Title Page

Protocol Title: A multicenter, evaluator-blinded, randomized, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for correction of temple hollowing

Protocol Number: 1878-702-008 Amendment 2

Product: JUVÉDERM VOLUMA® XC injectable gel

Brief Protocol Title: JUVÉDERM VOLUMA® XC injectable gel for correction of temple hollowing

Study Phase: Pivotal

Sponsor Name: Allergan

Legal Registered Address:

Allergan Sales LLC
5 Giralda Farms
Madison, NJ 07940
USA

Manufacturer:

Allergan
Route de Proméry
Zone Artisanale de Pré-Mairy, Pringy
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Regulatory Agency Identifying Numbers: IDE G190158 and NCT04414397

Emergency Telephone Number: Refer to the study contacts page

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Sponsor Signatory:

[redacted]
Vice President
Global Therapeutic Area Head, Clinical Development, Aesthetics

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

Protocol Amendment Summary of Changes Table

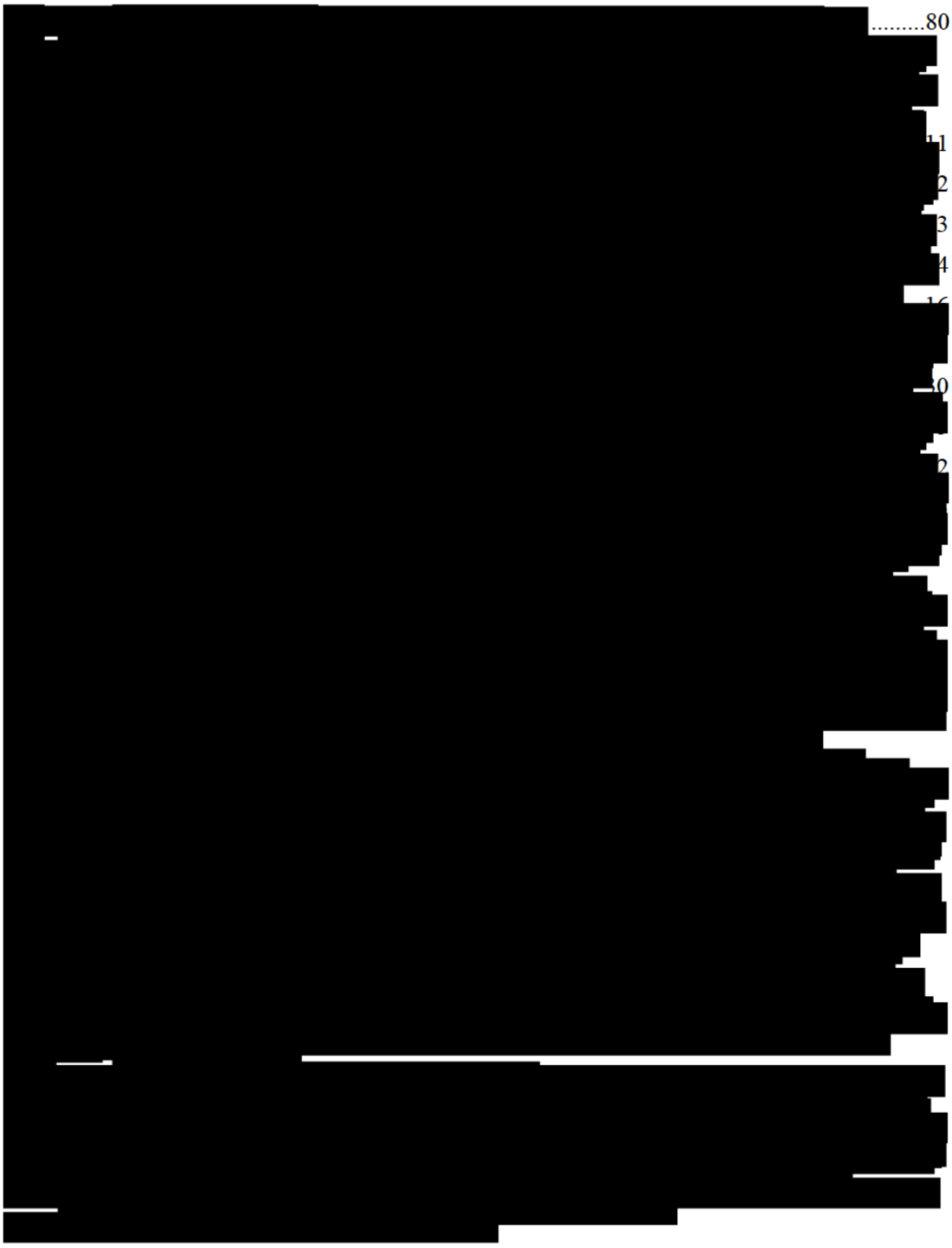
DOCUMENT HISTORY	
Document	**Date**
Amendment 2	May 10, 2021
Amendment 1	January 2020
Original Protocol	November 2019

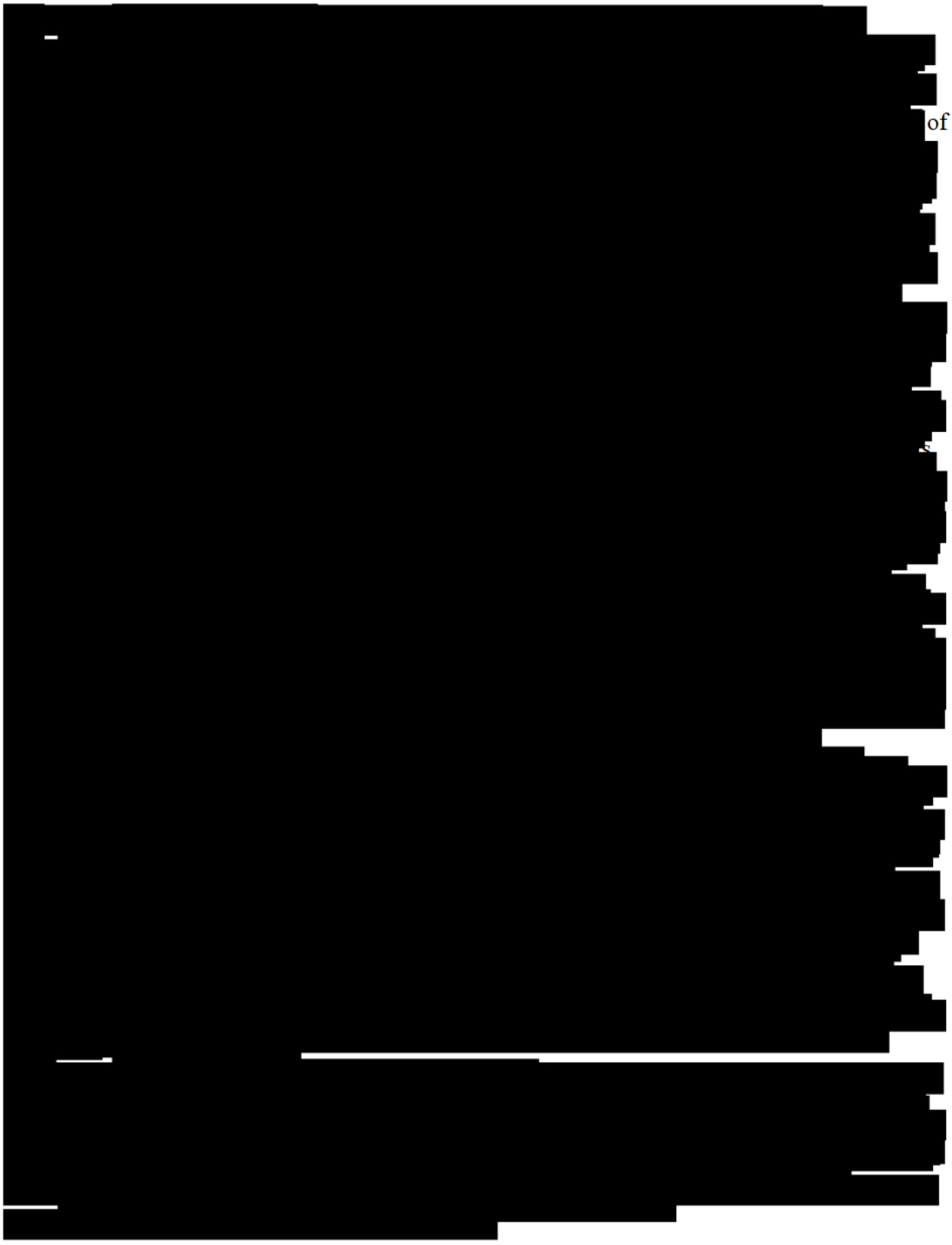
Amendment 2 (May 10. 2021)

Overall Rationale for the Amendment:

Interim analysis may be performed; minor edits.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added Regulatory Agency Identifying Numbers	As assigned.
[redacted]	[redacted]	[redacted]
Appendix 8	Moved Rationale/Summary of Changes for Amendment 1	Added Rationale/Summary of Changes Amendment 2





Objectives	Endpoints
Effectiveness To evaluate the effectiveness of VOLUMA XC injectable gel in adult participants seeking correction of temple hollowing	• Primary: Responder status based on the evaluating investigator's (EI) live assessment of temple hollowing using the Allergan Temple Hollowing Scale (ATHS) at Month 3
	• Secondary: Responder status based on EI assessments of global aesthetic improvement in the temple area using the Global Aesthetic Improvement Scale (GAIS) at Month 3
	• Secondary: Responder status based on participant assessments of global aesthetic improvement in the temple area using the GAIS at Month 3
	• Secondary: Change from baseline on FACE-Q Satisfaction with Facial Appearance questionnaire at Month 3
	• Secondary: Change from baseline on FACE-Q Satisfaction with Temples questionnaire at Month 3
Safety To evaluate the safety of VOLUMA XC injectable gel in adult participants seeking correction of temple hollowing	• Participant assessment of procedural pain • Participant assessment of injection site responses • Adverse events • Jaw Functional Limitation Scale • Vision Assessments: – Snellen visual acuity – confrontational visual fields – ocular motility • Concomitant medication and procedures

Overall Study 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 XC injected with 27 G 1/2" or 25 G 1" needles to the supraperiosteal plane in the temple area (up to 6 mL for initial and touch-up treatments combined) for the treatment group and delayed treatment for the control group

Number of Participants:

Up to 213 participants will be enrolled and screened to achieve 171 randomized (114 treatment group, 57 control group) and 135 evaluable participants (90 treatment group, 45 control group) at the Month 3 primary timepoint.

Number of Sites:

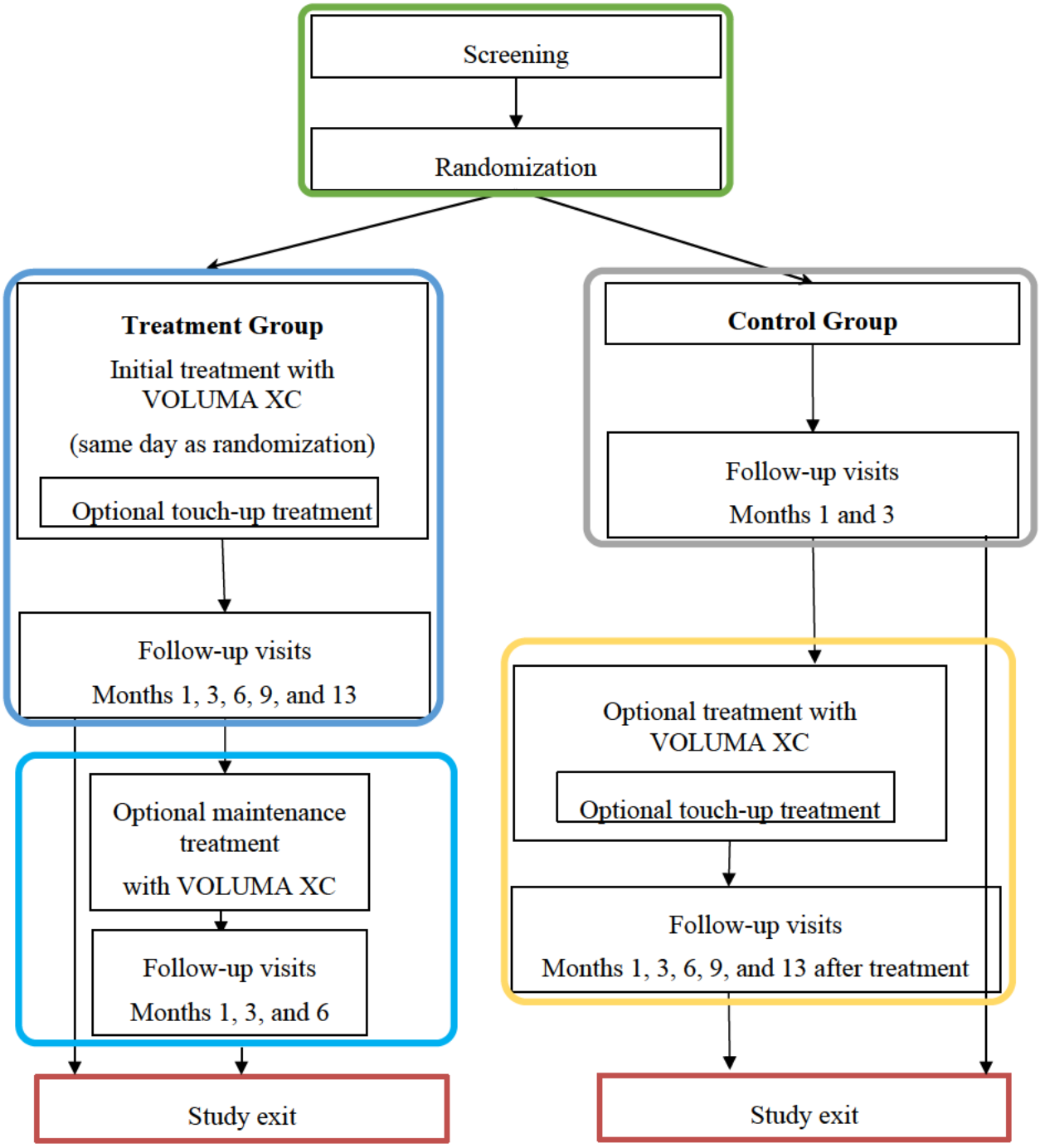
Up to 15 North American sites

Intervention Groups and Study Duration:

- Participants will be randomized on study intervention day in a 2:1 ratio of treatment group to control group. Screening period is up to 30 days for all participants.

[redacted]

1.2. Schema


Screening
Randomization
Treatment Group
Initial treatment with VOLUMA XC
(same day as randomization)
Optional touch-up treatment
Follow-up visits
Months 1, 3, 6, 9, and 13
Optional maintenance treatment with VOLUMA XC
Follow-up visits
Months 1, 3, and 6
Study exit
Control Group
Follow-up visits
Months 1 and 3
Optional treatment with VOLUMA XC
Optional touch-up treatment
Follow-up visits
Months 1, 3, 6, 9, and 13 after treatment
Study exit

1.3. Schedule of Activities

[redacted]

Table 1-1 Screening Visit Procedures: All Participants

Procedure	Screening
Visit Window (Days)	-30
Consent/authorization	X
Participant demographics	X
Height, weight, and vital signs[a]	X
Fitzpatrick skin phototype and sun exposure history	X
Smoking and tobacco use history	X
Medical/surgical/cosmetic/dental history	X
Urine pregnancy test[b]	X
ATHS (EI)	X
Inclusion/exclusion criteria (TI)[c]	X
Adverse events	X
Concomitant medications, procedures, therapies	X

[a] Includes blood pressure (systolic and diastolic; while participant is seated), pulse rate, and temperature.
[b] For female participants of childbearing potential; administered and confirmed negative prior to study intervention. A female is not considered of childbearing potential if she has been postmenopausal for at least 1 year or does not have a uterus at the time of study entry.
[c] TI will use EI ATHS scores to confirm participant's eligibility in the study.

Table 1-2 Treatment Group Procedures: Treatment Period

Procedure	Initial			Touch-up		
	Randomization[a] /Initial Tx	3 Days After Initial Tx	14 Days After Initial Tx	30 Days After Initial Tx / Touch-up Tx[b]	3 Days After Touch-up Tx	14 Days After Touch-up Tx
Visit Window (Days)		± 2	+ 4	+ 10	± 2	+ 4
Urine pregnancy test[c]	X[d]			X[e]		
ATHS (EI)[f]	X[d]					
Inclusion/exclusion criteria (TI)	X[d]					
3D facial digital imaging	X[d]		X	X[e]		X
FACE-Q (Participant) • Satisfaction with Facial Appearance • Satisfaction with Temples	X[d]					
Self-perception of age (Participant)	X[d]					
Jaw Functional Limitation Scale (Participant)	X[d]		X	X		X
Randomization[e]	X					
Vision Assessments: (TI or designee) • Snellen visual acuity • Confrontational visual fields • Ocular motility	X[g]		X	X[g]		X
Study intervention, intervention characteristics (TI)	X			X		
Injection ease and product moldability (TI)	X			X		
Procedural pain (Participant)	X			X		
Safety telephone call		X			X	
Safety e-diary[h] (Participant)	Continuous			Continuous		
Adverse events[i] (TI)	Continuous monitoring					
Concomitant medications and concurrent procedures (TI)	Continuous monitoring					

Tx = treatment

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

[b] [redacted]

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

[d] Done prior to randomization and study intervention.

[e] Done prior to study intervention.

[f] TI will use EI ATHS scores to confirm participant's eligibility in the study.

[g] On initial and touch-up treatment days, vision assessments will be performed by TI (or designee) before study intervention and at least 30 minutes after completing last injection procedure.

[h] The safety e-diaries are to be completed following each study intervention starting on the day of treatment.

[i] [redacted].

Table 1-3 Treatment Group Procedures: Follow-up Period

Procedure	Follow-up[a]				
	Month 1	Month 3	Month 6	Month 9	Month 13[b] /Exit Visit[c]
Visit Window (Days)	+ 10	± 7	± 15	± 7	± 15
Urine pregnancy test[d]					X
Weight		X			X
3D facial digital imaging	X	X	X		X
FACE-Q (Participant): • Satisfaction with Facial Appearance • Satisfaction with Temples	X	X	X		X
Jaw Functional Limitation Scale (Participant)	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		X
Self-perception of age (Participant)		X	X		X
GAIS (Participant)	X	X	X		X
ATHS (EI)	X	X	X		X
GAIS (EI)	X	X	X		X
Vision Assessments: (TI or designee) • Snellen visual acuity • Confrontational visual fields • Ocular motility	X				
Safety telephone call				X	
Reason for not receiving maintenance (Participant)					X
Adverse events[e] (TI)	Continuous monitoring				
Concomitant medications and concurrent procedures (TI)	Continuous monitoring				

a month = 30 days

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

[b] At the Month 13 visit, participants will be offered a maintenance treatment after completion of the Month 13 visit. Participants who accept maintenance treatment will undergo the additional procedures specified in Table 1-4. Participants who do not accept maintenance treatment will exit the study after the Month 13 procedures are completed.

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

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

[e] Will include a general, nondirected question about vision symptoms.

Table 1-4 Treatment Group Procedures: Maintenance Treatment and Follow-up Period

Procedure	Maintenance Treatment			Follow-up[b]		
	Maintenance Treatment[a] Visit	3 Days After Maintenance Treatment	14 Days After Maintenance Treatment	Month 1 After Maintenance Treatment	Month 3 After Maintenance Treatment	Month 6 After Maintenance Treatment/Exit Visit[c]
Visit Window (Days)		± 2	+ 4	+ 10	± 7	± 15
Urine pregnancy test[d]	X[e]					X
3D facial digital imaging	X[f]		X	X	X	X
Vision Assessments: (TI or designee) • Snellen visual acuity • Confrontational visual fields • Ocular motility	X[g]		X	X		
Study intervention, intervention characteristics (TI)	X					
Procedural pain (Participant)	X					
Safety telephone call (TI)		X				
Safety e-diary[h] (Participant)	Continuous					
FACE-Q (Participant) • Satisfaction with Facial Appearance • Satisfaction with Temples				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	X	X
Self-perception of age (Participant)				X	X	X
Jaw Functional Limitation Scale (Participant)			X	X		
GAIS (Participant)				X	X	X
ATHS (EI)				X	X	X
GAIS (EI)				X	X	X
Adverse events[i]	Continuous monitoring					
Concomitant medications and concurrent procedures	Continuous monitoring					

a month = 30 days

[a] A maintenance treatment is offered to participants who complete the Month 13 visit. The procedures must occur no later than 14 days after the Month 13 visit.

[b] Follow-up visit schedule is based on the date of the last study intervention (ie, maintenance treatment).

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

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

[e] Administered and confirmed negative prior to study intervention. If maintenance treatment is done on the same day of the Month 13 visit, this assessment does not need to be repeated.

[f] Prior to maintenance treatment. If maintenance treatment is done on the same day of the Month 13 visit, this assessment does not need to be repeated.

[g] Vision assessments will be performed by TI (or designee) before study intervention and at least 30 minutes after completing the injection procedures.

[h] The safety e-diaries are to be completed following each study intervention starting on the day of treatment.

[i] Will include a general, nondirected question about vision symptoms.

Table 1-5 Control Group Procedures: Control Period

Procedure	Randomization[a]	Follow-up[b]	
		Month 1	Month 3/ Study Exit[c]
Visit Window (Days)		+10	± 7
Urine pregnancy test[d]	X		
ATHS (EI)[e]	X[f]	X	X
Inclusion/exclusion criteria (TI)	X[f]		
3D facial digital imaging	X[f]	X	X
FACE-Q Satisfaction with Facial Appearance (Participant)	X[f]	X	X
FACE-Q Satisfaction with Temples (Participant)	X[f]	X	X
Self-perception of age (Participant)	X[f]		
Jaw Functional Limitation Scale (Participant)	X[f]		
Randomization	X		
GAIS (Participant)		X	X
GAIS (EI)		X	X
Weight			X
Adverse events (TI)	Continuous monitoring		
Concomitant medications and concurrent procedures (TI)	Continuous monitoring		

a month = 30 days

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

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

[c] At the Month 3 visit, the TI will discuss the option for the control group participant to receive study intervention. Participants who accept optional treatment, after completing the procedures under Month 3, will undergo the additional procedures specified in Table 1-6. Participants who do not accept optional treatment will exit the study after the Month 3 procedures are completed.

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

[e] TI will use EI ATHS scores to confirm participant's eligibility in the study.

[f] Done prior to randomization.

Table 1-6 Control Group Procedures: Delayed Treatment Period

Procedure	Optional Treatment			Touch-up Treatment			Follow-up[c]				
	Optional Tx[a] at Month 3	3 Days After Optional Tx	14 Days After Optional Tx	30 Days After Initial Tx / Touch-up Tx[b]	3 Days After Touch-up Tx	14 Days After Touch-up Tx	Month 1	Month 3	Month 6	Month 9	Month 13/Study Exit[d]
Visit Window (Days)		± 2	+ 4	+ 10	± 2	+ 4	+ 10	± 7	± 15	± 7	± 7
Urine pregnancy test[e]	X[f]			X[f]					X		
Jaw Functional Limitation Scale (Participant)	X[g]		X	X		X	X				
Vision Assessments: (TI or designee) • Snellen visual acuity • Confrontational visual fields • Ocular motility	X[h]		X	X[h]		X	X				
Study intervention, intervention characteristics (TI)	X			X							
Procedural pain (Participant)	X			X							
Safety telephone call (TI)		X			X					X	X
Safety e-diary[i] (Participant)	Continuous			Continuous							
3D facial digital imaging			X	X[g]		X	X	X	X		
FACE-Q (Participant) • Satisfaction with Facial Appearance • Satisfaction with Temples							X	X	X		
GAIS (Participant)							X	X	X		
ATHS (EI)							X	X	X		
GAIS (EI)							X	X	X		
Adverse events[j] (TI)	Continuous monitoring										
Concomitant medications and concurrent procedures (TI)	Continuous monitoring										

a month = 30 days; Tx = treatment

[a] An optional treatment is offered to control group participants at the Month 3 visit. The optional treatment procedures will be performed after completion of all Month 3 visit procedures. The optional treatment must be completed within 14 days after the Month 3 visit.

[b] [redacted] If no touch-up treatment is performed, the 30 Days After Initial Treatment visit becomes the Month 1 visit.

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

[d] If a participant withdraws for any reason prior to the Month 6 visit, attempts will be made to perform assessments along with a urine pregnancy test at an exit visit.

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

[f] Administered and confirmed negative prior to study intervention.

[g] Done prior to study intervention.

[h] On initial and touch-up treatment days, vision assessments will be performed by TI (or designee) before study intervention and at least 30 minutes after completing the injection procedures.

[i] The safety e-diaries are to be completed following each study intervention starting on the day of treatment.

[j] Will include a general, nondirected question about vision symptoms.

[redacted]

Jones 2013

[redacted]

Jones 2013

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2019

[redacted]

Sykes 2009

[redacted]

Rose 2013, Ross 2010

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(Kim 2005

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Atherton 2010, Gosain 1997

Guo 2012

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2019

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3. Objectives and Endpoints

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

Objectives	Endpoints
Effectiveness To evaluate the effectiveness of VOLUMA XC injectable gel in adult participants seeking correction of temple hollowing	• Primary: Responder status based on EI's live assessment of temple hollowing using the ATHS at Month 3
	• Secondary: Responder status based on EI assessments of global aesthetic improvement in the temple area using the GAIS at Month 3
	• Secondary: Responder status based on participant assessments of global aesthetic improvement in the temple area using the GAIS at Month 3
	• Secondary: Change from baseline on FACE-Q Satisfaction with Facial Appearance questionnaire at Month 3
	• Secondary: Change from baseline on FACE-Q Satisfaction with Temples questionnaire at Month 3
	[redacted]
	[redacted]
	[redacted]
Safety To evaluate the safety of VOLUMA XC injectable gel in adult participants seeking correction of temple hollowing	• Participant assessment of procedural pain • Participant assessment of ISRs • AEs • Jaw Functional Limitation Scale • Vision Assessments: – Snellen visual acuity – confrontational visual fields – ocular motility • Concomitant medications and procedures

4. Study Design

4.1. Overall Design

The design elements of this protocol have been reviewed with patients to obtain their perspectives in the following areas: schedule of events, length of study and visits, randomization ratio and duration of control period, and ICF language on possible adverse events.

This is a prospective, multicenter, evaluator-blinded, randomized, parallel-group, controlled study to evaluate the safety and effectiveness of VOLUMA XC injectable gel to correct temple hollowing.

The study will involve up to 15 investigational sites. The study population is represented by adults who are seeking correction of the temple hollowing and who meet the study criteria according to the study design.

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

Participants will stay in the study for up to 21 months depending on their randomization group. For the treatment group, each participant will be in the study for up to 21 months: up to 1 month for screening, up to 30 days of treatment, up to 13 months of follow-up after initial/touch-up treatment, and up to 6 months of follow-up after maintenance treatment. For the control group, each participant will be in the study for up to 4 months (up to 1 month for screening and 3 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 14 months (up to 30 days for treatment and 13 months of follow-up), for a total of up to 18 months.

	Treatment Group	Control Group
Screening	Up to 1 month	Up to 1 month
Control period	Not Applicable	3 Months
Treatment period	1-30 Days	1-30 Days (optional)
Treatment follow-up period	13 Months	13 Months
Maintenance treatment	1 Day (optional)	Not Applicable
Maintenance treatment follow-up	6 Months	Not Applicable

The study will compare the treatment to no treatment, with the primary timepoint set at Month 3.

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Pusic 2013

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Breithaupt 2015, Sykes 2015

5. Study Population

Adults with temple hollowing who are seeking restoration in the temple area. [redacted]

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

5.1. Inclusion Criteria

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

1.	**Age**
1.01	Participant must be 22 or over, at the time of signing the ICF
2.	**Sex**
2.01	Male and female
3.	**Type of Participant and Temple Hollowing Characteristics**
3.01	Participants in general good health
3.02	Participants seeking improvement of temple hollowing
3.03	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)
3.04	The temple hollowing is amenable to temporary correction in the TI's opinion
4.	**Informed Consent**
4.01	Capable of giving signed informed consent as described in Appendix 10.1.3, 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 e-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	Fluent and literate in English or Spanish

5.2. Exclusion Criteria

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

1.	**Medical Conditions**
1.01	The participant cannot achieve at least a 1-grade improvement 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 artery runs across the area to be injected, obscuring the field
1.06	Temporal arteritis or history of temporal arteritis
1.07	Temporomandibular joint dysfunction or any other jaw issues
1.08	Recurrent temporal headaches such as temporal tendinitis migraine
1.09	Active or recurrent inflammation or infection in either eye
1.10	Tendency to develop hypertrophic scarring
1.11	Active autoimmune disease
1.12	History of anaphylaxis or allergy to lidocaine (or any amide-based anesthetics), HA products, or Streptococcal protein
1.13	Current cutaneous or mucosal inflammatory or infectious processes (eg, acne, herpes), abscess, an unhealed wound, or a cancerous or precancerous lesion, above the subnasale
1.14	History of detached retina, retinal vascular occlusion (eg, vein or arterial occlusion), narrow angle glaucoma, neovascular eye disease, or severely impaired/absent eye function in 1 or both eyes
	Examples of neovascular eye disease include: diabetic retinopathy, age-related wet macular degeneration
2.	**Prior/Concomitant Therapy**
2.01	Prior facial reconstructive surgeries, facelift, or browlift as well as surgeries on the temple area (eg, biopsy)
2.02	Fat injection or permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face
2.03	Semipermanent soft-tissue filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) in the temple or mid-face within 36 months before enrollment
2.04	Temporary dermal filler injections above the subnasale within 24 months before enrollment
	Injections in the nasolabial fold are acceptable only if done at least 3 months prior to enrollment
2.05	Botulinum toxin treatment above the subnasale within 6 months before enrollment
2.06	Mesotherapy or cosmetic facial procedures above the subnasale within 6 months before enrollment
	Examples of mesotherapy or cosmetic facial procedures are face-lift, laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures

2.07	Has braces or other orthodontics or is planning such treatment during the study
2.08	Changes in use of over-the-counter or prescription oral or topical, anti-wrinkle 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, anti-wrinkle products above the subnasale within 30 days before enrollment or are planning to begin using such products during the study. 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
2.09	Is on a regimen of anti-coagulation therapy (eg, warfarin, clopidogrel)
2.10	Has received lasik surgery or other surgical intervention on the eye within 3 months prior to enrollment or is planning such a procedure
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.	**Other**
4.01	Has tattoos, piercings, facial hair, or scars above and including the subnasale that would interfere with visual assessment of the temple
4.02	Females who are pregnant, nursing, or planning a pregnancy
4.03	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
4.04	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
4.05	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.

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

Study Intervention Name	VOLUMA XC	Delayed Treatment
Device	JUVÉDERM VOLUMA XC	Same
Dose Formulation	20 mg/mL HA crosslinked with BDDE + 0.3% lidocaine (w/w gel)	Same
Route of Administration	Deep injection (supraperiosteal plane), injected with a 27 G 1/2" or 25 G 1" needle in the temple area	
Packaging and Labeling	Study intervention will be provided in prefilled syringes. Each syringe will be packaged with 27 G 1/2" needles for injection in a thermoform tray. The 25 G 1" needles will be provided separately. One or more trays will be packaged in a kit. Each kit and thermoform tray will be labeled as required per country requirements.	Same
Manufacturer	Allergan Route de Proméry Zone Artisanale de Pré-Mairy Pringy 74370, Annecy, France	Same
Number and Timing of Interventions	Initial treatment 30 days after initial treatment: Optional touch-up Month 13: Maintenance treatment	After Month 3 of control period: Optional initial treatment 30 days after optional initial treatment: Optional touch-up
Volume Per Intervention	Initial and touch-up combined: up to 3 mL/temple Maintenance treatment: up to 2 mL/temple Any single treatment: up to 2 mL/temple	[redacted]

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

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Table 6-2 Required Washout Intervals for Prohibited Medications or Procedures

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, touch-up, and maintenance) is administered.
30 days	• Any investigational product • Any new over-the-counter or prescription oral or topical, anti-wrinkle products above the subnasale
6 months	• Botulinum toxin injections above the subnasale • Mesotherapy or cosmetic facial procedures (eg, face-lift, laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) above the subnasale
3 months	• Temporary dermal filler injections in the nasolabial folds • Lasik surgery or other surgical intervention at the eye
24 months	• Temporary dermal filler injections above the subnasale
36 months	• Semipermanent dermal filler treatment (eg, calcium hydroxyapatite, poly-L-lactic acid) in the temple or mid-face

6.5.2. 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.

6.5.3. Rescue Medicine

Rescue medicine is not applicable.

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 case report form.

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

In addition, participants who receive the following prohibited treatment/medication will continue in the study until all required follow-up is complete but will not be eligible for further study intervention.

- Hyaluronidase treatment in the temple area
- Initiate a regimen of anti-coagulation therapy (eg, warfarin, clopidogrel)

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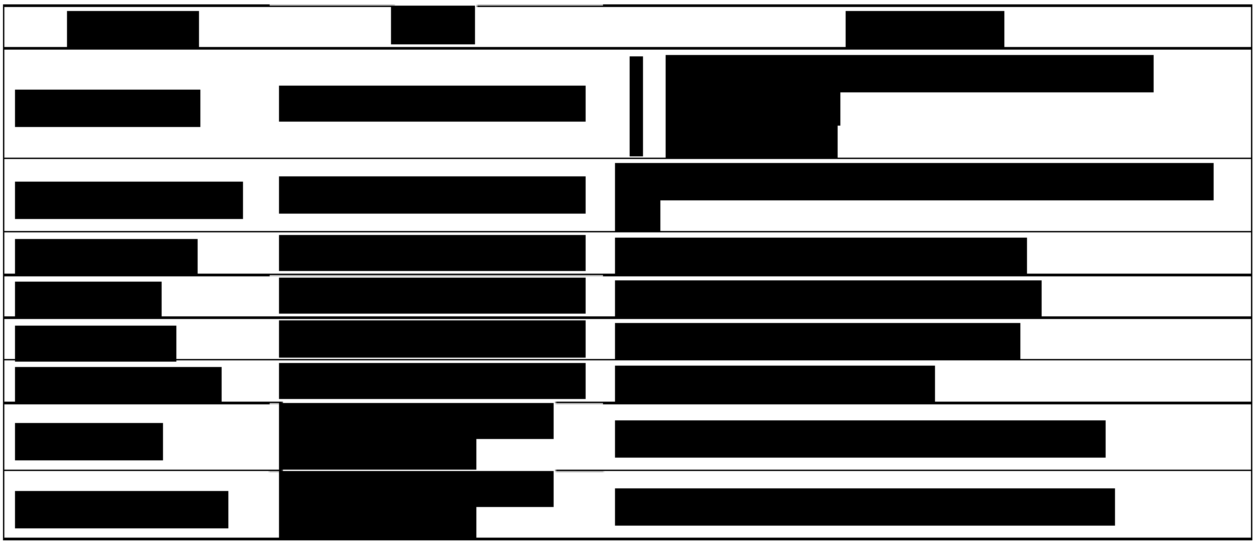


8.1.2. Primary Effectiveness Measure

The primary effectiveness measure is the EI's live assessment of temple hollowing, to be recorded for each temple, 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	• randomization and all in-office follow-up visits beginning at Month 1	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 frontal and lateral view photographs taken at baseline. Participants will use a mirror to assess their current appearance at each visit. All participant-reported effectiveness outcomes at a visit will be completed before the participant sees either the TI or EI at that visit.

The other secondary 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 final scoring and items will be determined based on the analysis of psychometric properties of the scale (as discussed in Section 4.2.4) and will be specified in the SAP.

[redacted]

Assessment	Timing	Measurement
Global aesthetic improvement of the temple area	All in-office follow-up visits starting from Month 1	5-point ordinal scale from -2 to 2 (details in Table 8-2)
FACE-Q Satisfaction with Facial Appearance	Randomization and all in-office follow up visits starting from Month 1	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	Randomization and all in-office follow up visits starting from Month 1	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

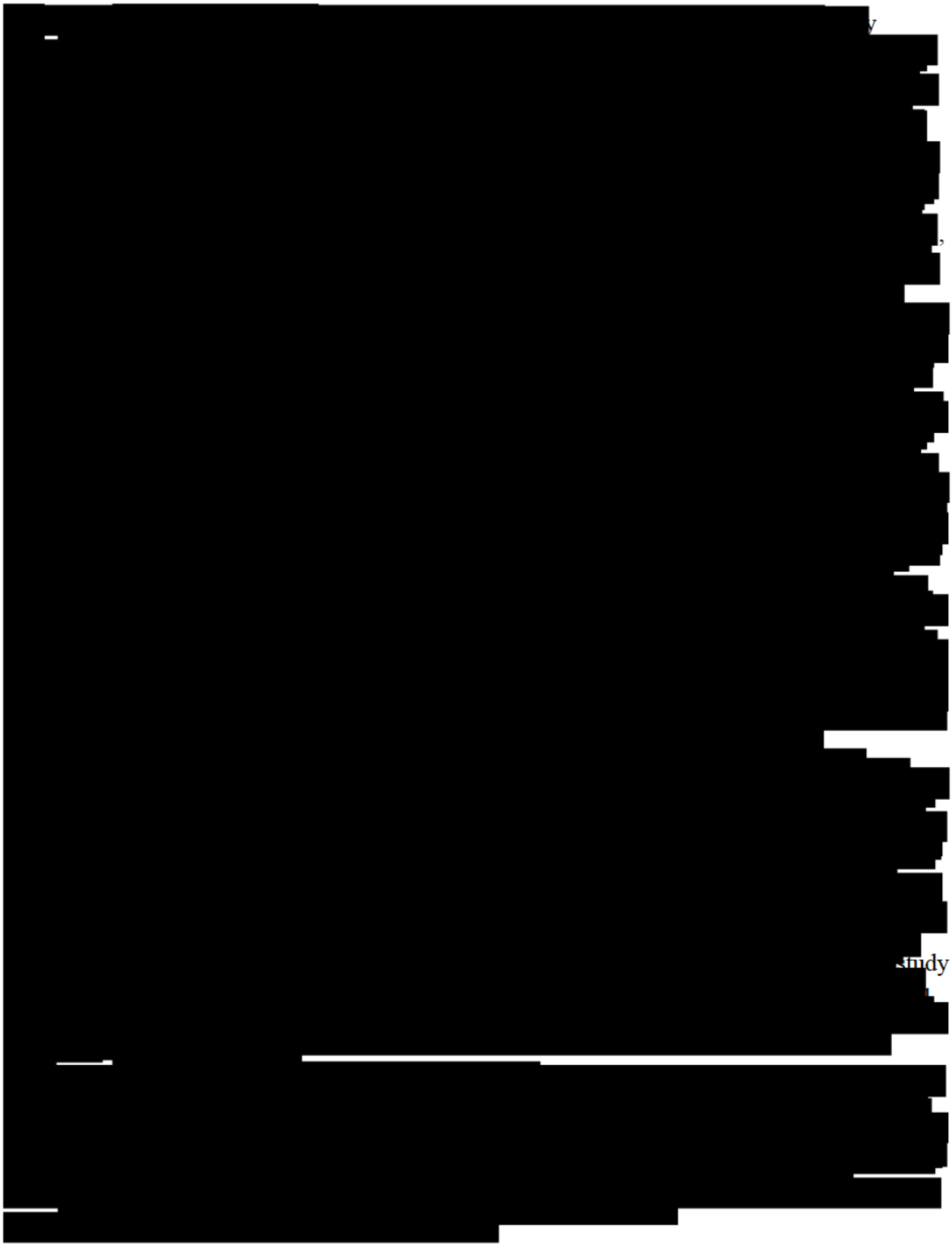
8.1.4. Other Effectiveness Measures

[redacted]

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)



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10.4. Appendix 4: Abbreviations

Abbreviation	Definition
3D	3-dimensional
AE	adverse event
AESI	adverse event of special interest
ATHS	Allergan Temple Hollowing Scale
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CE	Conformité Européene
DFU	directions for use
eCRF	electronic case report form
EI	Evaluating Investigator
GAIS	Global Aesthetic Improvement Scale
HA	hyaluronic acid
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IDE	investigational device exemption
IRB	institutional review board
ISO	International Organization for Standardization
ISR	injection site response
IWRS	interactive web response system
mITT	modified intent-to-treat
NCI	National Cancer Institute
NCT	national clinical trial number on www.clinicaltrials.gov
PI	Principal Investigator
PT	preferred term
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

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)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
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)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: 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, parallel-group, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for correction of temple hollowing
	Clinical Study Sponsor	Allergan
	Trial Phase Classification	Pivotal
	Trial Indication	Temple hollowing
	Trial Indication Type	Treatment
	Trial Type	Effectiveness Safety
	Trial Length	21 months
	Planned Country of Investigational Sites	US
	Planned Number of Subjects	213
	FDA-regulated Device Study	Yes
	FDA-regulated Drug Study	No
	Pediatric Study	No
Subject information	Diagnosis Group	Temple hollowing
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	22
	Planned Maximum Age of Subjects	None
	Sex of Participants	Both
	Stable Disease Minimum Duration	N/A
Treatments	Investigational Therapy or Treatment	JUVÉDERM VOLUMA® XC injectable gel
	Intervention Type	Device
	Pharmacological Class of Investigational Therapy	N/A
	Dose per Administration	[redacted]
	Dose Units	mL
	Dosing Frequency	Initial, touch-up, and maintenance (treatment group only) treatments
	Route of Administration	Injection
	Current Therapy or Treatment	N/A
	Added on to Existing Treatments	No
	Control Type	Delayed 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	Yes

10.7. Appendix 7: Medical Device AEs, ADEs, SAEs, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the investigator 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, ADE, and AESI

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 except for events in users or other persons, which only include events related to investigational devices.
- An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.
- An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's study device, which warrants ongoing monitoring and rapid communication by the PI to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. The following AESIs have been identified for the study intervention in this protocol: any incidence of visual disturbance (including, but not limited to, any loss of vision, blurry vision, double vision, pain in or around eye [excluding pain in temple area], blind spot or shadow in the visual field, trouble moving eyes, etc.).

10.7.2. Definition of SAE, SADE, and UADE

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

10.7.3. 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	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
MODERATE	An event that causes sufficient discomfort and interferes with normal everyday activities
SEVERE	An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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 DFU and DFU addendum 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
• See Section 8.3.3.

10.7.5. Reporting of SAEs

SAE Reporting to Sponsor or Designee
• Email is the preferred method to transmit SAE information. The email address is LC-Medical_Safety@Allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-877-605-4524 (backup number is +1-714-796-9567). • 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 PI to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.7.6. Reporting of SADEs

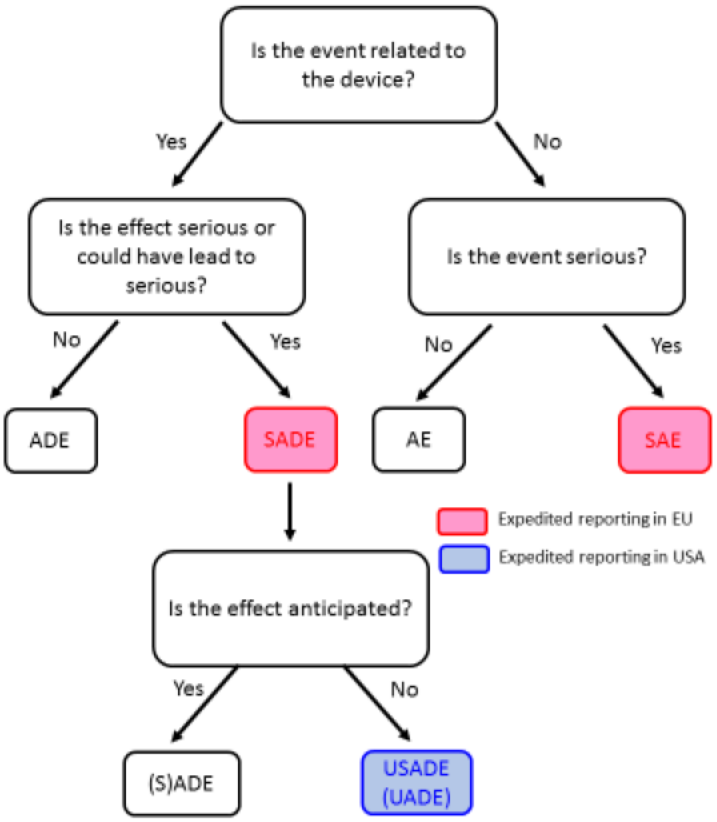
SADE Reporting to Sponsor or Designee
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating 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 IRBs as required by national regulations. • Contacts for SAE reporting can be found on the protocol title page.

10.7.7. Reporting of AESIs

AESI Reporting
• AESIs must be reported to the sponsor within 24 hours of awareness of the event by completing the appropriate eCRF and notifying Allergan study management personnel and the Medical Safety Physician by fax or email. • Contacts for SAE reporting can be found on the protocol title page. • Allergan will notify the FDA of any AESI within 10 days of Allergan's awareness of the event.

10.7.8. AE, ADE, SAE, SADE Determination Flow Chart

Adverse event reporting for countries other than the United States and European Union must follow the regulatory and ethical requirements for that country.



10.8. Appendix 8: Amendment 1 Summary of Changes

Amendment 1 (January 2020)

Overall Rationale for the Amendment:

Minor clarifications

Section # and Name	Description of Change	Brief Rationale
Table 1-6 Control Group Procedures: Delayed Treatment Period	Added to footnote d that a urine pregnancy test is among the assessments to be conducted for participants exiting the study prior to Month 6	To provide for pregnancy testing prior to study exit
5.2 Exclusion Criteria	Corrected exclusion criterion 4.02 to remove "not" and corrected numbering of exclusion criteria	To correct typo and formatting
8.1.3 Secondary Effectiveness Measures	Changed GAIS assessments from profile view photographs to frontal and lateral view photographs	To allow more complete views of the temple area in GAIS assessments