are much higher than the risks of a soft tissue filler treatment. Likewise, the amount of correction that can be achieved with a surgical procedure and a soft tissue filler differ. Because of these differences, the participant populations appropriate for treatment with soft tissue fillers and surgical treatments are not the same. The differences would make randomization difficult and would confound any comparisons with the study intervention.

4.2.2. Evaluator Blinded

Because the control group uses a delayed treatment design, it is not possible to blind the TI or participant to treatment. Therefore, a blinded EI will perform effectiveness assessments to reduce the bias associated with these assessments.

4.2.3. Allergan Transverse Neck Lines Scale

ATNLS is a 5-point photonumeric scale developed by Allergan to grade the severity of transverse neck lines. The ATNLS contains a morphed photograph showing all 5 severities of transverse neck lines as well as photographic images representing both sexes, different Fitzpatrick skin phototypes, race/ethnicity categories, and all 5 severities of transverse neck lines.

A scale validation study (Study 2029-601-000) was conducted to assess the intra-rater and inter-rater reliability of the ATNLS. Each of the 5 trained clinicians independently evaluated 99 participants in person and assigned each participant an ATNLS grade based on the live evaluation at 2 sessions 3 weeks apart. The intra-rater agreement was substantial (mean weighted Kappa = 0.74) and the inter-rater agreement was almost perfect (intra-class correlation

coefficient = 0.84), indicating substantial agreement among the raters as well as within the raters between the 2 in-person evaluation sessions. Additionally, the results demonstrated that a 1-point difference or higher is clinically significant.

Therefore, results confirmed that the ATNLS is validated and appropriate to be used as a primary effectiveness measure for this study.

4.2.4. FACE-Q Questionnaire

Patient-reported outcomes are being more often used in clinical research to provide insight on the results of the study intervention from the participant's perspective. The FACE-Q Appraisal of the Neck questionnaire was developed to provide highly reliable, valid, and responsive participant assessments. The scale has strong psychometric properties and the potential to provide clinically meaningful scores (Pusic 2013).

4.3. Justification for Dose

The volume of VOLITE XC to be injected for each participant will be determined by the TI and will take into consideration the participant's baseline condition of the neck and the desired outcome.

The maximum volume per neck treatment in this study is 3 mL each for initial and repeat treatments and 2 mL for touch-up treatment. At each treatment, a maximum of 1 mL may be injected via cannula. The allowable injection volume is based upon previously conducted VOLITE studies treating the neck, cheek, and forehead areas.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. The study primary completion date for the United States clinical trial registry is defined as the date of the last Month 1 primary endpoint visit.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit. Treatment group participants are considered completers if they complete the Month 6 visit and do not receive repeat treatment or if they complete the Month 4 visit after repeat treatment. Control group participants are considered completers if they complete the Month 6 visit and do not receive the optional treatment or if they complete the Month 6 visit after optional treatment.

If the participant is not able to present in-person to the site for the Study Exit visit due to national or regional travel restrictions, site closure as a result of these restrictions, or a participant declines an in-clinic visit due to pandemic or natural disaster-related health concerns, a telephone visit is permitted. The participant will be considered to have completed the study after the telephone visit. However, if a participant is later able to present in-person to the site within the visit window, assessments will be performed in-person and the data captured for the visit. Previous data recorded from the telephone visit will be captured as an unscheduled visit.

5. Study Population

Adults who are seeking improvement in neck appearance. The randomization target is a minimum of 16 participants of Fitzpatrick skin phototypes I/II, 16 of phototypes III/IV, and 16 of phototypes V/VI, with a minimum of 4 participants in each of the IV, V, and VI phototypes.

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

5.1. Inclusion Criteria

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

1.	**Age**
1.01	Participant must be 22 years of age or older at the time of signing the ICF
2.	**Sex**
2.01	Female or male
3.	**Type of Participant and Neck Characteristics**
3.01	Participants in general good health as determined by TI's judgment, including no known active pandemic infection
3.02	Participants seeking improvement of transverse neck lines
3.03	Has *moderate* or *severe* transverse neck lines (ATNLS Grade 2 or 3) on EI live assessment
3.04	The participant is able to achieve at least a 1-point improvement in ATNLS score with the allowed injection volume in the judgment of TI
4.	**Informed Consent**
4.01	Capable of giving signed informed consent as described in Section 10.1.3, Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
4.02	Written informed consent from the participant has been obtained prior to any study-related procedures
5.	**Other**
5.01	In the opinion of the TI, able and willing to follow study instructions (including compliance with the safety e-diary) and likely to complete all required study visits
5.02	Fluent and literate in English or Spanish

5.2. Exclusion Criteria

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

1.	**Medical Conditions**
1.01	The participant cannot achieve at least a 1-grade improvement from the EI's baseline score on the ATNLS given the allowed injection volume, in the opinion of the TI
1.02	Atrophic skin in the neck area that might not be suitable for injection, in the opinion of the TI
1.03	History of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), HA products, or Streptococcal protein
1.04	Neck deformity or significant skin laxity with severe redundant folds
1.05	Active autoimmune disease
1.06	Significant skin pigmentation disorders or discoloration in the neck area that would interfere with the visual assessment of the neck area
1.07	Current cutaneous inflammatory or infectious processes (eg. acne, herpes), abscess, an unhealed wound, or a cancerous or precancerous lesion on the neck
1.08	Tendency to develop hypertrophic scarring
1.09	History of thyroid cancer, skin cancer of the neck, radiation of the treatment area, or de novo cancer in the treatment area
1.10	Visual acuity of 20/100 or worse or abnormal confrontational visual fields or ocular motility
2.	**Prior/Concurrent Procedure**
2.01	Permanent soft tissue fillers in the neck area
2.02	Semi-permanent soft tissue fillers in the neck area within 2 years before enrollment
2.03	HA fillers or autologous fat in the neck area within 12 months before enrollment
2.04	Mesotherapy, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, microneedling, laser, or other cosmetic procedures in the neck area within 12 months before enrollment
2.05	Botulinum toxin in the neck area within 6 months before enrollment
2.06	Deoxycholic acid injections or cryolipolysis in the submentum area within 6 months before enrollment
2.07	Neck surgeries and procedures
2.08	Ongoing prescribed regimen of anticoagulation therapy (eg, warfarin) or is known to have a coagulation disorder
2.09	Any over-the-counter or prescription, oral or topical, anti-wrinkle products on the neck within 30 days before enrollment (participants 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)
3.	**Prior/Concurrent Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days before enrollment in this study
4.	**Other**
4.01	Neck tattoos, piercings, pigmentation, hair, or past trauma that would interfere with the visualization of the neck area for the effectiveness assessments
4.02	Pregnant, nursing, or planning a pregnancy
4.03	Planning a significant weight change > 10% of body weight during the study

4.04	TI's discretion based on participant's safety and/or study integrity (the participant has a condition or is in a situation that, in the TI's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study as judged by TI).
4.05	Directly or indirectly involved in the conduct and administration of this study as an investigator, sub-investigator, study coordinator, or other study staff member; employee of the sponsor; first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or enrolled in the study at another clinical site

5.3. Lifestyle Considerations

Within the first 12 hours after treatment, it is recommended that participants not apply make-up to the treatment area. Within the first 24 hours after treatment, it is recommended that participants avoid strenuous exercise, extensive sun or heat exposure, and consumption of alcoholic beverages. Exposure to any of these may cause temporary redness, swelling, and/or itching at the injection sites.

Participants will be advised not to have a massage, enter a hot spring or sauna, or receive excessive exposure to the sun or excessive exposure to temperatures below 0°C for 2 weeks following any study intervention (initial, touch-up, or repeat treatments).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants 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.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

Table 6-1 Study Interventions

Study Intervention	VOLITE XC	Delayed Treatment
Device	VOLITE XC	Same
Formulation	12 mg/mL HA crosslinked with BDDE + 0.3% lidocaine (w/w gel)	Same
Route of Administration	Subdermal and /or intradermal injection using a 32 G 1/2" needle with or without a 25 G 1 1/2" cannula to the neck area	Same
Packaging and Labeling	Study intervention will be provided in prefilled 1 mL single-use syringes. Each syringe will be packaged with 32 G 1/2" needles for injection in a thermoform tray. The 25 G 1 1/2" cannulas and introducer needles will be provided separately from the study intervention. One or more trays will be packaged in a kit. Each kit and thermoform tray will be labeled as required per country requirements. CAUTION–Investigational device. Limited by Federal (or United States) law to investigational use.	Same
Manufacturer	Allergan Route de Proméry, Zone Artisanale de Pré-Mairy 74370 Pringy, Annecy, France	Same
Number and Timing of Treatments	Initial treatment 30 days after initial treatment: Optional touch-up Month 6: optional repeat treatment	After Month 6 of control period: Optional initial treatment 30 days after optional initial treatment: Optional touch-up
Volume Per Treatment	Initial treatment: 3 mL Optional touch-up treatment: 2 mL Optional repeat treatment: 3 mL	Optional initial treatment: 3 mL Optional touch-up treatment: 2 mL
Storage Conditions	2 °C to 25 °C (36 °F to 77 °F)	Same

Immediately before dispensing the study intervention, the TI (or appropriately trained designee) will write the participant's identification number and the date on the label.

6.1.1. Medical Devices

1. The sponsor manufactured medical device provided for use in this study is VOLITE XC (copackaged with 32 G 1/2" needles); the 25 G 1 1/2" cannulas and introducer needles are provided separately, see Table 6-1).
2. Instructions for medical device use are provided in the IDFU included in the study binder.
3. All device deficiencies (including malfunction, use error, and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.7) and appropriately managed by the sponsor.

6.1.2. Instructions for Use and Administration

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 VOLITE XC according to the technique specified for this study. VOLITE XC is to be injected via needle with or without cannula subdermally and/or intradermally into the neck area using a fanning, tunneling (ie, linear retrograde and/or anterograde), and/or microdroplet technique (see treatment area in Figure 6-1). Needle/cannula selection and total injection volume will be determined by the TI in accordance with the maximum volume of 3 mL each for initial and repeat treatments and a maximum of 2 mL for optional touch-up treatment. At each treatment, a maximum of 1 mL may be injected via cannula. Topical anesthesia and/or ice may be applied prior to injection to reduce pain as directed by the TI.

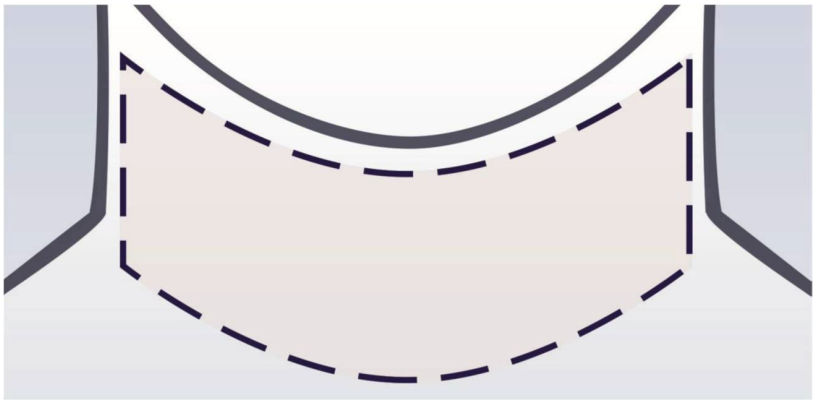
The participant is to arrive at the site without applying creams, lotions, or make-up to the neck area, and the neck area must be clean-shaven (male participants are to shave the day before and not the day of treatment). Prior to treatment, the participant will thoroughly wash the treatment area with soap and water, and the area will be swabbed with alcohol or other antiseptic and appropriately draped. The detailed injection technique guidelines are provided in the IDFU.

During each study visit, participants will be required to remove jewelry to ensure the treatment area is able to be assessed appropriately.

The anatomic area to be treated and assessed (Figure 6-1) is defined as:

- Superior border: horizontal line along the hyoid bone
- Inferior border: sternal notch and clavicles
- Lateral borders: vertical line dropped from each anterior tragus

Figure 6-1 Treatment and Assessment Area



6.2. Preparation/Handling/Storage/Accountability

1. The PI or designee must confirm appropriate temperature conditions have been maintained during transit and pretreatment storage for all study interventions and ensure any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only the TI may administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and temperature 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

Study intervention will be administered at the study visits summarized in the SoA (Section 1.3). Instructions for preparing and administering the study intervention are provided in the IDFU.

The EIs and image analysis technicians will remain blinded to each participant's assigned study intervention throughout the course of the study. The PIs/TIs, study coordinators, and participants will not be blinded to treatment, and the PI/TI and study coordinators 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 presence of the EIs.

In order to maintain the blind, the EI will not be present during any treatments and will not have access to any unblinding information (such as treatment eCRFs or device accountability logs). In addition, participants will be instructed not to discuss whether they have received treatment with the EI. Image analysis technicians will only have access to image files that will not contain any unblinding information (such as randomization status or visit name).

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the sites to verify that randomization/treatment has been done accurately.

The EI must remain blinded throughout the study. If a participant requires immediate medical attention by an unblinded physician, this must be provided by the TI whenever possible. In the event that no unblinded physician is available to provide such treatment, the investigational site or sponsor staff may break the blind so that the EI can provide treatment.

Design bias in this study is reduced through the use of a randomized control group and a blinded EI to assess effectiveness results.

6.4. Study Intervention Compliance

Study intervention compliance is not applicable because the TI administers the study intervention. The study site will keep an accurate record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concurrent Procedure

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

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

At screening and study exit and at each contact with the participant (by telephone or in person), study center staff will question each participant specifically on the use of concomitant medications. Study center staff must notify the sponsor immediately if a participant receives any concomitant medications not permitted by the protocol.

Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or the sponsor.

Therapy considered necessary for the participant'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 and recorded on the appropriate eCRF.

Given the ongoing COVID-19 pandemic, selected non-live vaccines (eg, messenger ribonucleic acid, non-replicating viral vector, protein subunit) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine is to be based on local guidance and an individual discussion between the treating physician and the participant.

The potential impact of VOLITE XC on SARS-CoV-2 vaccination is unknown. Therefore, the study device is recommended to be administered as follows:

- The initial, touch-up, and repeat treatments of VOLITE XC, when possible, are preferred to be given at least ± 14 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to Section 8.3 for instructions on reporting any AEs associated with the COVID-19 vaccine.

6.5.1. Rescue Medicine

Not applicable.

6.5.2. Prohibited Therapy

Participants must discontinue any of the medications and procedures listed in Table 6-2 for the specified period prior to baseline.

Table 6-2 Required Washout Intervals for Prohibited Therapy Prior to Baseline

Washout Period	Medication or Procedure
10 days	• Ongoing regimen of medications and/or substances known to increase coagulation time (eg, aspirin, ibuprofen)
30 days	• Any new over-the-counter or prescription, oral or topical, anti-wrinkle products for the neck area (participant must continue with the regimen throughout the study) • Any investigational product
6 months	• Botulinum toxin in the neck area • Deoxycholic acid injections or cryolipolysis in the submentum area
12 months	• HA fillers or autologous fat in the neck area • Mesotherapy, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, microneedling, laser, or other cosmetic procedures in the neck area
2 years	• Semi-permanent soft tissue fillers in the neck area

During the course of the study participants must not:

1. Receive injectable anesthesia during study treatment
2. Be on a regimen of medications (eg, aspirin, ibuprofen) known to increase coagulation time for 10 days before and 3 days after each study treatment
3. Use any over the counter or prescription, oral or topical, anti-wrinkle products on the neck that were not a stable regimen for at least 30 days prior to study enrollment. The regimen must be continued throughout the study.
4. Receive soft tissue fillers in the neck area including HA, poly-L-lactic acid, calcium hydroxylapatite polymethylmethacrylate, silicone, autologous fat
5. Undergo mesotherapy, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, microneedling, laser, or other cosmetic procedures in the neck area
6. Receive botulinum toxin in the neck area
7. Receive deoxycholic acid injections in the submentum area
8. Undergo surgeries to the neck
9. Receive any other investigational product
10. Receive hyaluronidase unless medically necessary. If hyaluronidase is used, the participant 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 participant as the primary consideration. When possible, the sponsor is to be notified before the prohibited medication/treatment is administered.

6.6. Dose Modification

The volume to be injected will be determined by the TI, with a maximum of 3 mL each for initial and repeat treatments and 2 mL for touch-up treatment. The rationale for these volumes is discussed in Section 4.3.

6.6.1. Retreatment Criteria

A touch-up treatment is recommended if the TI's evaluation of the participant's ATNLS score has not improved a minimum of 1-grade (in comparison to the EI's score at baseline), or if a 1-grade ATNLS improved has been achieved and both the participant and TI agree that optimal correction has not been achieved. The TI will have access to the EI-rated ATNLS scores to assist in making the determination of whether optimal correction has been achieved. All treatment group participants are eligible to receive repeat treatment at Month 6, if desired. If touch-up and repeat treatments are not administered, the TI will record in the eCRF the reasons for not giving these treatments.

6.7. Intervention after the End of the Study

No study intervention will be provided after the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and receives study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF. If a participant withdraws or is discontinued for any reason prior to the final study visit, attempts will be made to perform assessments at an exit visit.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Lost to follow-up	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Screen failure	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1. Discontinuation of Study Intervention

If a participant has a positive urine pregnancy test prior to randomization, the participant will be considered a screen failure. Participants who become pregnant or have a positive urine pregnancy test and have already been randomized and received treatment will continue in the study until all required follow-up is complete, but they will not be eligible for further study intervention.

In addition, participants who receive hyaluronidase treatment in the neck area will continue in the study until all required follow-up is complete (safety only) but will not be eligible for further study intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be discontinued at any time at the discretion of the PI/TI for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early study exit visit is to be conducted. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

In addition, a participant must be discontinued from the study if he/she:

- Receives soft tissue fillers in the neck area including HA, poly-L-lactic acid, calcium hydroxylapatite, polymethylmethacrylate, silicone, autologous fat
- Undergoes mesotherapy, photomodulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, microneedling, laser, or other cosmetic procedures in the neck area
- Receives botulinum toxin in the neck area
- Receives deoxycholic acid injections or cryolipolysis in the submentum area
- Undergoes surgeries to the neck

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

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

During the course of the study, it may be necessary to employ mitigation strategies to enable the PI to ensure participant safety and continuity of care. Acceptable mitigation strategies are identified and included in Section 8.

7.3. Lost to Follow-up

A participant 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or will continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8, Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns are to be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant is to continue or discontinue the study.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The PI/TI will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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 participant 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 participant be performed by the same TI, effectiveness assessments (ATNLS and GAIS) be performed by the same EI, and hydration measurements be performed by the same EI or designee. If it is not possible to use the same evaluator to follow the participant, it is recommended that qualified evaluators examine the participant together and discuss findings for at least 1 visit.
- Safety e-diaries will ensure that participants complete diaries on a daily basis by locking entry for prior days once they have passed.
- Safety e-diaries will be reviewed for potential AEs, at least at each office visit scheduled during the diary completion window up to the visit at which the diary device is returned, and ISRs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.1. Effectiveness Assessments

If travel restrictions or other changes in local regulations in light of a pandemic or natural disaster prevent the participant from in-person visits, some study assessments may be conducted remotely. For participant assessments the site or designee may provide other means to complete the questionnaires.

8.1.1. Primary Effectiveness Measure

The primary effectiveness measure is the EI's live assessment of transverse neck lines using the ATNLS described in Table 8-1. The anatomic area to be treated and rated is described in Section 6.1.2 and shown in Figure 6-1.

Table 8-1 Allergan Transverse Neck Lines Scale

Score	Grade	Description
0	None	No transverse neck lines
1	Minimal	Superficial transverse neck lines
2	Moderate	Moderate, effaceable transverse neck lines
3	Severe	Deep, non-effaceable transverse neck lines
4	Extreme	Non-effaceable transverse neck furrows with redundant skin

8.1.2. Secondary Effectiveness Measures

There are 3 secondary effectiveness measures, which include independent, noncollaborative assessments by both the EI and the participant of global aesthetic improvement on the neck area using the 5-point GAIS (Table 8-2) and participant responses on the FACE-Q Appraisal of the Neck questionnaire.

Table 8-2 Global Aesthetic Improvement Scale

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

Participants and EIs will assess global aesthetic improvement on the neck area by comparing to frontal view photographs taken at baseline. Participants will use a mirror to assess their current appearance at each visit. All participant-reported effectiveness outcomes at a visit will be completed before the participant sees either the TI or EI at that visit.

The other secondary endpoint measure is the participant responses on the FACE-Q Appraisal of the Neck questionnaire. The FACE-Q Appraisal of the Neck questionnaire used in this study is validated and will be used to assess the impact of treatment from the participant's perspective.

The FACE-Q scale is designed for self-completion by the participant. If a participant asks for clarification on or has difficulty answering a particular question on the FACE-Q questionnaire, investigational site staff may ask the participant to explain why they had difficulty responding or help by reading the question verbatim. Staff may not try to explain what the question means or rephrase the question. Instead, staff may suggest that participants must use their own

interpretation of the question. If the participant is still unable to answer the question, the questionnaire can be scored with missing data.

Assessment	Timing	Measurement
Global aesthetic improvement on the neck area (EI)	Treatment group: Months 1, 2, 4, and 6, and Months 1, 2, and 4 after repeat treatment Control group: Months 1, 2, 4, and 6, and Months 1, 2, 4, and 6 after optional treatment	5-point ordinal scale from -2 to 2 (details in Table 8-2)
Global aesthetic improvement on the neck area (Participant)	Treatment group: Optional Touch-up Tx Day 30, Months 1, 2, 4, and 6, and Months 1, 2, and 4 after repeat treatment Control group: Months 1, 2, 4, and 6 after optional treatment	5-point ordinal scale from -2 to 2 (details in Table 8-2)
FACE-Q Appraisal of the Neck	Treatment group: Randomization, Optional Touch-up Tx Day 30, Months 1, 2, 4, and 6, and Months 1, 2, and 4 after repeat treatment Control group: Randomization, Months 1, 2, 4, and 6, and Months 1, 2, 4, and 6 after optional treatment	10-item questionnaire assessing various aspects of the neck appearance. Participants respond to each item as how much have you been bothered by: Not at all A little Moderately Extremely

8.1.3. Other Effectiveness Measures

- Neck skin hydration measured by MoistureMeter® D instrument
- Participant questionnaires:
  - ANSS—Feel
  - ANSS—Appearance
  - ANSS—Psychosocial
  - ANTOS—Satisfaction with Treatment
  - ANTOS—Recommend

8.1.4. Exploratory Effectiveness Measures

- Neck skin topography measured by PRIMOS 3D imaging (at applicable study sites)

8.1.5. Demographics and Baseline Characteristics

Participant demographics and baseline characteristics to be collected at screening include sex, age, race, ethnicity, height, weight, Fitzpatrick skin phototype, sun exposure, nicotine and

alcohol use history, and medical/surgical/cosmetic procedure history. Height and weight will be collected at screening, and weight will also be collected at Month 1 and study exit due to its potential influence on the effectiveness measures. Vital sign measurements, including blood pressure (systolic and diastolic, while participant is seated), respiratory rate, heart rate, and temperature will also be performed.

8.1.6. Study Intervention Assessments

Characteristics of the study intervention will be collected and evaluated for anesthesia usage (topical, ice), needle/cannula (32 G 1/2" needle, 25 G 1 1/2" cannula), injection volume, injection plane (intradermal, subdermal), injection technique (fanning, tunneling, microdroplet), injection ease (11-point scale where 0 = difficult and 10 = easy), and product moldability (11-point scale where 0 = stiff and 10 = moldable).

8.2. Safety Assessments

If travel restrictions or other changes in local regulations in light of a pandemic or natural disaster prevent the participant from in-person visits, participant visits may be conducted via telephone or video conference or at an alternative location.

Safety measures include:

- Participant assessment of procedural pain after study injection on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable)
- The presence and severity of ISRs, which will be recorded in the participant's safety e-diary for 30 days starting on the day of each treatment. ISRs ongoing at the end of the diary will be documented on the ongoing ISR eCRF
- Snellen visual acuity, confrontational visual fields, and ocular motility assessments by the TI (or designee)
- AEs, including AESIs, as determined by the TI
- Monitoring of concomitant medications and concurrent procedures

The participant's safety e-diary will list the following ISRs that have been reported previously with HA soft tissue filler injections:

- Redness
- Pain after injection
- Tenderness to touch
- Firmness
- Swelling
- Lumps/bumps
- Bruising

- Itching
- Discoloration (not redness or bruising)

Participants will rate the severity of each ISR as mild, moderate, or severe according to the following definitions.

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.

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

A participant with any visual disturbance symptoms associated with vascular occlusion (including, but not limited to, any loss of vision, pain in or around eye, or blind spot or shadow in the visual field) will be referred immediately to a retinal specialist.

If there are any acute cognitive changes or any change in confrontational visual fields, ocular motility, or a worsening (1-line change or more) on the Snellen visual acuity assessment, the TI or designee will perform a neurological assessment (with urgent referral to the emergency room as appropriate), and the participant will be referred to an ophthalmologist or ophthalmology subspecialist for further assessment.

Females of Childbearing Potential

Urine pregnancy tests will be performed at the study center at screening, study exit, and before any study intervention for participants of childbearing potential. Participants who are postmenopausal for at least 1 year or have no uterus at the time of study entry are considered not of childbearing potential. Urine samples will be disposed of after testing.

Females of childbearing potential must avoid pregnancy during the study.

8.3. Adverse Events and Serious Adverse Events

AEs will be monitored throughout the study beginning with signing of the ICF. At each postbaseline visit, the TI will begin querying for AEs by asking each participant a general, nondirected question such as "Have you had any changes to your condition since your last visit?" Previous AEs, any ongoing ISRs from the safety diary, 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 and their severity can be found in Section 10.6, Appendix 6.

AEs/ADEs will be reported by the participant.

The PI/TI and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE/ADE or SAE/SADE and remain responsible for following up AEs/ADEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

Supplemental study case report forms are to be completed in the event of COVID-19-related missed/virtual visits or AEs (including capture of specific signs/symptoms of infection and testing results).

SARS-CoV-2 infections are to be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions. The following COVID-19-related supplemental eCRFs are to be completed (for both serious and nonserious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

Reactions known to be associated with the SARS-CoV-2 vaccine are to be reported as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All AEs associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs/ADEs from the signing of the ICF until the last follow-up visit will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

All SAEs/SADEs from the signing of the ICF until the last follow-up visit will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent 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 Section 10.6, Appendix 6. 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/ADE or SAE/SADE information after conclusion of the study participation. However, if the PI/TI learns of any SAE/SADE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the PI/TI must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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 Section 10.6, Appendix 6.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/ADE/SAE/SADE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/ADEs/SAEs/SADEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.6.4, Appendix 6.

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

- Details of all pregnancies will be collected after the start of study intervention and until the last follow-up visit.
- While not considered an AE, pregnancy of a study participant must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy.
- The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

8.3.6. Adverse Events of Special Interest

AESIs that warrant ongoing monitoring and rapid communication by the investigator to the sponsor are any visual disturbance symptoms associated with vascular occlusion (including, but not limited to, any loss of vision, pain in or around eye, or blind spot or shadow in the visual field), myocardial infarction, stroke, pulmonary embolism, pulmonary edema, and pneumothorax. Details are outlined in Section 10.6, Appendix 6.

8.3.7. Medical Device Deficiencies and Product Complaints

Medical devices are being provided for use in this study as the study intervention. In order to fulfill regulatory reporting obligations worldwide, the PI/TI is responsible for the detection and documentation of events meeting the definition of device deficiency and product complaint that occur during the study with such devices.

The definition of a medical device deficiency and product complaint can be found in Section 10.6.3, Appendix 6.

NOTE: Device deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Section 10.6, Appendix 6 of the protocol.

8.3.7.1. Time Period for Detecting Medical Device Deficiencies and Product Complaints

- Medical device events 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/TI learns of any device deficiency or product complaint at any time after a participant has been discharged from the study, and such an event is considered reasonably related to a medical device provided for the study, the PI/TI will promptly notify the sponsor.

The method of documenting medical device deficiencies and product complaints is provided in Section 10.6.4, Appendix 6.

8.3.7.2. Follow-up of Medical Device Deficiencies and Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The PI/TI is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency or complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the PI/TI.

8.3.7.3. Prompt Reporting of Device Deficiencies and Product Complaints to Sponsor

- Device deficiencies and product complaints that are potentially related to SAEs will be reported to the sponsor within 24 hours by entering into product complaint eCRF in EDC after the PI/TI determines that the event meets the protocol definition of a medical device deficiency.

8.3.7.4. Regulatory Reporting Requirements for Device Deficiencies

- The PI/TI will promptly report all device deficiencies 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 device deficiencies to the IRB.

8.4. Treatment of Overdose

Not applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.10. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

There are 2 hypotheses testing for the primary effectiveness endpoint, ATNLS responder status at Month 1 in the control period.

Hypothesis 1: The null hypothesis is that the ATNLS responder rate for the VOLITE XC group is equal to the responder rate for the control group. The alternative hypothesis is that the responder rates are not equal for the VOLITE XC group and the control group. These hypotheses are stated as:

$$H_0: P_v = P_c$$

$$H_a: P_v \neq P_c$$

where P_v and P_c denote the ATNLS responder rates for the VOLITE XC group at Month 1 after the last treatment (initial or touch-up) and for the control group at Month 1 after randomization, respectively.

The first hypothesis will be tested based on the multiple imputation (MI) method described in Section 9.4.2.2. If the 2-sided p-value is ≤ 0.05 and the ATNLS responder rate of VOLITE XC group is greater than that of the control group, then VOLITE XC will be considered statistically significantly higher (better) than the control group.

Hypothesis 2: The null hypothesis is that the ATNLS responder rate for the VOLITE XC group is less than or equal to 50%, and the alternative hypothesis is that the responder rate for the VOLITE XC group is greater than 50%. These hypotheses are stated as follows:

$$H_0: P_v \leq 50\%$$

$$H_a: P_v > 50\%$$

The second hypothesis will be tested using the VOLITE XC group responder rate derived from the multiple imputation method described in Section 9.4.2.2 against 50% by the 2-sided 95% CI. If the lower bound of the 95% CI is > 50%, then the ATNLS responder rate for VOLITE XC group at Month 1 will be considered statistically significantly greater (better) than 50%.

If both hypotheses are rejected, then VOLITE XC will be considered clinically effective.

9.2. Sample Size Determination

The primary effectiveness measure is the EI's live assessment of transverse neck lines using the 5-point ATNLS. The primary effectiveness endpoint is the ATNLS responder status at Month 1 of CP. A responder is defined as a participant with at least 1-grade improvement from baseline on the ATNLS based on the EI's assessment.

Up to 212 participants will be screened. Assuming a screen failure rate of 25%, a total of 159 participants will be randomized to either the treatment group or the control group in a 2:1 randomization ratio. Assuming an attrition rate of 10%, 96 and 48 participants in the treatment group and the control group, respectively, will provide at least 93% power to detect a between-group difference of 30% in the ATNLS responder rate at Month 1 of CP. This calculation is based

on a Chi-squared test at 5% significance level assuming 65% vs. 35% for the ATNLS responder rate of the treatment group vs. the control group, respectively. In addition, 96 participants in the treatment group will provide at least 84% power to detect a statistical difference in the ATNLS responder rate of the treatment group from 50% at Month 1 of CP. This calculation is based on a 1-sided 1-sample Z-test at 2.5% significance level assuming 65% for the ATNLS responder rate of the treatment group. The overall power to detect both a between-group difference of 30% in the ATNLS responder rate and the ATNLS responder rate of the treatment group greater than 50% at Month 1 of CP is at least 80%. This calculation is based on a simulation of 10,000 iterations for the hypothesis testing assumptions described above. With 20 investigational sites planned, it is recommended that no site randomizes more than 20 participants.

Assuming a 5% drop-out rate between randomization and initial treatment for the treatment group, and a 10% drop-out/study completion rate between randomization and optional treatment for the control group, it is estimated that at least 147 participants will be treated in the study. With 147 treated participants, the probability to observe at least 1 incidence of treatment-related AE is 94.9% assuming an incidence rate of 2% in the population based on the cumulative distribution function for the binomial distribution.

A blinded sample size re-estimation will be conducted when at least 50% of randomized participants have completed the Month 1 visit of CP. The blinded sample size re-estimation will be conducted via the following steps:

1. The overall ATNLS responder rate at the Month 1 of CP, $\hat{P}$, will be estimated based on the pooled data without unblinding the subject randomization list.
2. The ATNLS responder rate of the control group at Month 1 of CP, $\hat{P}_c$, will be estimated by the median of the following 3 values:
    a. Upper bound of the 95% CI of the ATNLS responder rate based on the cumulative rater qualification data of Study 2029-701-008
    b. Upper bound of the 95% CI of the ATNLS responder rate of the scale validation study 2029-601-000
    c. 35% as specified for the sample size estimation for this study
3. The ATNLS responder rate for the treatment group, $\hat{P}_v$, will be calculated based on the estimates obtained at steps No. 1 and 2 and the study randomization ratio of 2:1 using the following formula.

$$\hat{P}_v = \frac{3}{2}\hat{P} - \frac{1}{2}\hat{P}_c$$

4. The probability to reject both hypothesis testing for the primary effectiveness endpoint will be calculated via a simulation based on the estimates obtained at steps 2 and 3.
5. If the probability estimated at step 4 is less than 80%, then the sample size will be increased to achieve at least 80% power for the analyses of primary effectiveness endpoint.

Additional participants may be enrolled to achieve at least 80% overall power for testing both hypotheses. Up to 200 and 267 participants will be randomized and screened, respectively. Details will be specified in Section 2.5 of SAP.

The modules of PTTOU-1 for the two-group Chi-square test of equal proportions (unequal n's) and POT0-1 for the 1-sample Chi-square test of commercial software nQuery were used for the sample size and power calculation.

Due to local guidelines to prevent and mitigate the effects of a pandemic or natural disaster, it is understood that some participants may not be able to complete all site visits as indicated per protocol.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
ITT	All randomized participants.
Observed Primary Endpoint	All ITT participants with baseline and Month 1 assessments on the ATNLS
Safety	All randomized participants who have at least 1 study intervention (ie, VOLITE XC or no-treatment control).
VOLITE Treated	• All randomized participants who receive VOLITE XC treatment at the beginning of the control period • All randomized participants who receive optional VOLITE XC treatment after the control period
VOLITE Repeat Treatment	Participants in the VOLITE treated population who receive repeat treatment

Effectiveness analyses in the control period will be performed on the ITT population using the "as-randomized" assignment for each participant (ie, if a participant randomized to the control group is treated in error at the start of the study, the assessments for that participant will nonetheless be included in the control group analysis).

Safety analyses in the control period will be conducted on the safety population using the actual treatment received.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section including procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

In general, descriptive statistics will be presented unless otherwise specified. Categorical variables will be summarized with response frequencies and percentages. Continuous variables will be summarized by descriptive statistics for the number of participants, mean, median,

standard deviation, Q1, Q3, minimum, and maximum. Where appropriate, 2-sided 95% CIs for mean or proportion will be provided as part of the summary.

Every attempt will be made to collect complete data and limit the occurrence of missing data. Imputation of missing data will be performed for the primary effectiveness analyses as described in Section 9.4.2.2 and for the secondary effectiveness analyses as described in Section 9.4.3. Deviations from the analyses planned in the statistical plan will be documented in the clinical study report.

9.4.2. Primary Endpoint

9.4.2.1. Definition of Endpoint

The primary endpoint is the responder status based on the EI's live assessment of transverse neck lines using ATNLS at Month 1 after the last treatment (initial or touch-up) for VOLITE XC group and after randomization for control group, where a "responder" is a participant with at least 1-grade improvement on the ATNLS.

9.4.2.2. Main Analytical Approach

If there are ITT participants with missing primary effectiveness endpoint, the following missing-data handling method is planned for the primary analysis.

- Multiple imputation by fully conditional specification method for ordinal data (via SAS procedure MI FCS logistic statement) with 30 imputed datasets is applied to participants with missing primary endpoint using the model below:

  Month 1 ATNLS = $\beta 0 + \beta 1 \times$ Age $+ \beta 2 \times$ Sex $+ \beta 3 \times$ Fitzpatrick skin type $+ \beta 4 \times$ Body mass index $+ \beta 5 \times$ Site $+ \beta 6 \times$ Baseline ATNLS

- The imputation will be performed by treatment group. After imputation, the change from baseline will be calculated and the responder status will be determined at the participant level.

Analyses of individual imputed datasets will be performed by SAS procedure FREQ and then pooled by SAS procedure MIANALYZE to tabulate the aggregated responder rates and 95% CIs within and between VOLITE XC and control groups and to generate an associated p-value for the comparison of responder rates between groups.

If there are no ITT participants with missing primary effectiveness endpoint, then a 2-sided Fisher's exact test with 5% significance level will be used to compare responder rates between treatment and the control group. In addition, responder rates and 95% CIs based on the Clopper-Pearson exact binomial method will be calculated for VOLITE XC group and control group.

9.4.2.3. Sensitivity Analyses

Two sensitivity analyses will be performed: (1) observed data for the Observed Primary Endpoint population and (2) non-responder imputation for the ITT population where participants with missing baseline or Month 1 ATNLS assessments will be considered as non-responders.

The poolability of site for the primary effectiveness analysis will be evaluated by including investigational site, treatment, and the interaction of site with treatment as predictor variables in a multivariate logistic regression analysis along with the FIRTH option, with responder status (1 = yes and 0 = no) on the ATNLS at Month 1 as the dependent variable using the ITT population. The interaction between site and treatment will be considered significant if the p-value of this interaction is less than 0.15. Investigational sites with less than 6 participants in the ITT population will be excluded. The primary effectiveness endpoint will also be summarized using descriptive statistics by site regardless of the sample size of each site.

9.4.3. Secondary Effectiveness Endpoints

The hypothesis testing for the secondary effectiveness endpoints listed below will be conducted to assess the difference between VOLITE XC group and control group for the ITT population. Missing data of secondary effectiveness endpoints will be imputed by the MI method. If there are no ITT participants with missing data for the secondary effectiveness endpoints, then the Fisher's exact test will be conducted for the GAIS by EI responder status and the paired t-test (or Wilcoxon signed rank test, if normality does not hold) and 2-sample independent t-test (or Wilcoxon rank-sum test, if normality does not hold) will be conducted for the within-group and between-group comparisons of change from baseline in Rasch-transformed score of FACE-Q Appraisal of the Neck at Month 1, respectively. Details of the analytical methods with missing data imputation will be specified in the SAP.

- Responder status based on the EI's assessments of GAIS where a responder is defined as a participant who shows improvement in the overall aesthetic assessment of the neck (Improved or Much Improved on GAIS) at Month 1
- Change from baseline to Month 1 on participant responses on the Rasch-transformed score of FACE-Q Appraisal of the Neck questionnaire.

The third secondary effectiveness endpoint is responder status based on the participant's assessments of GAIS where a responder is defined as a participant with improvement in the overall aesthetic assessment of the neck (Improved or Much Improved on GAIS) at Month 1. This endpoint will be analyzed based on the observed data without hypothesis testing.

The analysis for responder status based on EI's assessments of GAIS between VOLITE XC and control groups at Month 1

The corresponding null and alternative hypotheses are:

$$H_0: P_v = P_c$$

$$H_a: P_v \neq P_c$$

where P_v and P_c denote the GAIS responder rates based on EI's assessments for the VOLITE XC group at Month 1 after the last treatment (initial or touch-up) and for the control group at Month 1 after randomization, respectively.

The aggregated statistics after MI including the between-group difference in the GAIS by EI responder rate, the corresponding 2-sided 95% CI and p-value will be tabulated. The pooled GAIS by EI responder rate and the 95% CI will be tabulated by treatment group separately.

If the 2-sided p-value is ≤ 0.05 and the GAIS by EI responder rate of the VOLITE XC group is greater than that of the control group, then VOLITE XC will be considered statistically significantly better than the control group.

The analysis for change from baseline in the Rasch-transformed score of FACE-Q Appraisal of the Neck within VOLITE XC group at Month 1

The corresponding null and alternative hypotheses are:

$$H_0: \mu_{vd} \leq 0$$

$$H_a: \mu_{vd} > 0$$

where μ_{vd} denotes the mean difference between Month 1 and baseline in the Rasch-transformed score of FACE-Q Appraisal of the Neck questionnaire for the VOLITE XC group at Month 1 after the last treatment (initial or touch-up).

The aggregated statistics after MI for the change from baseline in Rasch-transformed score of FACE-Q Appraisal of the Neck at Month 1, the associated 2-sided 95% CI, and 1-sided p-value of paired t-test will be presented.

If the 1-sided p-value is ≤ 0.025 and the mean change from baseline in the Rasch-transformed score of FACE-Q Appraisal of the Neck at Month 1 is > 0, then the Rasch-transformed score in FACE-Q Appraisal of the Neck at Month 1 will be considered statistically significantly greater (better) than that at baseline for the VOLITE XC group.

The analysis for change from baseline in the Rasch-transformed score of FACE-Q Appraisal of the Neck between VOLITE XC and control groups at Month 1

The corresponding null and alternative hypotheses are:

$$H_0: \mu_v = \mu_c$$

$$H_a: \mu_v \neq \mu_c$$

where μ_v and μ_c denote the mean change from baseline in the Rasch-transformed score of FACE-Q Appraisal of the Neck questionnaire for the VOLITE XC group at Month 1 after the last treatment (initial or touch-up) and for the control group at Month 1 after randomization, respectively.

The aggregated statistics after MI for the change from baseline in Rasch-transformed score of FACE-Q Appraisal of the Neck at Month 1, the associated 2-sided 95% CI, and 2-sided p-value of independent t-test will be presented.

If the 2-sided p-value is ≤ 0.05 and the mean change from baseline in Rasch-transformed score of FACE-Q Appraisal of the Neck of VOLITE XC group is greater than that of the control group, then VOLITE XC will be considered statistically significantly greater (better) than the control group.

The summary for responder status based on participant's assessments of GAIS for the VOLITE XC and control groups at Month 1

The GAIS responder rate based on the participant's assessment at Month 1 and the corresponding 2-sided 95% CI based on the Clopper-Pearson exact binomial method for both VOLITE XC and control groups will be summarized.

A gatekeeping procedure will be used for hypothesis testing in the table below for the primary and secondary effectiveness endpoints to control the overall type I error rate at 0.05 level. Both primary hypotheses must be rejected in order to test the secondary endpoints in the sequential order specified below.

Order	Category	Endpoint	Description	Methodology
1	Primary	ATNLS responder status at Month 1 of CP	(1) Number (%) of responders' comparison between VOLITE XC and control groups (2) Number (%) of responders within VOLITE XC group.	(1) Multiple imputation with aggregated statistics for the between-group difference in ATNLS responder rate p-value and corresponding 2-sided 95% CI at 0.05 significance level (2) Lower bound of 95% CI (obtained from the multiple imputation method) compared with 50%
2	Secondary	GAIS responder status assessed by the EI at Month 1 of CP	Number (%) of responders' comparison between VOLITE XC and control groups	Multiple imputation with aggregated statistics for the between-group difference in GAIS by EI responder rate p-value and corresponding 2-sided 95% CI at 0.05 significance level

3	Secondary	Change from baseline of Rasch-transformed score of participant responses to FACE-Q Appraisal of the Neck questionnaire at Month 1 of CP	Mean change from baseline within VOLITE XC group	Multiple imputation with aggregated statistics for the within-group change from baseline of Rasch-transformed score of FACE-Q p-value and corresponding 95% CI at 0.025 significance level
4	Secondary	Change from baseline of Rasch-transformed score of participant responses to FACE-Q Appraisal of the Neck questionnaire at Month 1 of CP	Mean change from baseline comparison between VOLITE XC and control groups	Multiple imputation with aggregated statistics for the between-group change from baseline of Rasch-transformed score of FACE-Q responder rate p-value and corresponding 95% CI at 0.05 significance level

9.4.4. Other Effectiveness Endpoints

All analyses for other effectiveness endpoints listed below will be defined in the SAP.

- Responder status based on the EI's live assessment of transverse neck lines using ATNLS at other applicable visits
- Responder status based on the EI's assessment of the neck using GAIS at other applicable visits
- Responder status based on participant's assessment of the neck using GAIS at other applicable visits
- Change from baseline in participant responses to FACE-Q Appraisal of the Neck questionnaire at other applicable visits
- Participant responses to FACE-Q Appraisal of the Neck questionnaire at each measurement visit
- Percentage of participants showing improvement on the FACE-Q Appraisal of the Neck questionnaire at each measurement visit
- Change from baseline in neck skin hydration measured by MoistureMeter® D instrument at each measurement visit

- Participant responses to individual items in each of the questionnaires (ANSS—Feel, ANSS—Appearance, ANSS—Psychosocial, ANTOS—Satisfaction with Treatment, ANTOS—Recommend) at each measurement visit. If a total score algorithm is available, a summary of the mean change from baseline in total score will be provided.

9.4.5. Exploratory Effectiveness Endpoints

All analyses for exploratory effectiveness endpoints listed below will be defined in the SAP.

- Change from baseline in neck skin topography assessment using PRIMOS 3D images at each measurement visit (applicable study sites only)

9.4.6. Safety Analyses

The safety analyses will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include procedural pain, ISRs, Snellen visual acuity, confrontational visual fields, ocular motility, AEs, and concomitant medications and procedures.

Procedural pain, Snellen visual acuity, confrontational visual fields, and ocular motility will be summarized using descriptive statistics. ISRs reported by participants will be summarized at the participant level by symptom incidence, maximum reported severity, and ISR duration for initial, touch-up, and repeat treatments separately. Summaries will include the incidence rate for each ISR. The summary of procedural pain, ISRs, Snellen visual acuity, confrontational visual fields, and ocular motility will be done separately for each treatment group. Concomitant medications and procedures will be listed.

9.4.6.1. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first study treatment for treatment group or of randomization for control group (participants are grouped as treated). An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

Overall summary of AEs will be presented for the following:

- TEAEs
- Treatment-related TEAEs
- Treatment-related TEAEs at injection site
- Treatment-related TEAEs not at injection site
- TESAEs
- Treatment-related TESAEs
- Treatment-related TESAEs at injection site
- Treatment-related TESAEs not at injection site

- TEAE leading to withdrawal of study treatment
- Deaths

The incidence of TEAEs and treatment-related TEAEs will be presented according to the following:

- By primary system organ class and preferred term
- By primary system organ class, preferred term, and maximum severity

The incidence of treatment-related TEAEs will also be presented for the following:

- By maximum severity, time to onset, duration, and outcome

The summary will include incidence rate as well as total number of events. AEs that may occur before randomization will be listed but not summarized.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to withdrawal of study treatment if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

The analyses for treatment versus control groups will be for AEs occurring during the 1-month control period. The analyses will be repeated to summarize AE results for treated participants over the treatment period prior to repeat treatment. Similarly, the analyses will be repeated to summarize AE results over the repeat treatment phase for participants who receive repeat treatment.

The definitions of an AE and SAE are provided in Section 10.6, Appendix 6.

9.4.7. Other Analyses

9.4.7.1. Demographics and Baseline Characteristics Analyses

Demographic parameters (sex, age [years], race, ethnicity) will be summarized descriptively in total and by treatment group for the ITT population.

Baseline characteristics will be summarized in total and by treatment group for the ITT population as follows:

- Weight (kg), height (cm), and body mass index (kg/m^2)
- Fitzpatrick skin phototype (each phototype, and by phototype groups I/II, III/IV, and V/VI)
- Sun exposure (hours per day)

- Nicotine use history (status, amount/frequency, nicotine product, and duration in years)
- Alcohol use history (status, amount/frequency, and duration in years)

Vital signs will be listed.

9.4.7.2. Study Intervention Administration Analyses

Study intervention characteristics will be summarized with descriptive statistics for anesthesia usage, injection volume, injection ease, and product moldability. Injection instrument, injection plane, and injection technique will be summarized using frequency and percentages.

9.4.7.3. Subgroup Analyses

The primary effectiveness endpoint will be summarized by baseline ATNLS score, injection volume, injection instrument, race, sex, Fitzpatrick skin phototype, and investigational site. Details of the analysis for site poolability in the primary effectiveness analysis can be found in Section 9.4.2.3.

9.5. Interim Analyses

No interim analysis is planned for this study.

9.6. Data Monitoring Committee

No data monitoring committee is planned for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH/ISO 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 participants.
- 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
- During the course of the study, if it ever becomes necessary to remain home or to shelter-in-place per local, regional, or state orders, the sponsor will engage with study site staff in efforts to ensure the safety of participants, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage participant continuity of care. This may include alternative methods for assessments (eg, telephone contacts or virtual site visits) in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB. Investigators are to notify the sponsor if any urgent safety measures are taken to protect the participants against any immediate hazard.

10.1.2. Financial Disclosure

Investigators and subinvestigators 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.

10.1.3. Informed Consent Process

- The PI or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- In the event of a pandemic or natural disaster, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. Any verbal consent must be dated and documented in the source document.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; any identifiable participant information will only be transferred in accordance with the signed ICF.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participants who will be required to give consent for their personal data to be used as described in the ICF.
- The participant 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.

- Management of privacy incidents relating to clinical trial participant personal data, as well as handling of data participant rights requests (if applicable), is to be handled in accordance with the agreed upon clinical trial agreement provisions.

10.1.5. 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.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, PRIMOS 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.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor assumes accountability for actions delegated to other individuals (eg, vendors).
- Study monitors will perform ongoing source data review to confirm that the safety and rights of participants 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 as stated in the clinical trial agreement. 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.

- In the event of a pandemic or natural disaster, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB, and the study site.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant 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).

10.1.8. Study and Site Start and Closure

For the purpose of clinical trial registries, the study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor or 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 participants by the PI
- Discontinuation of further study intervention development
- If a vascular embolic AE leading to skin necrosis, vision loss, myocardial infarction, stroke, pulmonary embolism, or pulmonary edema occurs or a pneumothorax 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 VOLITE XC treatment, the sponsor will suspend any further enrollment and treatments at the investigational site while performing a root cause analysis. If the AE is a result of a deviation from the injection procedure, the investigator may be retrained and allowed to continue enrolling participants. 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.

If the study is prematurely terminated or suspended, the sponsor shall inform all PIs, the regulatory authorities, and any contract research organizations used in the study of the reason(s) for the termination or suspension. The IRBs are 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 participants enrolled in the study, and each PI or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.9. Publication Policy

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

10.1.10. 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 to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations (including those that may be due to a pandemic or natural disaster) will be discussed with the PI upon identification. Significant protocol deviations will be reported to the IRB according to the IRB's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable. See Section 8.2.

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

Not applicable. See Section 10.6, Appendix 6.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
2D	2-dimensional
3D	3-dimensional
ADE	adverse device event
AE	adverse event
AESI	adverse event of special interest
ANSS	Allergan Neck Satisfaction Scale
ANTOS	Allergan Neck Treatment Outcomes Scale
ATNLS	Allergan Transverse Neck Lines Scale
BDDE	1,4-Butanediol diglycidyl ether
CDISC	Clinical Data Interchange Standards Consortium
CE	Conformité Européene
CFR	Code of Federal Regulations
COVID-19	coronavirus disease-2019
CP	control period
CRF	case report form
eCRF	electronic case report form
EDC	electronic data capture
EI	Evaluating Investigator
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	hyaluronic acid
ICF	informed consent form
ICH	International Council for Harmonisation
IDE	investigational device exemption
IDFU	investigational directions for use
IRB	institutional review board
ISO	International Organization for Standardization
ISR	injection site response
ITT	intent-to-treat
MI	multiple imputation
NCI	National Cancer Institute
NCT	national clinical trial number on www.clinicaltrials.gov
PI	Principal Investigator
PRIMOS	phaseshift rapid in-vivo measurement of skin
SADE	serious adverse device event
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TI	Treating Investigator
Tx	treatment
UADE	unanticipated adverse device effect
w/w	by weight

10.5. Appendix 5: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

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 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
Other	Different than the one(s) previously specified or mentioned (NCI)
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 trial
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 participant has removed itself from the study (NCI)

10.6. Appendix 6: AEs, ADEs, SAEs, SADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the PI and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.6.1. Definition of AE, ADE, and AESI

AE, ADE, and AESI Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, 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. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. • An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study device, which warrants ongoing monitoring and rapid communication by the PI to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. The following AESIs have been identified for the study intervention in this protocol: visual disturbance symptoms associated with vascular occlusion (including, but not limited to, any loss of vision, pain in or around eye, blind spot or shadow in the visual field, trouble moving eyes), myocardial infarction, stroke, pulmonary embolism, pulmonary edema, and pneumothorax.

10.6.2. Definition of SAE, SADE, and UADE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe 2. A permanent impairment of a body structure or a body function including chronic diseases 3. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE 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 including physical or mental impairment
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
UADE definition
• 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."

10.6.3. Definition of Device Deficiency and Product Complaint

Device Deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.
Product Complaint Definition
• A product complaint is any complaint related to the investigational medical device. • For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (eg, printing illegible), missing components/product, device damage or not working properly, or packaging issues. • Product complaints concerning the investigational device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion. • For medical devices, a product complaint also includes: o All deaths of a subject using the device o Any illness, injury, or AE in the proximity of the device o An AE that could be a result of using the device o Any event needing medical or surgical intervention including hospitalization while using the device • Malfunctions, use errors, or inadequacy in the information supplied by the manufacturer.
Serious Health Threat definition
• Signal from any AE or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users, or other persons. • This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

10.6.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency/Product Complaint Recording
• When an AE/SAE/device deficiency/product complaint 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/SAE/device deficiency/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate eCRF in EDC. • It is **not** acceptable for the PI to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE/SAE/device deficiency eCRF in EDC. • There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee. • 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 AE/SAE. • For device deficiencies and product complaints, it is very important that the PI 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 a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity
The PI will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories: • 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 or 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 participant. • 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, NOT when it is rated as severe.

Assessment of Causality
• The PI is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency/product complaint. • Each AE will be classified according to four different levels of causality: 1) not related; 2) possible; 3) probable; or 4) causal relationship. The sponsor and investigators will use the following definitions of each of these 4 levels as follows: • **Not related**: relationship to the device, comparator, or procedures can be excluded when: the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; the AE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the AE; the event involves a body-site or an organ that cannot be affected by the device or procedure; the AE can be attributed to another cause (eg, an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors); or the event does not depend on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the AE.

- **Possible**: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
- **Probable**: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
- **Causal relationship**: the AE is associated with the investigational device, comparator, or with procedures beyond reasonable doubt when: the event is a known side effect of the product category the device belongs to or of similar devices and procedures; the event has a temporal relationship with investigational device use/application or procedures; the event involves a body-site or organ that the investigational device or procedures are applied to; the event involves a body-site or organ that the investigational device or procedures have an effect on; the AE follows a known response pattern to the medical device (if the response pattern is previously known); the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the AE (when clinically feasible); other possible causes (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; harm to the subject is due to error in use; or the event depends on a false result given by the investigational device used for diagnosis, when applicable.
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the AE.
- The PI will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concurrent procedure, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IDFU in his/her assessment.
- For each AE/SAE/device deficiency/product complaint, the PI **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency/product complaint and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the PI has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the PI always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The PI may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency/product complaint
• The PI is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE/SAE/device deficiency/product complaint as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the PI/TI will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF in EDC. • The PI/TI will submit any updated SAE data in EDC within 24 hours of receipt of the information.

10.6.5. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours
• In the event of an SAE, whether associated with study device or not, the PI/TI will notify sponsor immediately, within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system. • SAEs that occur prior to the site having access to the EDC system, or if EDC is not operable, are to be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to sponsor within 24 hours of the site being made aware of the SAE. • Contacts for SAE reporting can be found on the protocol title page.

10.6.6. Reporting of SADEs

SADE Reporting to Sponsor or Designee
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the PI/TI determines that the event meets the definition of a device deficiency. • Device deficiencies that occur prior to the site having access to the EDC system, or if EDC is not operable, are to be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to sponsor within 24 hours of the site being made aware of the SAE. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs as required by national regulations. • Contacts for SAE reporting can be found on the protocol title page.

10.6.7. Reporting of AESIs

AESI Reporting
• AESIs must be reported to the sponsor within 24 hours of awareness of the event by completing the appropriate eCRF and notifying sponsor study management personnel and the Medical Monitor by fax or email. • Contacts for AESI reporting can be found on the protocol title page. • An AESI must also be entered into the CRF within 24 hours. • Additionally, sites must enter the AESI into the EDC system within 24 hours of awareness of the AESI. • AbbVie will notify the FDA of any AESI within 10 days of AbbVie's awareness of the event.

10.7. 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 4 (August 2023)

Overall Rationale for the Amendment:

To provide updated language and corrections to the study design for clarity and consistency and to provide additional details and updates to the statistical analysis for comprehensiveness.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3. Objectives and Endpoints 9.4.3 Secondary Effectiveness Endpoints	Switched order of secondary effectiveness endpoints	For consistency
1.3 Schedule of Activities Table 1-3 Control Group Procedures	Removed urine pregnancy test procedure from Month 4 in the Optional Treatment Period	For clarity
Table 1-3 Control Group Procedures 4.1 Overall Design (last bullet)	Replaced "Post-Control Treatment Period" with "Optional Treatment Period"	For clarity
Table 1-1 Screening Visit Procedures: All Participants 8.1.5 Demographics and Baseline Characteristics	Updated footer a to change "pulse" rate to "heart" rate	To match eCRF
5.2 Exclusion Criteria 6.5 Concomitant Therapy 10.6.4 Recording and Follow-Up of AE and/or SAE and Device Deficiencies	Updated language of "Concomitant Therapy" to "Concurrent Procedure"	To match eCRF
Table 6-1 Study Interventions	Added Storage Conditions 2 °C to 25 °C (36 °F to 77 °F)	For comprehensiveness
6.6.1 Retreatment Criteria	Updated to provide clarity on retreatment criteria	For clarity
8.2 Safety Assessments	Updated text for females of childbearing potential	For clarity
9.1 Statistical Hypotheses	Switched order of primary hypotheses.	For clarity
9.2 Sample Size Determination	Added details to sample size determination	For comprehensiveness
9.3. Populations for Analyses	Replaced mITT with ITT population	To reduce potential bias
9.4.2.2 Main Analytical Approach	Added site to ATNLS Month 1 model	Included site as a predictor in the imputation of missing ATNLS values at Month 1.
9.4.2.3 Sensitivity Analyses	Added poolability analysis	For comprehensiveness

Section # and Name	Description of Change	Brief Rationale
9.4.3 Secondary Effectiveness Endpoints	Added secondary effectiveness endpoint hypotheses in statistical notion. Updated within-treatment FACE-Q analysis from 2-sided paired t-test at 0.05 level to 1-sided paired t-test at 0.025 level. Added alpha control methodology.	For clarity and comprehensiveness
9.4.7.3 Subgroup Analyses	Added site and sex.	For consistency with SAP and standards.

Amendment 3 (January 2023)

Overall Rationale for the Amendment:

To extend the control period to 6 months, add a blinded sample size re-estimation once at least 50% of randomized participants complete the primary timepoint, and increase the potential total randomized participants to up to 200.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added NCT number and updated contact information	For comprehensiveness and accuracy
1.1 Synopsis, 1.2 Schema, Table 1-3 Control Group Procedures, 4.1 Overall Design, 4.4 End of Study Definition, Table 6-1 Study Interventions	Added control group visits at Months 2, 4, and 6 in the control period	To provide longer follow-up comparisons to the treatment group
1.1 Synopsis, 4.1 Overall Design, 9.2 Sample Size Determination	Added a blinded sample size re-estimation once at least 50% of participants complete the primary timepoint, changed dropout rate from 15% to 10% between randomization and Month 1, and increased potential randomized participants from 159 to 200	To determine whether and how many additional participants will be needed to achieve 80% power and to reflect expected dropout rate
1.2 Schema, Table 1-2 Treatment Group Procedures	Removed post-control period for treatment group	With follow-up visits extended to 6 months for the control group, the control period for the treatment group now extends to start of repeat treatment period
1.3 Schedule of Activities	Revised last sentence before Table 1-2 and Table 1-3 to clarify that the GAIS must be the last assessment performed by the EI and participant	For clarity
Table 1-2 Treatment Group Procedures	Added pretreatment vision assessments to footnote a to clarify that they do not need to be repeated if screening and randomization occur on the same day	To avoid duplicate assessments at same visit
Table 1-2 Treatment Group Procedures	Added footnote g to GAIS assessments at Optional Repeat Tx to clarify that they are done prior to treatment	For clarity (inadvertently left off table)
Table 1-2 Treatment Group Procedures, Table 1-3 Control Group Procedures, 8.1.2 Secondary Effectiveness Measures	Added FACE-Q Appraisal of the Neck and all participant questionnaires (ANSS, ANTOS, GAIS) to Optional Touch-up Tx Day 30	To avoid potential bias from participants completing these assessments after TI evaluation of need for touch-up Tx

Section # and Name	Description of Change	Brief Rationale
Table 1-2 Treatment Group Procedures, Table 1-3 Control Group Procedures	Removed the "X" from safety e-diary columns for all Day 3, Day 14, and Month 1 visits and clarified in footnote i that diaries are to be completed daily and returned to site	For clarity on when the e-diary is to be started and completed
Table 1-3 Control Group Procedures	Added "or designee" to skin hydration procedure	For clarity (inadvertently left off table)
6.5 Concomitant Therapy	Added details about COVID-19 vaccines	For comprehensiveness
8 Study Assessments and Procedures	Clarified that hydration assessments are performed by EI or designee	For clarity
8.2 Safety Assessments, 8.3.5 Pregnancy	Removed sensitivity specification for urine pregnancy tests and revised wording for pregnancy reporting	To align with new protocol template language
8.3 Adverse Events and Serious Adverse Events	Added details about reporting COVID-19 AEs	For comprehensiveness
8.3.7 Medical Device Deficiencies and Product Complaints, 10.6 AEs, ADEs, SAEs, SADEs, and Device Deficiencies	Added details about product complaints and clarified that safety reporting would be in EDC system	For comprehensiveness
10.1.6 Data Quality Assurance	Changed "source data verification" and its description to "source data review"	To reflect risk-based monitoring process
10.4 Abbreviations	Added COVID-19 and SARS-CoV-2 definitions	For comprehensiveness

Amendment 2 (January 2022)

Overall Rationale for the Amendment:

To change the statistical hypothesis to be greater than 50% and add ISR severity definitions.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Corrected schema to add missing Month 1 visit in post-control period for control group	For correction
8.2 Safety Assessments	Added ISR severity definitions	For comprehensiveness
9.1 Statistical Hypotheses, 9.4.2.2 Main Analytical Approach	Changed statistical hypothesis to be greater than 50%	To take a more conservative approach in determining the clinical effectiveness of the device

Amendment 1 (November 2021)

Overall Rationale for the Amendment:

To provide more robust data on participants treated with cannula, take a more conservative approach in calculating the primary endpoint, revise SAE reporting procedures, and correct/clarify procedures.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated safety reporting email addresses	For accuracy
1.1 Synopsis, 4.1 Overall Design	Revised minimum number of participants treated with cannula from 30 to 40	To provide more robust data on participants treated with cannula

Section # and Name	Description of Change	Brief Rationale
Table 1-2 Treatment Group Procedures	Deleted vision assessments at Month 4 after repeat treatment	To align with timing of vision assessments after initial and touch-up treatments
Table 1-3 Control Group Procedures	Deleted inclusion/exclusion criteria assessments at optional initial and touch-up treatment visits	To correct SoA to show that inclusion/exclusion criteria are assessed only once at randomization
Table 1-2 Treatment Group Procedures, Table 1-3 Control Group Procedures, 3 Objectives and Endpoints, 8.1.3 Other Effectiveness Measures, 9.4.4 Other Effectiveness Endpoints	Added specific names of participant satisfaction and psychosocial questionnaires	To provide clarity on specific questionnaires
Table 1-2 Treatment Group Procedures, Table 1-3 Control Group Procedures	Added sentence to footnote h to specify that any worsening in vision assessments at pre and post treatment visits requires a neurological assessment	To provide clarity on when neurological assessment needs to be performed
Table 6-1 Study Interventions	Added "single-use" to the packaging and labelling description	To provide clarity
6.1.2 Instructions for Use and Administration	Changed "hyoid bone" to "horizontal line along the hyoid bone"	To clarify instructions for use
6.1.2 Instructions for Use and Administration, 8.1.6 Study Intervention Assessments	Changed "microdepot" to "microdroplet"	To clarify terminology for injection technique
8.2 Safety Assessments	Added "at time of study entry" to childbearing potential definition	To align with definition in SoA
8.3.5 Pregnancy	Added elective abortion as SAE	For comprehensiveness
9.1 Statistical Hypotheses, 9.4.2.2 Main Analytical Approach	Added statistical test for the 50% responder rate threshold of primary endpoint	To take a more conservative approach in determining the clinical effectiveness of the device
9.4.7.3 Subgroup Analyses	Updated subgroup analyses to add injection instrument and remove investigational site	To characterize results by needle/cannula and to align with the poolability analysis described in the SAP for results by investigational site
10.1.4 Data Protection	Added details to data protection	For comprehensiveness
10.1.10 Compliance with Protocol	Removed "at the site" from monitoring	To allow for remote monitoring
10.4 Abbreviations	Added ANSS, ANTOS, and EDC to abbreviations list	For clarity
10.6.2 Definition of SAE, SADE, and UADE	Added chronic diseases and physical or mental impairment birth defects to SAE definition	For comprehensiveness
10.6.3 Definition of Device Deficiency	Added serious health threat definition	For comprehensiveness
10.6.4 Recording and Follow-up of AE	Added levels of causality	For comprehensiveness

Section # and Name	Description of Change	Brief Rationale
and/or SAE and Device Deficiencies		
10.6.5 Reporting of SAEs, 10.6.6 Reporting of SADEs	Revised SAE reporting from email/fax to EDC	To align with new reporting procedures

11. References

Niforos F, Ogilvie P, Cavallini M, Leys C, Chantrey J, Safa M, et al. VYC-12 injectable gel is safe and effective for improvement of facial skin topography: a prospective study. Clin Cosmet Investig Dermatol. 2019;12:791-798.

Ogilvie P, Safa M, Chantrey J, Leys C, Cavallini M, Niforos F, et al. Improvements in satisfaction with skin after treatment of facial fine lines with VYC-12 injectable gel: patient-reported outcomes from a prospective study. J Cosmet Dermatol. 2020;19(5):1065-1070.

Ogilvie P, Thulesen J, Leys C, Sykianakis D, Chantrey J, Safa M, et al. Expert consensus on injection technique and area-specific recommendations for the hyaluronic acid dermal filler VYC-12L to treat fine cutaneous lines. Clin Cosmet Investig Dermatol. 2020;13:267-274.

Pusic AL, Klassen AF, Scott AM, Cano SJ. Development and psychometric evaluation of the FACE-Q satisfaction with appearance scale: a new patient-reported outcome instrument for facial aesthetics patients. Clin Plast Surg. 2013;40(2):249-260.

Tseng F, Yu H. Treatment of horizontal neck wrinkles with hyaluronic acid filler: a retrospective case series. Plast Reconstr Surg Glob Open. 2019;7(8):e2366. DOI:10.1097/GOX.0000000000002366.

Vanaman M, Fabi SG. Décolletage: regional approaches with injectable fillers. Plast Reconstr Surg. 2015;136(5 Suppl):276S-281S.