Title Page

Protocol Title: A multicenter, evaluator-blinded, randomized, no-treatment controlled study to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA® with Lidocaine for correction of temple hollowing in Chinese population

Protocol Number: 1878-701-008

Amendment Number: 3

Compound: JUVÉDERM® VOLUMA® with Lidocaine

Management Class of Medical Device: Class III medical device that required approval to conduct clinical trial: Yes ☐ No ☒

Similar product within mainland China? Yes ☐ No ☒

Study Phase: N/A

Short Title: JUVÉDERM® VOLUMA® with Lidocaine for correction of temple hollowing in Chinese population

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Regulatory Agency Identifying Number: NCT number to be determined

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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 3	January 2022
Amendment 2	December 2020
Amendment 1	August 2020
Original Protocol	December 2019

Amendment 3 (January 2022)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment is to include acceptable protocol modifications due to travel restrictions or other pandemic or natural disaster-related reasons.

Section No. and Name	Description of Change	Brief Rationale
Cover page	Added contacts for emergency and non-emergency events, safety concerns, updated the SAE/SADE reporting fax and email, and added additional signatories	To align with current SOPs and templates
Section 1.3/ Schedule of Activities: Table 1-2 and Table 1-3	Modified from 3D digital imaging to 3D facial imaging	To clarify it is facial imaging
Section 1.3/ Schedule of Activities: Table 1-2	Changed footnote for vital sign at randomization visit from f to g	To correct a typographical error
Section 1.1/ Synopsis, Section 1.3/ Schedule of Activities, Section 2.3/ Benefit/Risk Assessment, Sections 4.1/ Overall Design, Section 4.4/ End of Study Definition, Section 5.1/ Inclusion Criteria, Section 7.2/ Participant Discontinuation Withdrawal from the Study, Section 8/ Study Assessment and Procedures, Section 8.1/ Efficacy Assessments, Section 8.2/ Safety Assessments, Section 8.3/ Adverse Events and Serious Adverse Events, Section 9.2/ Sample Size Determination, Section 10.1.1/ Regulatory and Ethical Considerations, Section 10.1.3/ Informed Consent Process,	Added language for protocol modifications due to pandemic and natural disaster	To align with the 'Guidelines for the management of drug clinical trials during COVID-19', SOPs, and template to reduce the impact of the pandemic on the clinical trial and the follow-up of the subjects

Section No. and Name	Description of Change	Brief Rationale
Section 10.1.6/ Data Quality Assurance, and Section 10.1.10/ Compliance with the Protocol		
Section 4.1/ Overall Design and Section 9.2/ Sample Size Determination	Updated number of investigational sites and sample size calculations	Added new site to support the enrollment
Section 5.2/ Exclusion Criteria,	Modified exclusion criteria number 4.01 by adding "which will have impact to study treatment, evaluation, and outcome	To clarify only excluding participant who has abnormal and clinically significant results that will have impact to study treatment, evaluation, and outcome according to TI or designee
Section 6.1.2/ Instructions for Use and Administration	Added related Chinese guidelines on treatment safety	To provide references for treatment safety management
Section 8.1/ Effectiveness Assessments	Added language of assessments procedures	To maintain consistency of assessments between visits and evaluators
Section 8.2.1/ Clinical Safety Laboratory Assessments	Removed reference to laboratory manual	Update
Section 8.3.5/ Pregnancy	Clarified that pregnancy outcomes can include elective or therapeutic abortions	To align with current SOPs and templates
Section 10.1.4/ Data Protection	Added language to clarify that facial images are included	To align with current SOPs and templates
Section 11/ References	Added reference	Update

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A multicenter, evaluator-blinded, randomized, no-treatment controlled study to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA® with Lidocaine for correction of temple hollowing in Chinese population

Short Title: JUVÉDERM® VOLUMA® with Lidocaine for correction of temple hollowing in Chinese population

Rationale: JUVÉDERM® VOLUMA® with Lidocaine (hereafter, VOLUMA with Lidocaine) is a temporary HA filler that is a structural gel developed specifically to provide a safe, minimally invasive method to create and restore facial volume. This protocol is designed as a pivotal study to collect safety and effectiveness data on VOLUMA with Lidocaine for correction of temple hollowing in Chinese patients in order to support NMPA approval for such intended use.

Objectives and Endpoints

The objectives of this study are to evaluate the safety and effectiveness of VOLUMA with Lidocaine injectable gel in adult participants seeking correction of temple hollowing.

Objectives	Endpoints	
Effectiveness To evaluate the effectiveness of VOLUMA with Lidocaine injectable gel in adult participants seeking correction of temple hollowing	Primary	• Responder status based on the Evaluating Investigator's (EI's) live assessment of temple hollowing using ATHS at Month 6 after last treatment for treatment group and after randomization for control group.
	Secondary	• Responder status based on the EI's assessment of the temple area using GAIS at Month 6 after last treatment for treatment group and after randomization for control group.
		• Responder status based on the participant's assessment of the temple area using GAIS at Month 6 after last treatment for treatment group and after randomization for control group.
		• Change from baseline on FACE-Q Satisfaction with Facial Appearance questionnaire at Month 6 after last treatment for treatment group and after randomization for control group.
		• Change from baseline on FACE-Q Satisfaction with Temples questionnaire at Month 6 after last treatment for treatment group and after randomization for control group.
Safety To evaluate the safety of VOLUMA with Lidocaine injectable gel in adult participants seeking correction of temple hollowing	• Participant assessment of procedural pain • Participant assessment of ISRs • AEs • Jaw Functional Limitation Scale • Vital signs	

Overall Design

- Multicenter, randomized, controlled, parallel-design study in participants with minimal, moderate, or severe temple hollowing (Grade 2, 3, or 4 on the ATHS)
- Single-blind: EIs are blinded; treating investigators (TIs) and participants are not blinded
- VOLUMA with Lidocaine injected with 27 G 1/2" or 25 G 1" needles to the supraperiosteal plane in the temple area (up to 3 mL per temple for initial and touch-up treatments combined) for the treatment group and delayed treatment for the control group

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

Number of Participants:

168 participants will be randomized (112 treatment group, 56 control group) to achieve 135 evaluable participants (90 treatment group, 45 control group) at the Month 6 primary timepoint.

Intervention Groups and Duration:

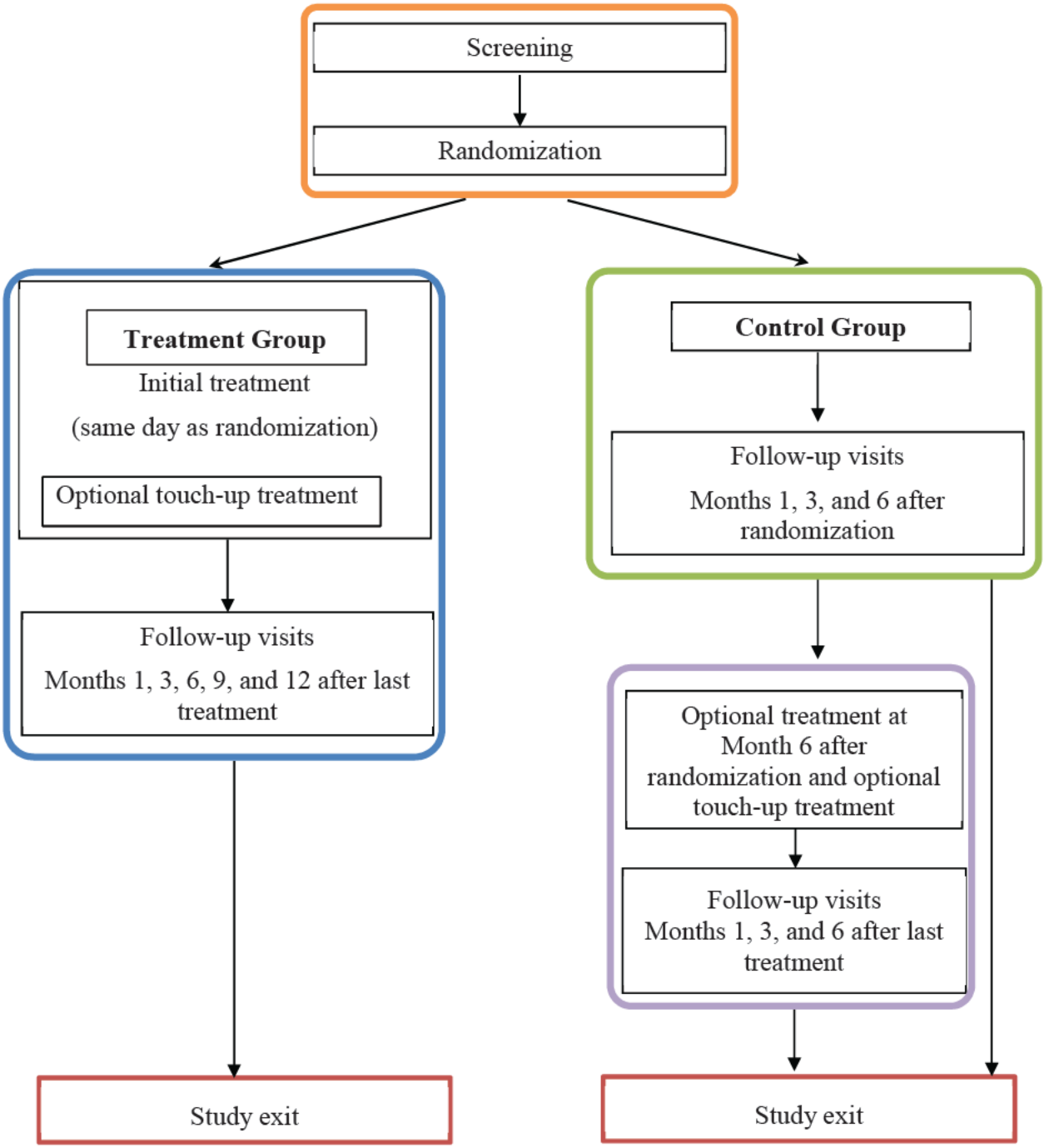
- Participants will be randomized in a 2:1 ratio of treatment group to control group. Screening period is up to 30 days for all participants.
- Treatment group participants receive initial treatment and optional touch-up treatment at 1 month if the TI thinks that optimal correction has not been achieved and agreed upon by both the participant and TI. Telephone calls to assess safety will be made 3 days after each treatment, and follow-up visits will occur at Months 1, 3, 6, 9, and 12 after last treatment.
- Control group participants are followed for 6 months after randomization (no-treatment control period) and then either exit the study or receive optional treatment (initial and touch-up, if needed) in the post-control period. Telephone calls to assess safety will be made 3 days after each treatment, and follow-up visits will occur at Months 1, 3, and 6 after last treatment.

Data Monitoring Committee: No

Protocol modifications due to travel restrictions or other pandemic or natural disaster-related reasons:

During the course of the study, should it ever become 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, phone contacts or virtual site visits) or alternative locations for safety data collection in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by IEC. Investigators should notify the sponsor if any urgent safety measures are taken to protect the participants against any immediate hazard.

1.2. Schema



1.3. Schedule of Activities

Study procedures are recommended to be done in sequence as listed in the below schedules, but the sequence is not mandatory unless otherwise specified.

Should it ever become 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 phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided throughout Section 8. Every effort should 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 throughout Section 8.

Table 1-1 Screening Visit Procedures: All Participants

Procedure	Screening within 30 days
Consent	X
Participant demographics	X
Height, weight, and vital signs[a]	X
Medical/surgical/cosmetic/dental history	X
Lab testing (urinalysis, hematology, chemistry)	X
Pregnancy test[b]	X
ATHS (EI)[c]	X
Inclusion/exclusion criteria	X
Adverse events	X
Concomitant medications, procedures, therapies	X

Note: All screening procedures must be performed onsite.

[a] Includes blood pressure (systolic and diastolic; while participant is seated), respiratory rate, pulse rate, and temperature.
[b] For female participants of childbearing potential; administered and confirmed negative prior to randomization or 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. Can be urine or blood pregnancy test according to site requirements.
[c] TI will use EI ATHS scores to confirm participant's eligibility in the study.

Table 1-2 Treatment Group Procedures

Procedure	Control Period					Post-control Period
	Randomization/Initial Treatment (Day 1)	Telephone Call 3 (±2) Days after Initial Treatment	Optional Touch-up Month 1 (+1w) after Initial Treatment	Telephone Call 3 (±2) Days after Touch-up	Month 1 (+1w), Month 3 (±2w), Month 6 (±2w)[a] after Last Treatment	Month 9 (±2w), Month 12 (±2w) after Last Treatment/Study Exit[a,b]
Randomization[c]	X					
Pregnancy test[d]	X		X			X
Study intervention (TI)	X		X[e]			
3D facial imaging	X[f]		X[g]		X	X
FACE-Q (Participant) • Satisfaction with Temple • Satisfaction with Facial Appearance	X[f]				X	X
Self-perception of age (Participant)	X[f]				X	X
Study intervention characteristics, injection ease, product moldability (TI)	X		X			
Procedural pain (Participant)	X		X			
Vital Signs (blood pressure, pulse rate, respiratory rate, temperature) (TI)	X[g]		X[g]		X	X
ATHS (EI)	X[f]				X	X
Treatment satisfaction questions (Participant) • Satisfaction with treatment • Natural look and feel of the results • How treatment met expectation • Likelihood of continuing the treatment • Willingness to recommend treatment					X	X
Lab testing (urinalysis, hematology, chemistry)					X[h]	X[i]
GAIS (Participant)					X	X
GAIS (EI)					X	X
Weight	X				X	X
Safety telephone call (TI)		X		X		
Safety 30-day diary[j] (Participant)	X		X			
Jaw Functional Limitation Scale (Participant)[k]	X[f]		X[g]		X[l]	
Adverse Events (TI)	Continuous monitoring					
Concomitant medications, procedures, therapies (TI)	Continuous monitoring					

Note: If the participant is not able to present in-clinic to the site 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 or virtual visit is permitted. However, if a participant is later able to present in-clinic to the site within the visit window, assessments may be performed in-clinic and the data will be captured for the visit.

[a] All follow-up visits are scheduled from the date of the last treatment: If no touch-up treatment is performed, initial treatment will also be the last treatment.

[b] All study exit procedures are to be performed for participants who withdraw from the study.

[c] All screening procedures (including pregnancy test) must be performed before randomization; randomization must occur before initial treatment.

[d] For female participants of childbearing potential; administered and confirmed negative before randomization or study intervention. Pregnancy testing need not be repeated if study pregnancy testing has been conducted within 7 days before randomization/initial treatment. In post-control period to be conducted only at study exit visit. A female participant 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. Can be urine or blood pregnancy test according to site requirements.

[e] 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.

[f] Must be completed before randomization.

[g] Must be completed before study interventions.

[h] Performed at Month 6 visit only.

[i] If participants exit the study before Month 6, then lab testing is needed at Exit Visit.

[j] The 30-day daily safety diaries are to be completed following each treatment starting on the day of treatment and are considered complete if all days are completed until the visit 1 month after treatment.

[k] Assessment on Day 14 after each treatment will be recorded along with safety diaries, while for other visits it will be performed on-site.

[l] Performed at Month 1 visit only.

Table 1-3 Control Group Procedures

Procedure	Control Period			Post-control Period				
	Randomization (Day 1)	Telephone Call 3 (±2) Days After Randomization	Month 1 (+1w), Month 3 (±2w), Month 6 (±2w)[a] After Randomization/ Study Exit[a]	Optional Initial Treatment (same day as Month 6 after Randomization Visit)	Telephone Call 3 (±2) Days after Initial Treatment	Optional Touch-up Month 1 (+1w) after Initial Treatment	Telephone Call 3 (±2) Days After Touch-up	Month 1 (+1w), Month 3 (±2w), Month 6 (±2w) after last Treatment[b]/ Study Exit
Randomization[c]	X							
Pregnancy test[d]	X		X	X		X		X
3D facial imaging	X[e]		X			X[f,g]		X
FACE-Q (Participant) • Satisfaction with Temple • Satisfaction with Facial Appearance	X[e]		X					X
ATHS (EI)	X[e]		X					X
Self-perception of age (Participant)	X[e]							X
GAIS (Participant)			X					X
GAIS (EI)			X					X
Vital signs (blood pressure, pulse rate, respiratory rate, temperature) (TI)			X			X[f]		X
Study intervention (TI)				X		X[g]		
Procedural pain (Participant)				X		X		
Study intervention characteristics, injection ease, product moldability (TI)				X		X		
Weight	X		X					X
Treatment satisfaction questions (Participant) • Satisfaction with treatment • Natural look and feel of the results • How treatment met expectation • Likelihood of continuing the treatment • Willingness to recommend treatment								X
Laboratory testing (urinalysis, hematology, chemistry)								X[h]
Safety telephone call (TI)		X			X		X	
Safety 30-day diary[i] (Participant)				X		X		
Jaw Functional Limitation Scale (Participant)[j]	X[e]			X[f]		X[f]		X[k]
Adverse events (TI)	Continuous monitoring							
Concomitant medications, procedures, therapies (TI)	Continuous monitoring							

Note: If the participant is not able to present in-clinic to the site 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 or virtual visit is permitted. However, if a participant is later able to present in-clinic to the site within the visit window, assessments may be performed in-clinic and the data will be captured for the visit.

[a] During the control period all follow-up visits are scheduled from the date of randomization.

[b] During the post-control period, all follow-up visits are scheduled from the date of the optional last treatment: If no touch-up treatment is performed, optional initial treatment will also be the optional last treatment.

[c] All screening procedures (including pregnancy test) must be performed before randomization; randomization must occur before initial treatment.

[d] For female participants of childbearing potential; administered and confirmed negative before randomization or study intervention. Pregnancy testing need not be repeated if study pregnancy testing has been conducted within 7 days before randomization. Pregnancy testing to be conducted only at treatment visits and study exit visit. A female participant 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. Can be urine or blood pregnancy test according to site requirements.

[e] Must be completed before randomization.

[f] Must be completed before study interventions.

[g] 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.

[h] Performed at Month 6 after last treatment only. If participants exit the study after last treatment in the post-control period, then laboratory testing is needed at Exit Visit.

[i] The 30-day daily safety diaries are to be completed following each treatment starting on the day of treatment and are considered complete if all days are completed until the visit 1 month after treatment.

[j] Assessment on Day 14 after each treatment will be recorded along with safety diaries, while for other visits it will be performed on-site.

[k] Performed at Month 1 visit only.

2. Introduction

JUVÉDERM® VOLUMA® with Lidocaine (hereafter, VOLUMA with Lidocaine) is a temporary HA filler that is a structural gel developed specifically to provide a safe, minimally invasive method to create and restore facial volume. VOLUMA with Lidocaine has an HA concentration of 20 mg/mL, which has been shown to provide volumizing properties in the restoration of mid-face volume (Jones 2013), and it is expected to provide similar results when used to volumize the temporal fossa for the correction of temple hollowing.

VOLUMA with Lidocaine is a sterile, biodegradable, nonpyrogenic, viscoelastic, clear, colorless, homogenized, HA gel implant (dermal filler). The HA is produced by *Streptococcus* species of bacteria and is mixed with phosphate buffer and crosslinked by adding a minimum amount of BDDE to form a 3D HA gel. The HA concentration is 20 mg/mL, and 0.3% w/w lidocaine hydrochloride is added to enhance participant comfort. Additional information about VOLUMA with Lidocaine is provided in the IB.

2.1. Study Rationale

VOLUMA with Lidocaine is specifically designed for volumizing and has demonstrated effectiveness in restoring age-related volume deficit to the mid-face (Jones 2013). VOLUMA with Lidocaine received the CE mark in 2008 to restore volume of the face and received FDA approval in 2013 for correction of age-related volume deficit in the mid-face. It is currently being used in Europe to restore volume to the temple area, among other areas of the face.

In a recent open-label, single-site study involving 30 participants, Baumann (2019) showed that VOLUMA with Lidocaine can be safely and effectively used to treat temple hollowing. However, further evidence collected under a more rigorous study design is required to fully characterize the safety and effectiveness of VOLUMA with Lidocaine for treating temple hollowing. This protocol is designed as a pivotal study to collect safety and effectiveness data on VOLUMA with Lidocaine for correction of temple hollowing in Chinese patients in order to support NMPA approval for such intended use.

2.2. Background

Temple hollowing can have several different causes. As the face ages, multiple layers of the temple (defined as the area bounded by the superior temporal line, the frontal process of the zygomatic bone, and the zygomatic arch) are affected, which results in a loss of the convex curve of the temple. The changes include an increased concavity of the temporal bone, decreased volume of the temporalis muscle, and decreased size of the temporal fat pad (Sykes 2009). In

addition to aging, temple hollowing can also occur in patients with HIV and antiretroviral lipoatrophy (Rose 2013, Ross 2010). A coronal incision used to provide surgical exposure to the anterior and lateral craniofacial skeleton can also result in temple hollowing (Kim 2005).

Regardless of the cause of temple hollowing, the loss of volume in the temple area results in bony margins (the zygomatic arch below and the temporal line medially) that appear more prominent and a face that appears more skeletonized (Moradi 2011, Sykes 2009).

Treatments for temple hollowing have included surgical implants (eg, Mersilene mesh and calcium hydroxylapatite cement) to elevate the temporalis muscle and overlying tissues (Atherton 2010, Gosain 1997) and the placement of titanium mesh to create a new surface contour (Guo 2012). However, because of the significant risks that are associated with these procedures, they have been reserved for severe cases of temple hollowing where a large volume correction or significant contouring is needed.

For less severe cases of temple hollowing, where a smaller volume correction is needed, HA fillers provide a better treatment option due to the simple treatment procedure, predictable results, and proven safety record. Several studies have described the use of HA-based soft-tissue fillers to successfully treat temple hollowing.

Baumann (2019) conducted an open-label, single-site US study of 30 participants to examine the use of VOLUMA with Lidocaine in the treatment of temple hollowing. A total of 98% of participants had long-lasting (12 months) results and high patient satisfaction. Most participants perceived themselves as looking younger than at baseline. After initial treatment (but not touch-up treatment), mild to moderate self-limited jaw pain was noted by 40% (12/30) of the participants during mastication. The investigator reported that all other AEs were consistent with what may be expected by an HA filler. Headache was reported by a third of the participants.

Ueland (2019) conducted a prospective, comparative study of the safety and effectiveness of VOLUMA with Lidocaine versus autologous fat for treatment of temple hollowing after lateral orbital wall decompression in thyroid eye disease. Of the 29 participants, 17 were treated bilaterally with VOLUMA with Lidocaine in the right temple and autologous fat in the left temple, and 12 were treated unilaterally (5 VOLUMA with Lidocaine and 7 autologous fat). Photographs scored by 3 investigators on a 3-point temporal hollowing scale showed better results for VOLUMA with Lidocaine through 2 years ($p < 0.001$). Soft tissue thickness as measured by ultrasound also showed a significantly greater increase for VOLUMA with Lidocaine through 2 years ($p = 0.005$). The most common complications for VOLUMA with Lidocaine were bruising, irregular surface, and swelling that resolved without treatment.

2.3. Benefit/Risk Assessment

The injection procedure, anesthetic agents, or VOLUMA with Lidocaine may cause some of the risks and/or discomforts listed below. Unforeseeable risks or results are also a possibility. The risk of developing a serious complication is small. If a complication occurs, participants will be advised to contact the TI who will use his/her medical judgment 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 VOLUMA with Lidocaine injectable gel. Risks related to the injection procedure include redness, itching, pain, tenderness, swelling, bruising, and lumps and bumps, which are common to dermal filler injection procedures in general. The use of a small gauge needle to deliver VOLUMA with Lidocaine used in this study is intended to minimize tissue trauma. The inclusion of 0.3% lidocaine in the formulation is meant to reduce pain during the injection, and this needs to be taken into account when administering concomitant additional anesthetics as well as in relation to participants' medical history (ie, allergy to lidocaine). Risks associated with the anesthetic agent include allergic reactions that may manifest as an anaphylactic reaction, skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient loss of skin color.

Prior to administering any topical pretreatment anesthesia, the TI will thoroughly review the 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.

Due to the location of the treatment area, tenderness, or pain in the jaw when chewing may be experienced, but it can usually be treated with acetaminophen and generally will resolve within a few days.

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 soft-tissue fillers. It is anticipated that the safety and effectiveness of temple hollowing treatment are similar to those identified in other studies using JUVÉDERM® products for temple hollowing and for similar indications such as correction of mid-face volume.

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 VOLUMA with Lidocaine.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of VOLUMA with Lidocaine may be found in the IB.

3. Objectives and Endpoints

The objectives of this study are to evaluate the safety and effectiveness of VOLUMA with Lidocaine injectable gel in adult participants seeking correction of temple hollowing.

Objectives	Endpoints	
Effectiveness To evaluate the effectiveness of VOLUMA with Lidocaine injectable gel in adult participants seeking correction of temple hollowing	Primary	• Responder status based on the EI's live assessment of temple hollowing using ATHS at Month 6 after last treatment for treatment group and after randomization for control group.
	Secondary	• Responder status based on the EI's assessment of the temple area using GAIS at Month 6 after last treatment for treatment group and after randomization for control group.
		• Responder status based on the participant's assessment of the temple area using GAIS at Month 6 after last treatment for treatment group and after randomization for control group.
		• Change from baseline on FACE-Q Satisfaction with Facial Appearance questionnaire at Month 6 after last treatment for treatment group and after randomization for control group.
		• Change from baseline on FACE-Q Satisfaction with Temples questionnaire at Month 6 after last treatment for treatment group and after randomization for control group.
	Other	• Responder status based on the EI's live assessment of temple hollowing using ATHS at specific scheduled visits.
		• Responder status based on the EI's assessment of the temple area using GAIS at specific scheduled visits.
		• Responder status based on the participant's assessment of the temple area using GAIS at specific scheduled visits.
		• Change from baseline on FACE-Q Satisfaction with Facial Appearance questionnaire at specific scheduled visits.
		• Change from baseline on FACE-Q Satisfaction with Temples questionnaire at specific scheduled visits.
		• Treatment satisfaction questions (include following items) at specific scheduled visits: Participant satisfaction with treatment; Participant satisfaction with how natural the effects of the treatment feel; Participant satisfaction with how natural the effects of the treatment look; Participant response on the treatment meeting expectation; Participant response on interest to continue to use the treatment; Participant response on willingness to recommend treatment to a friend.
		• Participant response to the participant's self-perception of age at specific scheduled visits.
		• Temple volume change as assessed on 3D image volumetric analysis at specific scheduled visits.
Safety To evaluate the safety of VOLUMA with Lidocaine injectable gel in adult participants seeking correction of temple hollowing	• Participant assessment of procedural pain • Participant assessment of ISRs • AEs • Jaw Functional Limitation Scale • Vital signs	

4. Study Design

4.1. Overall Design

This is a prospective, multicenter, evaluator-blinded, randomized, parallel-group, no-treatment controlled study to evaluate the safety and effectiveness of VOLUMA with Lidocaine HA injectable gel to correct temple hollowing.

The study will involve up to 9 investigational sites. The study population is represented by Chinese adults who are seeking correction of temple hollowing and who meet the study criteria according to the study design.

Participants will be randomized in a 2:1 ratio of treatment group to control group.

Participants will stay in the study for up to 14 months depending on their randomization group. For the treatment group, each participant will be in the study for up to 14 months: up to 1 month for screening, up to 30 days of treatment, and up to 12 months of follow-up after last treatment. For the control group, each participant will be in the study for 7 months (up to 1 month for screening and 6 months for follow-up) and then may exit or opt to receive study intervention. Control participants who opt to receive study intervention will be in the study for an additional 7 months (up to 30 days for treatment and 6 months of follow-up), for a total of 14 months.

The study will compare the treatment to no treatment, with the primary timepoint set at Month 6 (for treatment group, 6 months after last treatment; for control group, 6 months after randomization). Each site will have a PI who is responsible for the overall conduct of the study at that site and may also serve as the TI. The TI performs all study treatments and safety assessments, and the blinded EI evaluates ATHS and GAIS.

The study design is single-blind where 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 they will secure the randomization and other records (eg, records of study treatments and prior study assessments) from potential discovery by the blinded EIs. The TIs will not discuss the randomized treatment assignments with or in the presence of the EIs. Additional precautions to keep blinding are outlined in Section 6.3.

During the course of the study, should it ever become 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, phone contacts or virtual site visits) or alternative locations for safety data collection in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by IEC. Investigators should 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. Participant Input into Design

The design elements of this protocol have been reviewed with patients/patient partners to obtain their perspectives in the following areas: schedule of events, parameter invasiveness, frequency of parameter compared to standard of care, length of study and visits, how study drug is administered or how device is being used.

4.2.2. No-treatment Control

The no-treatment control was chosen primarily because no HA filler is currently NMPA- -approved for use in correction of temple hollowing; 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 no-treatment control. Meanwhile, a sham injection exposes control participants to the pain associated with facial injections and puts them at risk for infection or ISRs with no clinical benefit.

While surgical options to treat temple hollowing are available, they are not appropriate controls for a soft-tissue filler injection. 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.

4.2.3. Evaluator Blinded

Because the control group uses a no-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.

4.2.4. Allergan Temple Hollowing Scale

Photonumeric scales have become a standard for assessing the results of soft-tissue filler treatments worldwide. The ATHS is a 5-point ordinal scale developed by Allergan to grade the severity of temple hollowing. The ATHS contains a morphed photograph showing all 5 severities of temple hollowing as well as photographic images of participants representing different Fitzpatrick skin types, race categories, both sexes, and all 5 severities of temple hollowing (0 = Convex, 1 = Flat, 2 = Minimal, 3 = Moderate, 4 = Severe).

A scale validation study (Carruthers 2016, Study FSV-001) was conducted to assess the inter- and intra-rater reliability of the ATHS. Each of the 8 trained clinicians independently evaluated the participants in person and assigned each participant an ATHS grade based on the live evaluation. Three weeks later, the same 8 trained clinicians re-evaluated the same participants and assigned each participant an ATHS grade based on the live evaluation and without reliance on prior memory. Both the inter- and intra-rater agreement were substantial (> 0.60), indicating substantial agreement among the raters as well as within the raters between the 2 in-clinic evaluation sessions, respectively. Additionally, the results demonstrated that a 1-point difference or higher is clinically significant. Therefore, results confirmed that the ATHS is validated and appropriate to be used as a primary effectiveness measure for this study.

4.2.5. 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 Satisfaction with Facial Appearance scale 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). The current version of the FACE-Q Satisfaction with Temples scale is based on existing qualitative research to assess satisfaction in the temple area. The scale developers will conduct additional research to assess the psychometric properties of the scale, finalize the list of questions, and create the scoring algorithm.

4.3. Justification for Dose

The volume of VOLUMA with Lidocaine to be injected for each participant will be determined by the TI and will take into consideration the participant's degree of temple hollowing, the desired outcome, and the need to maintain balance and proportion with other facial features.

In the study conducted by Baumann (2019) with VOLUMA with Lidocaine, participants could receive up to 2 mL per temple for their initial injection and a maximum of 3 mL per temple for initial and touch-up treatment combined. In the Ueland (2019) study, participants received a

maximum of 2 mL in a single temple treated with VOLUMA with Lidocaine. Based on these studies, the maximum allowable injection volume for this study was set at 3 mL in each temple for initial and touch-up combined, with a 2 mL maximum allowable volume per temple per treatment session.

For investigational use in this clinical study, the study intervention will be injected deeply (supraperiosteal plane) with the supplied 27 G 1/2" or 25 G 1" needles to correct temple hollowing. The technique specified for this study is selected because it is a safe and easy -to -follow method for injection (Breithaupt 2015, Sykes 2015). The detailed recommended injection technique is provided in the IDFU and IB.

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.

Treatment group participants will be considered completers if they complete the Month 12 after last treatment visit. Control group participants will be considered completers if they complete the Month 6 after randomization visit and do not receive optional treatment or if they complete the Month 6 after optional last treatment visit.

There are no pandemic or natural disaster-related protocol modifications for the Study Exit Visit.

If the participant is not able to present in-clinic to the site 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, the participant will be asked to return to the site at a later time. Once the participant is able to present in-clinic to the site, assessments will be performed in-clinic and the data will be captured for the visit.

5. Study Population

Chinese adults with temple hollowing who are seeking restoration in the temple area.

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 18 or over, at the time of signing the ICF
2.	**Sex**
2.01	Male or female
3.	**Type of Participant and Temple Hollowing Characteristics**
3.01	Participants seeking improvement of temple hollowing
3.02	Has Minimal, Moderate, or Severe temple hollowing (Grade 2, 3, or 4 on the ATHS) for each temple on EI live assessment (both temples must qualify but do not need to have the same score)
4.	**Informed Consent**
4.01	Capable of giving signed informed consent 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
4.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable
5.	**Other**
5.01	Able, as assessed by the TI, and willing to follow study instructions (including compliance with the safety diary) and likely to complete all required study visits
5.02	Is able to complete effectiveness self-assessments without the use of glasses (contact lens use is acceptable if they will be used for all participant self-assessments)
5.03	Participant must be in good health as determined by medical history, physical examination, vital signs, and investigator's judgment, including no known active pandemic infection.

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 for each temple from the EI's baseline score on the ATHS given the allowed injection volume, in the opinion of the TI
1.02	Has temple hollowing due to trauma, congenital malformations, or lipodystrophy, either congenital or acquired
	Additional examples include: congenital myotonic dystrophy, HIV-associated lipodystrophy, or acquired generalized lipodystrophy
1.03	Has experienced trauma to the temple area within 6 months before enrollment or has residual deficiencies, deformities, or scarring
1.04	Atrophic skin in the temple area that might not be suitable for injection, in the opinion of the TI
1.05	Temporal arteritis or history of temporal arteritis
1.06	Temporomandibular joint dysfunction or any other jaw issues
1.07	Recurrent temporal headaches such as temporal tendonitis migraine

1.08	Tendency to develop hypertrophic scarring
1.09	Active autoimmune disease
1.10	History of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), HA products, or *Streptococcal* protein
1.11	Current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes), abscess, an unhealed wound, or a cancerous or precancerous lesion, above the subnasale
2.	**Prior/Concomitant Therapy**
2.01	Prior facial reconstructive surgeries, face-lift, or brow lift as well as surgeries on the temple area (eg, biopsy)
2.02	Fat injection or permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) in the temple area
2.03	Fat injection or permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) in facial areas other than the temples within 12 months before enrollment
2.04	Semipermanent soft-tissue filler treatment (eg, calcium hydroxylapatite, poly-L-lactic acid) in the temple or mid-face within 36 months before enrollment
2.05	Temporary dermal filler injections above the subnasale within 12 months before enrollment
2.06	Temporary dermal filler injections in the nasolabial fold or below the subnasale within 3 months prior to enrollment
2.07	Botulinum toxin treatment above the subnasale or at masseter muscle within 6 months before enrollment
2.08	Mesotherapy or cosmetic facial procedures above the subnasale within 6 months before enrollment
	Examples of mesotherapy or cosmetic facial procedures are laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures
2.09	Has braces or other orthodontics
2.10	Changes in use of over-the-counter or prescription oral or topical, antiwrinkle products above the subnasale within 30 days before enrollment or planned changes during the study
	Participants are not eligible for this study if they have begun using any new over-the-counter or prescription oral or topical, antiwrinkle products above the subnasale 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
2.11	Is on a regimen of anticoagulation therapy (eg, warfarin, clopidogrel)
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
4.	**Diagnostic Assessments**
4.01	Abnormal and clinically significant results on hematology, clinical chemistry, or urinalysis, which according to the TI or designee will have impact to study treatment, evaluation and outcome.
5.	**Other Exclusions**
5.01	Has tattoos, piercings, facial hair, or scars above and including the subnasale that would interfere with visual assessment of the temple
5.02	Females who are pregnant, nursing, or planning a pregnancy
5.03	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
5.04	Directly or indirectly involved in the conduct and administration of this study
	Directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, 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
5.05	Plans a significant weight change (more than 10% of body weight) during the study

5.3. Lifestyle Considerations

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

For 2 days after study intervention, it is recommended that participants avoid unnecessary external compression of the treatment site that could cause displacement or indentation where the product has been placed. Participants will be advised not to have a massage, enter a hot spring or sauna, receive excessive sun exposure, or go swimming during the week following any study intervention.

5.4. Screen Failures

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

Participants may undergo a touch-up treatment 30 days after the initial treatment if agreed upon by both the participant and TI. See Section 6.6.1 for details.

6.1. Study Intervention Administered

Table 6-1 Study Interventions

Device	VOLUMA with Lidocaine
Dose Formulation	20 mg/mL HA crosslinked with BDDE + 0.3% lidocaine (w/w gel)
Route of Administration	Deep injection (supraperiosteal plane), injected with a 27 G 1/2" or 25 G 1" needle in the temple area
Model and Specification	Study intervention will be provided in prefilled 1 mL syringes. Each syringe will be packaged with 27 G 1/2" needles for injection in a thermoform blister. Two blisters will be packaged in a kit. Each kit and thermoform blister will be labeled as required per country requirements. The 25 G 1" needles will be provided separately.
Manufacturer	Allergan Route de Promery Zone Artisanale de Pré-Mairy Pringy 74370, Annecy, France
Number and Timing of Interventions	**Treatment group:** Day 1: Initial treatment Month 1 after initial treatment: Optional touch-up **Control group (optional):** Month 6 after randomization: optional initial treatment Month 1 after optional initial treatment: optional touch-up
Volume Per Intervention	Initial and touch-up combined: up to 3 mL/temple Any single treatment: up to 2 mL/temple

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

6.1.1. Medical Devices

The Allergan-manufactured medical device provided for use in this study is VOLUMA with Lidocaine (copackaged with needles, see Table 6-1). Instructions for medical device use are provided in the IDFU and IB.

All device deficiencies (including malfunctions, use error, and inadequate labeling) shall be documented and reported by the PI/TI throughout the clinical investigation (see Section 8.3.6) and appropriately managed by the sponsor.

6.1.2. Instructions for Use and Administration

For investigational use in this clinical study, VOLUMA with Lidocaine must be injected supraperiosteally following a specified injection technique to obtain optimal correction of temple hollowing and aesthetic improvement with minimal safety concern. Study intervention is limited to the temple area. The 27 G 1/2" or 25 G 1" needles supplied with the investigational product must be used.

The TIs must be experienced in the use and administration of HA implants and be practicing in the field of aesthetic medicine, plastic/cosmetic/reconstructive surgery, or dermatology. Before the study begins, the TIs will receive training in the administration of VOLUMA with Lidocaine according to the technique specified for this study. This injection technique is selected since this is a safe and easy-to-follow method for injection (Breithaupt 2015, Sykes 2015).

Anesthesia (ice, topical anesthesia, or local injectable anesthesia) may be administered per the TI's standard practice but must be limited to the treatment area.

The TIs will use aseptic injection technique, and the following procedures must be used to ensure participant safety.

- Determine up to 3 injection sites and mark.
- Inspect and palpate injection sites to identify the location of any superficial vessels, including the superficial temporal artery, and avoid injecting into any vessels.
- Insert the needle at the marked points at an 85° to 90° angle to the plane of the temple until it reaches the periosteum.
- If resistance is felt before reaching the periosteum, withdraw and re-orient the needle.
- Before injection, attempt to aspirate the needle. If blood is observed, withdraw and re-orient the needle.
- Inject VOLUMA with Lidocaine into the treatment area slowly using gentle, even pressure on the syringe.
- Stop injecting immediately if any resistance is felt or if the participant complains of severe pain.

If a vessel occlusion occurs, stop the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines or the Chinese Society of Aesthetic and Plastic Doctor guidelines, which include hyaluronidase injection (Alam 2008, Breithaupt 2015, Carruthers 2015, Minimally invasive Anti-aging Committee 2015).

The detailed recommended injection technique is provided in the IDFU and IB.

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). Include participant identification number, device serial or lot number, and date of treatment.
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

Prior to initiation of study intervention, 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. For all treatments, the right side will be treated first. Randomization will be within each study site. All participants will be centrally randomized using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

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

If participants are withdrawn, they will not be replaced.

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 they will secure the randomization and other records (eg, records of study interventions and prior study assessments) from potential discovery by the

blinded EI. The TIs will not discuss the randomized treatment assignments with or in the presence of the EIs.

In order to maintain the blind, the EI will not be present during any treatment visits 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/dispensing 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.

Instructions for preparing the study intervention are provided in the IDFU and IB.

Design bias in this study is reduced through the use of a randomized control group, a blinded EI to assess effectiveness results, and the inclusion of objective measures of temple volume that are determined by a blinded image analysis technician.

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. Concomitant Therapy

The use of any concomitant procedure or medication, prescription or over-the-counter, is to be recorded on the participant's eCRF at each visit along with the reason the therapy is taken.

Any procedure/surgery, medication or vaccine (including over-the-counter, prescription medicines, vitamins, herbal supplements, or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

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

6.5.1. Rescue Medicine

Rescue medicine is not applicable.

6.5.2. Prohibited Therapy and Washout Before the Study

Participants must discontinue any of the medications listed in Table 6-2 for the specified period prior to baseline. These medications are prohibited for the duration of the study. Other medications being used at screening may be continued.

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, or herbal supplements) NOTE: The 10-day washout period must continue for 3 days after study intervention (initial and touch-up) is administered
30 days	• Any investigational product • Any new over-the-counter or prescription oral or topical, antiwrinkle products above the subnasale
3 months	• Temporary dermal filler injections in the nasolabial folds or below the subnasale
6 months	• Botulinum toxin injections above the subnasale or at masseter muscle • Mesotherapy or cosmetic facial procedures (eg, laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) above the subnasale
12 months	• Temporary dermal filler injections above the subnasale
	• Fat injection or permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) in facial areas other than the temples
36 months	• Semipermanent dermal filler treatment (eg, calcium hydroxylapatite, poly-L-lactic acid) in the temple or mid-face

6.5.3. Permitted Interventions

All interventions are permitted except those listed as prohibited in Section 6.5.4. Topical or injectable anesthesia may be used during treatment according to routine practice, but it must be limited to the treatment areas only.

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact the sponsor.

The sponsor or designee is to be contacted if there are any questions regarding concomitant or prior therapy.

6.5.4. Prohibited Interventions During the Study

Participants must abstain from the following interventions from before the start of study intervention until completion of the follow-up visits:

- Other investigational product
- Botulinum toxin injections above the subnasale or at masseter muscle

- Mesotherapy or cosmetic facial procedures (eg, face-lift, brow lift, facial reconstructive surgery, surgery on the temple area [eg, biopsy], laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) above the subnasale
- Braces or any orthodontic procedures
- Permanent facial implants or fat injection
- Semi-permanent dermal filler above the subnasale
- Temporary dermal filler injected above the subnasale (other than study intervention)
- Undergo any tattooing or piercing procedures above and including the subnasale
- Allergen desensitization therapy

The following medications are prohibited or restricted throughout the study:

- Hyaluronidase for aesthetic purposes (eg, to reverse overcorrection)

Participants must abstain from the following interventions from 10 days before until 3 days after any study intervention:

- Regimen of medications or substances known to increase coagulation time (eg, aspirin, ibuprofen, or herbal supplements)

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

6.6. Dose Modification

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

6.6.1. Retreatment Criteria

A participant may receive touch-up treatment if optimal correction has not been achieved at Month 1 after initial treatment for treatment group and Month 1 after optional initial treatment for control group, in the opinion of the TI and is agreed upon by both participant and TI.

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.

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 Lost to follow-up Other Physician decision Protocol deviation Site terminated by sponsor Study terminated by sponsor Withdrawal by participant	Death

7.1. Discontinuation of Study Intervention

Pregnancy will discontinue a participant from receiving further study intervention. Participants who become pregnant and have already received a study intervention or who have been randomized to control group will continue in the study until all required follow-up is complete.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

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.

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 withdrawn at any time at the discretion of the investigator 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 discontinuation visit is to be conducted, as shown in the SoA (Section 1.3). See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- 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.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the PI/TI must document this in the site study records.
- For any participant who withdraws from the study, the date and reason for withdrawal will be recorded on the eCRF. If a treatment-related AE is ongoing at the time of withdrawal, the TI will attempt to follow the participant until the AE has been resolved or 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 investigator to ensure participant safety and continuity of care. Acceptable mitigation strategies are identified and included in Section 8.
- The investigator should contact the sponsor before discontinuing a participant from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or 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 Appendix 10.1.8.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). 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 study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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 investigator 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 IECs 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, or when impacted by a pandemic or a natural disaster. 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, and effectiveness assessments (ATHS and GAIS) be performed by the same EI. If it is not possible to use the same evaluator to follow the participant, it is recommended that evaluations overlap (examine the participant together and discuss findings) for at least 1 visit.
- Where possible, participant questionnaires are to be completed prior to other assessments at each visit, with the FACE-Q questionnaires completed first and the GAIS to be completed last.
- Safety diaries will be reviewed for potential AEs, at least at each site visit scheduled during the diary completion window up to the visit at which the diary is returned.
- If the participant is not able to present in-clinic to the site 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 or virtual visit is permitted to collect effectiveness and safety measures. The remaining visit assessments will be marked as not completed and the participant will be considered to have completed the study. However, if a participant is later able to present in-clinic to the site within the visit window, assessments will be performed in-clinic and the data will be captured for the visit.

8.1. Effectiveness Assessments

8.1.1. Intervention Administration Assessments

Characteristics of the study intervention will be collected and evaluated for anesthesia usage, needle gauge, number of injections, volume injected, injection area, injection plane, injection ease, injection technique, and product moldability at all treatment visits.

Assessment	Measurement
Anesthesia usage	• Method of anesthesia (topical, injectable, ice) • Anesthesia dose • Anesthesia time
Needle gauge	Inject with 27 G 1/2" or 25 G 1" needle
Number of injections	Total number of performed injections per each injection area
Injection volume	Volume injected in each injection area
Injection area	Treated areas (left temple, right temple)
Injection plane	Plane injected (supraperiosteal, other)
Injection technique	Technique used (bolus, other)
Injection ease	11-point ordinal scale: 0 = difficult, 10 = easy
Product moldability	11-point ordinal scale: 0 = stiff, 10 = moldable

8.1.2. Primary Effectiveness Measure

The temple area of assessment was defined as the area between the temporal fusion line, the zygomatic arch, the lateral orbital rim, and the hairline. The primary effectiveness measure is the EI's live assessment of temple hollowing, to be recorded for each temple separately, using the ATHS described in Table 8-1.

Table 8-1 Allergan Temple Hollowing Scale

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

Assessment	Timing	Measurement
ATHS	Treatment group: all on-site visits except touch-up treatment visit Control group: all on-site visits except optional touch-up treatment visit	EI's live assessment of temple hollowing using the ATHS

8.1.3. Secondary Effectiveness Measures

There are 4 secondary effectiveness measures, to be recorded at the participant level rather than for each temple. The secondary effectiveness measures include independent, noncollaborative assessments by both the EI and the participant of global aesthetic improvement in the temple area using the 5-point GAIS (Table 8-2).

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 of the temple area by comparing to profile 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 every on-site visit except (optional) touch-up visit. Touch-up treatment decision is to be made before other applicable assessments.

The other secondary effectiveness measures are the participant responses on the FACE-Q questionnaires: Satisfaction with Facial Appearance and Satisfaction with Temples. In the FACE-Q Satisfaction with Facial Appearance questionnaire the responses to the 10 items will be summed and converted to a Rasch-transformed score that ranges from 0 to 100 (higher score

indicates increased satisfaction) using the algorithm developed by the FACE-Q scale developers. In the FACE-Q Satisfaction with Temples questionnaire, the responses to the items will be summed and converted to a Rasch-transformed score that ranges from 0 to 100 (higher score indicates increased satisfaction) using the algorithm being developed by the FACE-Q scale developers.

The FACE-Q scales are 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 questionnaires, investigational site staff may ask the participant to explain why he or she 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 of the temple area	Treatment group: all on-site visits starting from Month 1 after last treatment visit Control group: Month 1, 3, 6 after randomization visit and Month 1, 3, 6 after optional last treatment visit	Single item questionnaire assessing global aesthetic improvement in the temple area on 5-point ordinal scale from -2 to 2 (details in Table 8-2)
FACE-Q Satisfaction with Facial Appearance	Treatment group: randomization and all on-site visits starting from Month 1 after last treatment visit Control group: randomization and Month 1, 3, 6 after randomization visit and Month 1, 3, 6 after optional last treatment visit	10-item questionnaire assessing satisfaction with various aspects of facial appearance. Participants respond to each item as: 1 Very Dissatisfied 2 Somewhat Dissatisfied 3 Somewhat Satisfied 4 Very Satisfied
FACE-Q Satisfaction with Temples	Treatment group: randomization and all on-site visits starting from Month 1 after last treatment visit Control group: randomization and Month 1, 3, 6 after randomization visit and Month 1, 3, 6 after optional last treatment visit	Multiple item questionnaire assessing satisfaction with various aspects of the temples. Participants respond to each item as: 1 Very Dissatisfied 2 Somewhat Dissatisfied 3 Somewhat Satisfied 4 Very Satisfied

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, and effectiveness assessments (ATHS and GAIS) be performed by the same EI. If it is not possible to use the same evaluator to follow the participant, it is recommended that evaluations overlap (examine the participant together and discuss findings) for at least 1 visit.

8.1.4. Other Effectiveness Measures

Other effectiveness measures include:

- Treatment satisfaction questions:
  - Participant satisfaction with treatment on a 5-point scale ranging from 1 (very dissatisfied) to 5 (very satisfied)
  - Participant satisfaction with how natural the effects of the treatment feel on a 5-point scale ranging from 1 (very dissatisfied) to 5 (very satisfied) and participant satisfaction with how natural the effects of the treatment look on a 5-point scale ranging from 1 (very dissatisfied) to 5 (very satisfied)
  - Participant response on the treatment meeting expectation (yes/no)
  - Participant response on interest to continue to use the treatment (yes/no)
  - Participant response on willingness to recommend treatment to a friend (yes/no)
- Participant response to the participant's self-perception of age question to provide feedback on how old or young (in years) he/she looks based on facial appearance
- Volume change of each temple from baseline as assessed by 3D imaging

Assessment	Timing	Measurement
Satisfaction with treatment	Treatment group: all on-site visits after last treatment Control group: all on-site visits after optional last treatment	Direct question. Participants respond to item as: 5 Very satisfied 4 Satisfied 3 No opinion 2 Dissatisfied 1 Very dissatisfied
Natural look and feel of the results	Treatment group: all on-site visits after last treatment Control group: all on-site visits after optional last treatment	Two direct questions, one on natural look and one on natural feel. Participants respond to each item as: 5 Very satisfied 4 Satisfied 3 No opinion 2 Dissatisfied 1 Very dissatisfied
Treatment meeting expectation	Treatment group: all on-site visits after last treatment Control group: all on-site visits after optional last treatment	Direct question. Participants' possible answers are: • Yes • No
Likelihood of continuing treatment	Treatment group: all on-site visits after last treatment Control group: all on-site visits after optional last treatment	Direct question. Participants' possible answers are: • Yes • No
Willingness to recommend treatment	Treatment group: all on-site visits after last treatment Control group: all on-site visits after optional last treatment	Direct question. Participants' possible answers are: • Yes • No
Participant's self-perception of age	Treatment group: randomization and all on-site visits after last treatment Control group: randomization and all on-site visits after optional last treatment	Direct question. Participants are asked to provide feedback on how, in the past week, they have perceived their facial appearance makes them look.
Temple volume	All on-site visits starting from randomization visit for both groups	Change in temple volume calculated by image analysis technician from baseline and follow-up 3D images

There are no pandemic or natural disaster-related protocol modifications for the 3D facial imaging. If a site visit is missed at which this assessment was planned, the assessment may be performed as an unscheduled or follow-up visit.

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

8.2. Safety Assessments

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 diary. Safety diaries will be recorded daily for 30 days starting on the day of treatment.
- AEs from TI observation and inquiry at scheduled follow-up visits
- Participant's assessment of jaw function on the Jaw Functional Limitation Scale. Assessment on Day 14 after each treatment will be recorded along with safety diaries, while for other visits it will be performed on-site.
- Monitoring of concomitant medications and concurrent procedures

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

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

Participants are to bring the safety diaries to the visits 1 month after each treatment for review by the TI, and the TI will determine if the ISR qualifies as an AE. The ongoing ISRs will be reported on the ISR eCRF.

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

Vital sign measurements, including blood pressure (systolic and diastolic, while participant is seated), temperature, pulse, and respiratory rate will also be performed.

There are no pandemic or natural disaster-related protocol modifications for physical examinations or blood draws for laboratory testing. If a site visit is missed at which physical

examinations or laboratory testing was planned, this assessment may be performed as an unscheduled or follow-up visit.

If travel restrictions or other changes in local regulations in light of a pandemic or natural disaster prevent the participant from in-clinic visits, participant visits may be conducted via phone, video conference, or remotely.

8.2.1. Clinical Safety Laboratory Assessments

Hematology and blood chemistry tests will be performed as described in Appendix 10.2.

At screening, the TI will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.

The TI must review the laboratory report and document this review and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the TI to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study are to be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology is to be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded as an SAE or AE in the eCRF.
- Urine or blood pregnancy tests will be used at the study site at screening, before each study treatment, and at study exit for female participants of childbearing potential.
- If a participant who underwent at least 1 treatment withdraws from the study before the Month 6 visit, he/she must be followed up for hematology test, clinical chemistry, and routine urinalysis at study exit for safety.

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 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 or SAE/SADE and their severity can be found in Appendix 10.7.

AEs/ADEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The PI/TI and any qualified 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).

Pandemic infections should be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol.

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

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

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.

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 Appendix 10.7. 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 Appendix 10.7.

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 TI 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).

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

If a participant dies during participation in the study or during a recognized follow-up period, the PI/TI will provide the sponsor medical safety physician with a copy of any postmortem findings including histopathology.

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

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

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, IECs, 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 along with the IB and will notify the IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the last follow-up visit.
- If a pregnancy is reported, the PI/TI is to inform the sponsor within 24 hours of learning of the pregnancy.
- The PI/TI shall (1) instruct the participant to notify her physician of the presence of the investigational device and (2) follow the pregnancy to term or termination. Best practices are to be followed in order to ensure the welfare of the participant and the fetus. The sponsor medical safety physician will contact the PI/TI to obtain information about the pregnancy outcome. The participant will continue to be followed, and the pregnancy will be documented as a protocol deviation.
- The pregnancy outcome of a spontaneous or elective abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

8.3.6. Medical Device Deficiencies

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 that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 10.7.

NOTE: Device deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 10.7 of the protocol.

8.3.6.1. Time Period for Detecting Medical Device Deficiencies

- 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 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 is provided in Appendix 10.7.

8.3.6.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- The device deficiency will be reported to the sponsor by email. If email is unavailable, then fax will be used.
- The same individual will be the contact for the receipt of device deficiency reports and SAEs.

8.3.6.3. Prompt Reporting of Device Deficiencies to Sponsor

- Device deficiencies that are potentially related to SAEs will be reported to the sponsor within 24 hours after the PI/TI determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency will be reported to the sponsor by email. If email is unavailable, then fax will be used.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.3.6.4. 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 IEC.

8.4. Treatment of Overdose

Overdose is not applicable for this study.

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 parameters are not evaluated in this study.

9. Statistical Considerations

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

In general, descriptive statistics will be presented. 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. No imputation of missing data is planned, except for the primary effectiveness analyses as described in Section 9.4.2.2. Deviations from the analyses planned in the SAP will be documented in the clinical study report.

Statistical analysis activities will be conducted by the Coordinating Investigator or by a third party delegated by the Coordinating Investigator.

9.1. Statistical Hypotheses

The null and alternative hypotheses are:

H_o: $P_v = P_c$
H_a: $P_v \neq P_c$

where P_v and P_c denote the responder rates for the treatment group at Month 6 after last control-period treatment, and control group at Month 6 after randomization, respectively (responder is defined as a participant with at least 1-grade improvement on the ATHS in both temples based on the EI's live assessment of temple hollowing). The null hypothesis for effectiveness is that the responder rate at Month 6 is the same for the treatment and control groups. The alternative hypothesis is that the ATHS responder rate for the treatment group is different from the control group at Month 6.

9.2. Sample Size Determination

The primary effectiveness measure is the change from baseline on the 5-point ATHS at Month 6. The change can range from -4 to +2. The primary effectiveness variable is the ATHS responder status, which is determined by an improvement of 1 grade or more (ie, a change score of -4 to -1) in both temples.

Under a 2:1 randomization ratio, a total of 90 participants in the treatment group and 45 participants in the control group at the primary timepoint will provide at least 90% power to detect a difference of 30% in the responder rates between the groups. This calculation is based on a 2-sided Fisher's exact test at the 5% level, using responder rates of 65% and 35% for both temples simultaneously for participants in the treatment and control groups, respectively. The assumption of a 65% treatment responder rate is a conservative estimate based on the observed responder rate in previous filler studies for other facial areas. Also, while a 30% difference from control is greater than a minimally important difference, a 35% responder rate is a reasonable upper limit of expectation for the control group, based on validation results of the ATHS and control group responder rates observed in previous filler studies. Furthermore, assuming a dropout rate of 20% after randomization through the Month 6 visit, 168 randomized participants are needed, with 112 participants in the treatment group and 56 participants in the control group (2:1 ratio).

If the underlying true responder rate is 65%, 90 participants in the treatment group results in a binomial likelihood of 86.5% to observe a responder rate of at least 60%.

With up to 9 investigational sites planned, it is recommended that no site randomize more than twice the proportional share of 1 more site = 2 × [168/(n+1)]. The recommended minimum is 8 participants per site, which will guarantee that each treatment group has at least 2 participants at each site (allowing for mixed randomization blocks of 3 and 6 that incorporate the 2:1 randomization ratio).

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

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. If more than 20% of the randomized participants fail to complete the primary timepoint ATHS assessment in-clinic, additional participants will be enrolled.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
mITT	All randomized participants who have nonmissing baseline ATHS. This population will be used as the full analysis set.
PP	All participants in the mITT population with nonmissing primary effectiveness endpoint (ie, nonmissing ATHS for Month 6 for each temple) and with no significant protocol deviations that could affect the primary effectiveness endpoint. A significant deviation that occurs after the primary endpoint would not lead to exclusion from the PP analysis.
Safety	All randomized participants who have at least 1 study treatment intervention (ie, VOLUMA with Lidocaine or no treatment).

Analyses of safety variables will be performed on the safety population, with participants grouped as treated. Unless specified otherwise, all other analyses will be performed on the mITT population, with participants grouped as randomized. The PP population will be used to perform PP sensitivity analysis, with participants grouped as randomized, for the primary endpoint.

9.4. Statistical Analyses

The SAP will be finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.4.1. General Considerations

The effectiveness analyses will be based on the mITT population in general, and PP sensitivity analysis of the primary endpoint will be based on the PP population. Baseline for effectiveness is defined as the last nonmissing effectiveness assessment before randomization.

All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. A gatekeeping procedure will be used for hypothesis testing of the primary endpoint (ATHS responder) and 2 of the secondary endpoints (responder rates for EI and participant assessments of GAIS) following a predefined sequence to control the overall type I error rate at the 0.05 level. The primary hypothesis must be rejected in order to test the responder rate for EI assessment of GAIS. Additionally, statistical significance must be established for the responder rate for EI assessment of GAIS in order to assess the hypothesis for the responder rate for participant assessment of GAIS.

9.4.2. Primary Endpoint

9.4.2.1. Definition of Endpoint

Primary effectiveness endpoint:

- Responder status based on the EI's live assessment of temple hollowing using ATHS at Month 6 after last treatment for treatment group and after randomization for control group, where a "responder" is a participant with at least 1-grade improvement on the ATHS in both temples.

9.4.2.2. Main Analytical Approach

The primary effectiveness analysis will be performed on the mITT population. The study intervention will be determined to be clinically effective if the following criterion is met:

- The ATHS responder rate for the treatment group is statistically superior to the responder rate for the control group at Month 6

Two-sided Fisher's exact test with 5% significance level will be used to compare responder rates between treatment and the control group. If the 2-sided p-value is ≤ 0.05, which implies that the responder rate is different for treatment than for the control group, and the point estimate of the responder rate for the treatment group is greater than for the control group, then treatment will be considered clinically effective. In addition, responder rates and 95% CIs will be displayed within and between treatment and control groups.

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

- Multiple imputation by the fully conditional specification method for ordinal data (via SAS procedure MI with FCS logistic statement) will be done with 5 imputed datasets for participants with missing primary endpoint, using the model below:
- Month 6 ATHS = $\beta_0 + \beta_1 \times$ Baseline ATHS + $\beta_2 \times$ Month 1 ATHS + $\beta_3 \times$ Month 3 ATHS
- Intermittent missing ATHS at Month 1 and Month 3 will be imputed by similar models using ATHS at previous visits as covariates.
- The imputation will be performed by treatment group and by side (left and right).
- After imputation, the changes from baseline will be calculated, from which the responder status will be determined.
- Analyses of individual imputed datasets will be performed by SAS procedure FREQ and then pooled by SAS procedure MIANALYZE to display combined responder rates and 95% CIs within and between treatment and control groups and to generate an associated p-value for the comparison of responder rates between groups.

9.4.2.3. Sensitivity Analyses

Since multiple imputation will be used for the primary analysis if the observed dataset is not complete for the primary endpoint, a sensitivity analysis will then be done using observed data, without imputation of missing data.

If so, a second sensitivity analysis will be done after imputation for missing data by baseline-observation carried-forward (for reversion to baseline), which effectively handles participants with missing primary effectiveness as nonresponders.

The primary analysis using 2-sided Fisher's exact test or multiple imputation (depending on whether any participants have missing primary effectiveness endpoint as mentioned in Section 9.4.2.2) will also be repeated on the PP population as a third sensitivity analysis.

9.4.3. Secondary Endpoints

Secondary effectiveness endpoints:

- Responder status based on the EI's assessment of the temple area using GAIS at Month 6 after last treatment for treatment group and after randomization for control group, where a "responder" is a participant with grade "improved" or "much improved" on GAIS.
- Responder status based on the participant's assessment of the temple area using GAIS at Month 6 after last treatment for treatment group and after randomization for control group, where a "responder" is a participant with grade "improved" or "much improved" on GAIS.
- Change from baseline on FACE-Q Satisfaction with Facial Appearance questionnaire at Month 6 after last treatment for treatment group and after randomization for control group.
- Change from baseline on FACE-Q Satisfaction with Temples questionnaire at Month 6 after last treatment for treatment group and after randomization for control group.

The following analysis will be performed for the secondary effectiveness endpoints:

- For the responder status based on the EI's and participant's assessments of GAIS at Month 6, the responder rates with 95% exact CI will be summarized, and p-value for between treatment group comparisons will be based on 2-sided Fisher's exact test using observed data.
- Change from baseline on participant responses on FACE-Q Satisfaction with Facial Appearance and with Temples questionnaires, for the Rasch-transformed score (0-100), will be analyzed using a repeated measures mixed-effects model, and the p-value for the between treatment group comparison will be provided for Month 6.

9.4.4. Additional Endpoints

Other effectiveness endpoints:

- Primary and secondary measures at other visits
- Full-scale ATHS scores at each measurement visit
- Full-scale EI assessment of GAIS at each measurement visit
- Full-scale participant assessment of GAIS at each measurement visit
- Percentage of participants showing improvement on the FACE-Q Satisfaction with Facial Appearance questionnaire, for the Rasch-transformed score, at each measurement visit
- Participant responses to FACE-Q Satisfaction with Facial Appearance questionnaire, for the Rasch-transformed score (0-100), unadjusted for baseline, at each measurement visit
- Percentage of participants who respond as Somewhat Satisfied or Very Satisfied for 3-5 items (to be specified in the SAP) on the FACE-Q Satisfaction with Facial Appearance questionnaire at Month 6
- Percentage of participants showing improvement on the FACE-Q Satisfaction with Temples questionnaire, for the Rasch-transformed score, at each measurement visit
- Participant responses to FACE-Q Satisfaction with Temples questionnaire, for the Rasch-transformed score (0-100), unadjusted for baseline, at each measurement visit
- Percentage of participants who respond as Somewhat Satisfied or Very Satisfied for 3-5 items (to be specified in the SAP) on the FACE-Q Satisfaction with Temples questionnaire at Month 6
- Participant's satisfaction with treatment questions and age perception question, at each measurement visit
- Volume change of each temple from baseline as assessed by 3D imaging, at each measurement visit

The following analyses will be performed for the other effectiveness variables. There are 5 variables underlying the primary and secondary variables:

- Overall score of ATHS at each measurement visit, baseline and change from baseline, summarized with response frequencies and descriptive statistics for each treatment group, using the temple with worse baseline score to represent the participant (using the left side if both temples have the same baseline score).
- Overall score of EI assessment of GAIS at each measurement visit, baseline and change from baseline, summarized with response frequencies and descriptive statistics for each treatment group.
- Overall score of participant assessments of GAIS at each measurement visit, baseline and change from baseline, summarized with response frequencies and descriptive statistics for each treatment group.

- Participant responses to FACE-Q Satisfaction with Facial Appearance questionnaire, for item-level scores for ordinal categories from 1 to 4 for each of 10 items at each measurement visit, baseline and change from baseline, summarized with response frequencies and descriptive statistics for each treatment group.
- Participant responses to FACE-Q Satisfaction with Temples questionnaire, for item-level scores for ordinal categories from 1 to 4 for each of 12 items at each measurement visit, baseline and change from baseline, summarized with response frequencies and descriptive statistics for each treatment group.

Other analyses for additional endpoints will be detailed in the SAP.

9.4.5. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include procedural pain, ISRs, AEs, jaw function assessment, vital signs, concomitant medications and procedures and clinical laboratory values.

Procedural pain will be summarized using response frequencies and descriptive statistics. ISRs reported by participants will be summarized at the participant level by symptom incidence, maximum reported severity, number of ISR days, maximum reported contiguous duration (maximum successive days of the ISR) and total duration days (number of days from first onset day to last occurrence) for initial and touch-up, separately. The summary of procedural pain and ISRs will be done separately for the initial treatment group and the optional treatment group.

9.4.5.1. 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
- Discontinued due to TEAE
- Deaths

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

- by primary SOC and PT
- by primary SOC, PT, and maximum severity

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

- by maximum severity, time to onset, duration, action taken and outcome

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation 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 PT for the same participant, the participant will be counted only once for that PT using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

9.4.5.2. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) at baseline (screening) and changes from baseline at each assessment will be presented by data listings. No summary statistics are planned for vital signs.

9.4.6. Other Analyses

9.4.6.1. Study Intervention Administration Analyses

Study intervention characteristics will be summarized with descriptive statistics for anesthesia usage, injection volume, injection ease (11-point scale where 0 = difficult and 10 = easy) and product moldability (11-point scale where 0 = stiff and 10 = moldable). Injection technique and planes of injection will be summarized using frequency and percentages.

9.4.6.2. Subgroup Analyses

No subgroup analysis is planned for this study.

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 Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH/ISO GCP guidelines
  - Applicable laws and regulations, including NMPA order No. 25 (China Medical Device GCP)
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IEC by the PI and the study site's device trial management department and reviewed and approved by the IEC before the study is initiated.
- Any amendments to the protocol will require IEC 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 IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
  - Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example ICH guidelines and the IEC
- During the course of the study, should it ever become 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, phone contacts or virtual site visits) or alternative locations for safety data collection in agreement with the sponsor. In all cases, these alternative measures must be allowed by local regulations and permitted by IEC. Investigators should 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 as needed. 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 or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IEC or study site.
- 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 or the participant's legally authorized representative.
- 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 (including facial images) will only be transferred in accordance with the signed Informed Consent provisions.
- 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 informed consent.
- 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 IEC 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), should 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, 3D imaging data). The PI is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The PI must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The PI must permit study-related monitoring, audits, IEC 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 or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; 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 for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

- Data management activities will be conducted by the Coordinating Investigator or by a third party delegated by the Coordinating Investigator.
- In the event of a pandemic or natural disaster, remote monitoring of data may be employed if allowed by the local regulatory authority, IEC, 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 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 1.51 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

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 IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the PI
- Discontinuation of further study intervention development

Per ISO 14155, if a study is prematurely terminated or suspended due to safety issues, the sponsor shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IEC is also to be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the PI, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the

protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each PI or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.9. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the sponsor.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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 at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the PI upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The PI will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations (including those that may be due to a pandemic or natural disaster) will be reported to the IEC according to the IEC's reporting requirements. Participants will be asked questions to evaluate compliance with safety diaries.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	Red blood cell indices: Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration % Reticulocytes	White blood cell count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Urea Nitrogen/urea Creatinine Glucose, fasting	Potassium Sodium Calcium	Aspartate Amino Transferase Alanine amino Transferase Alkaline phosphatase	Total, direct bilirubin Total protein Cholesterol, chloride, albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen/bilinogen, nitrite, leukocyte esterase/leukocyte neutrophil esterase/leukocyte • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Human chorionic gonadotropin pregnancy test at screening and test on admission days as needed for women of childbearing potential			

Investigators must document their review of each laboratory safety report.

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

Not applicable. See Appendix 10.7.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
3D	3-dimensional
ADE	adverse device effect
AE	adverse event
ATHS	Allergan Temple Hollowing Scale
BDDE	1,4-butanediol diglycidyl ether
CDISC	Clinical Data Interchange Standards Consortium
CE	Conformité Européene
CI	confidence interval
eCRF	electronic case report form
EI	Evaluating Investigator
FDA	United States Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	hyaluronic acid
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDFU	investigational directions for use
IEC	independent ethics committee
ISO	International Organization for Standardization
ISR	injection site response
IWRS	interactive web response system
mITT	modified intent-to-treat
NCI	National Cancer Institute
NCT	national clinical trial number on www.clinicaltrials.gov
NMPA	National Medical Products Administration
PI	Principal Investigator
PP	per-protocol
PT	preferred term
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TI	Treating Investigator
USADE	unanticipated serious adverse device effect

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)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
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: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	A multicenter, evaluator-blinded, randomized, no-treatment controlled study to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA® with Lidocaine for correction of temple hollowing in Chinese population
	Clinical Study Sponsor	Allergan
	Trial Phase Classification	N/A
	Trial Indication	Temple hollowing
	Trial Indication Type	Treatment
	Trial Type	Effectiveness Safety
	Trial Length	14 months
	Planned Country of Investigational Sites	China
	Planned Number of Subjects	168
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	No
	Pediatric Study	No
Subject information	Diagnosis Group	Temple hollowing
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	None
	Sex of Participants	Both
	Stable Disease Minimum Duration	N/A
Treatments	Investigational Therapy or Treatment	JUVÉDERM® VOLUMA® with Lidocaine
	Intervention Type	Device
	Pharmacological Class of Invest. Therapy	N/A
	Intervention per Administration	Up to 3 mL/temple (initial and touch-up combined); any single treatment: up to 2 mL/temple
	Intervention Units	mL
	Dosing Frequency	Initial and touch-up treatments
	Route of Administration	Injection
	Current Therapy or Treatment	N/A
	Added on to Existing Treatments	No
	Control Type	No-treatment control
	Comparative Treatment Name	None

Parameter Group	Parameter	Value
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Trial is Randomized	Yes
	Randomization Quotient	2:1
	Trial Blinding Schema	Single-blind
	Stratification Factor	None
	Adaptive Design	No
	Study Stop Rules	No

10.7. Appendix 7: 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.

10.7.1. Definition of AE and ADE

AE and ADE 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.

10.7.2. Definition of SAE, SADE, and USADE

If an event is not an AE per the 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 that hypothetically might have caused death if it were more severe. 2. A permanent impairment of a body structure or a body function 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
SADE Definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition
• A USADE is defined as a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

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 inadequate labeling.

10.7.4. Recording and Follow-up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
• When an AE/SAE/device deficiency 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 information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF. • 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 page. • 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, 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.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The PI will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, 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 and IB in his/her assessment.
- For each AE/SAE/device deficiency, the PI **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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 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 sponsor or designee.

- The PI may change his/her opinion of causality in light of follow-up information and send an 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

- 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 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 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.
- The PI will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours

- Contacts for SAE reporting can be found on the protocol title page.
- Email is the preferred method to transmit SAE information.
- Facsimile transmission of the SAE information is also acceptable.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE form, sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

10.7.6. 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 determines that the event meets the definition of a device deficiency. • 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 IECs as required by national regulations. • Contacts for SAE reporting can be found on the protocol title page.

10.8. Appendix 8: Protocol Amendment History

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

Amendment 2 (December 2020)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment is to update the safety laboratory assessments in alignment with the investigative sites' capabilities.

Section No. and Name	Description of Change	Brief Rationale
8.2 (Safety Assessments)	Removed the term *Other* as an injection site response listed in the participant's safety diary	Correction
8.2.1 (Clinical Safety Laboratory Assessments)	Revised the term *laboratory manual* to *laboratory requirements*	Correction
10.2 (Appendix 2)/Clinical Laboratory Tests/Table 10-1	For clinical chemistry assessments, removed the parameter *indirect bilirubin*, revised assessment of glucose from nonfasting to fasting glucose, and revised the parameter of *blood urea nitrogen* to *urea nitrogen/urea*	Correction
10.2 (Appendix 2)/Clinical Laboratory Tests/Table 10-1	For routine urinalysis, added the parameter *bilinogen* and revised the parameter *leukocyte esterase by dipstick* to *leukocyte esterase/leukocyte neutrophil esterase/leukocyte*	Correction

Amendment 1 (August 2020)

Overall Rationale for the Amendment:

The primary purpose of this protocol amendment was to update the needle size to include a 25 G 1" needle and update study processes as summarized below.

Section No. and Name	Description of Change	Brief Rationale
1.1/Synopsis	Added the option of using a 25 G 1" needle	Update
1.2/Schema	Added 'after randomization' after 'Optional treatment at Month 6' for the control group	Improve clarity
1.3/Schedule of Activities	Added that pregnancy test is to be administered prior to randomization (for participants in the control group)	Improve clarity
Table 1-3	Added 'After Randomization' in the column 'Month 1 (+1w), Month 3 (±2w), Month 6 (±2w)' for the control group	Improve clarity

Section No. and Name	Description of Change	Brief Rationale
Table 1-3	Added a pregnancy test at study exit and updated corresponding language in footnotes for the control group	Update
Table 1-3	Removed 3D imaging and vital sign assessments from the optional initial treatment visit due to duplication with that at Month 6 after randomization/study exit	Improve clarity
Table 1-3	Updated language in footnote h) to clarify the specific visit at which laboratory testing is to be conducted	Improve clarity
4.3/Justification for Dose	Added the option of using a 25 G 1” needle	Update
Table 6-1	Added the option of using 25 G 1” needles and clarified that they will be provided separately.	Update
6.1.2/Instructions for Use and Administration	Added the option of using a 25 G 1” needle	Update
8.1.1/Intervention Administration Assessments	Added that injection technique will be included in the evaluation of the study intervention	Update
8.1.1/Intervention Administration Assessments	Added the option of using a 25 G 1” needle	Update
8.2/Safety Assessments	Added description of how ISRs will be monitored	Update

11. References

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