NCT03418545

Study ID: 1932-701-008

Title: A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLBELLA® XC injectable gel for correction of infraorbital hollowing

Statistical Analysis Plan Date: 16Dec2019

1. Title Page

STATISTICAL ANALYSIS PLAN

A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLBELLA® XC injectable gel for correction of infraorbital hollowing

Protocol Number:	1932-701-008
Development Phase:	Pivotal
Product Name:	JUVÉDERM VOLBELLA® XC injectable gel
Study Statistician:	[redacted]
Sponsor:	Allergan, plc. 2525 Dupont Drive Irvine, CA 92612

2. Table of Contents

2.1 List of Tables

3. List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
3D	3-dimensional
ADE	adverse device effect
AE	adverse event
AIHS	Allergan Infraorbital Hollows Scale
ATC	Anatomical Therapeutic Chemical
CFB	change from baseline
CI	confidence interval
CP	Control Period
eCRF	electronic case report form
EI	Evaluating Investigator
GAIS	Global Aesthetic Improvement Scale
HA	hyaluronic acid
ISR	injection site response
ITT	intent-to-treat
IWRS	Interactive Web Response System
LOCF	last observation carried forward
LS	least squares
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
PID	participant identification
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event
TI	Treating Investigator
TP	Treated Period
VIT	VOLBELLA Initially Treated
VOT	VOLBELLA Optionally Treated
VRT	VOLBELLA Repeat Treatment
WHO	World Health Organization

4. Introduction

This statistical analysis plan details comprehensive, technical specifications of the statistical analyses of the effectiveness and safety data outlined and/or specified in the final protocol Amendment 1 of Study 1932-701-008. Specifications of tables, figures, and data listings are contained in a separate document. This SAP will be approved prior to database lock.

4.1 Study Design Summary

4.1.1 Overall Design

This is a prospective, multicenter, evaluator-blinded, randomized, controlled study to evaluate the safety and effectiveness of JUVÉDERM VOLBELLA XC HA injectable gel to correct infraorbital hollowing. Once screened, participants will be randomized to either a treatment or control group. The treatment group will receive treatment at the start of the study and an optional touch-up treatment 1 month later. They will be followed for safety and effectiveness for 12 months with the option for a repeat treatment and an additional 1 month of follow-up. Participants randomized to the control group will complete a 3-month no-treatment control phase after randomization and will be offered optional treatment and optional touch-up treatment 1 month later. They will be followed only for safety for 9 months.

At screening, after written informed consent has been given, the TI will document the participant's demographic, height, weight, vital signs, Fitzpatrick skin phototype, and history of sun exposure, smoking, and medical, surgical, dental, and cosmetic procedures. Female participants of childbearing potential will undergo urine pregnancy tests. The EI will rate participants on the 5-point photonumeric AIHS to determine eligibility for the study. The TI will ensure the participant's anatomy is amenable to correction to an AIHS rating of 0 or 1 [redacted] Before randomization, participants will undergo [redacted] imaging. All participants will be randomized 3:1 to the treatment group or the control group and 1:1 to receive the first treatment on the right or left side. The same order must be used for all treatments.

Treatment group: Before treatment, participants randomized to the treatment group will complete the following assessments

- FACE-Q Appraisal of Lower Eyelids questionnaire
- TI (or designee) safety assessments
    - Snellen visual acuity using a Snellen eye chart
    - confrontational visual fields
    - ocular motility

The TI will use supplied 32G ½" needles and 27G 1½" cannulas (as provided by Allergan) based on the TI's preference to inject JUVÉDERM VOLBELLA XC submuscularly/supraperiosteally to correct infraorbital hollowing. Topical or local anesthesia or ice will be applied as necessary. [redacted]. The following assessments will be performed on the treatment day after treatment:

- TI assessments
    - product moldability
    - Snellen visual acuity [redacted]
    - confrontational visual fields [redacted]
    - ocular motility ([redacted]
    - AEs
    - Recording of concomitant medications and procedures
- Participant assessments
    - procedural pain on an 11-point scale
    - daily safety diary to record the presence and severity of ISRs for 30 days after treatment

Participants will receive a safety follow-up telephone call at 3 days after treatment. Participants will return for an office visit at 14 days after treatment to undergo [redacted] imaging, and the TI will perform all safety assessments. The participant will not see the blinded EI at the Day 14 visit. Thirty days after treatment, the participant and the TI will discuss the results of the initial treatment. [redacted]

[redacted], optional touch-up treatment may be performed if agreed upon by the participant and TI. The touch-up treatment visits, procedures, and follow-up are identical to those for the initial treatment. If no touch-up is performed, that visit becomes the Month 1 visit, and the visit is conducted as described below.

Routine follow-up visits for safety and effectiveness will occur at 1, 3, 6, 9, and 12 months after the last treatment. At each visit, the following assessments will be performed:

- [redacted]
- TI (or designee) safety assessments
    - ocular motility
    - AEs
    - Recording of concomitant medications and concurrent procedures
- EI effectiveness assessments
    - AIHS
    - improvement in the infraorbital hollows using the Global Aesthetic Improvement Scale (GAIS)
- EI safety assessments
    - presence or absence of Tyndall effect [redacted]
- Participant assessments
    - improvement in the infraorbital hollows using the GAIS, [redacted]
    - [redacted]
    - FACE-Q Appraisal of Lower Eyelids questionnaire
    - [redacted]
    - [redacted]
    - [redacted]

After completion of the Month 12 visit, participants will be offered an optional repeat treatment. Alternatively, participants will complete the study after all Month 12 visit procedures are complete. The procedures and assessments to be performed at repeat treatment and at follow-up

visits after repeat treatment are identical to those after the initial treatment, with the exception that no touch-up will be offered. Participants will be followed for 1 month after repeat treatment and then exit the study.

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

- AEs
- recording of concomitant medications and concurrent procedures
- EI effectiveness assessments
    - AIHS
    - [redacted]
    - improvement in the infraorbital hollows using the GAIS (Months 1 and 3 only)
- EI safety assessments
    - presence or absence of Tyndall effect [redacted]

After the Month 3 procedures are complete, participants will be offered optional treatment and will be followed for safety only for 9 months after last treatment. Control group participants who decline optional treatment will exit the study after the Month 3 visit procedures are complete.

The optional treatment visit for the control group will be identical to the treatment visit for the treatment group. Control participants who receive treatment will follow the same follow-up visit schedule as the treatment group, including optional touch-up, for 9 months after last treatment; however, only the following safety assessments will be performed at follow-up visits:

- [redacted]
- TI (or designee) safety assessments
    - Snellen visual acuity [redacted]
    - confrontational visual fields ([redacted]
    - ocular motility [redacted]

- AEs
- Recording of concomitant medications and procedures

- EI safety assessments
  - presence or absence of Tyndall effect [redacted]

4.1.2 Number of Participants

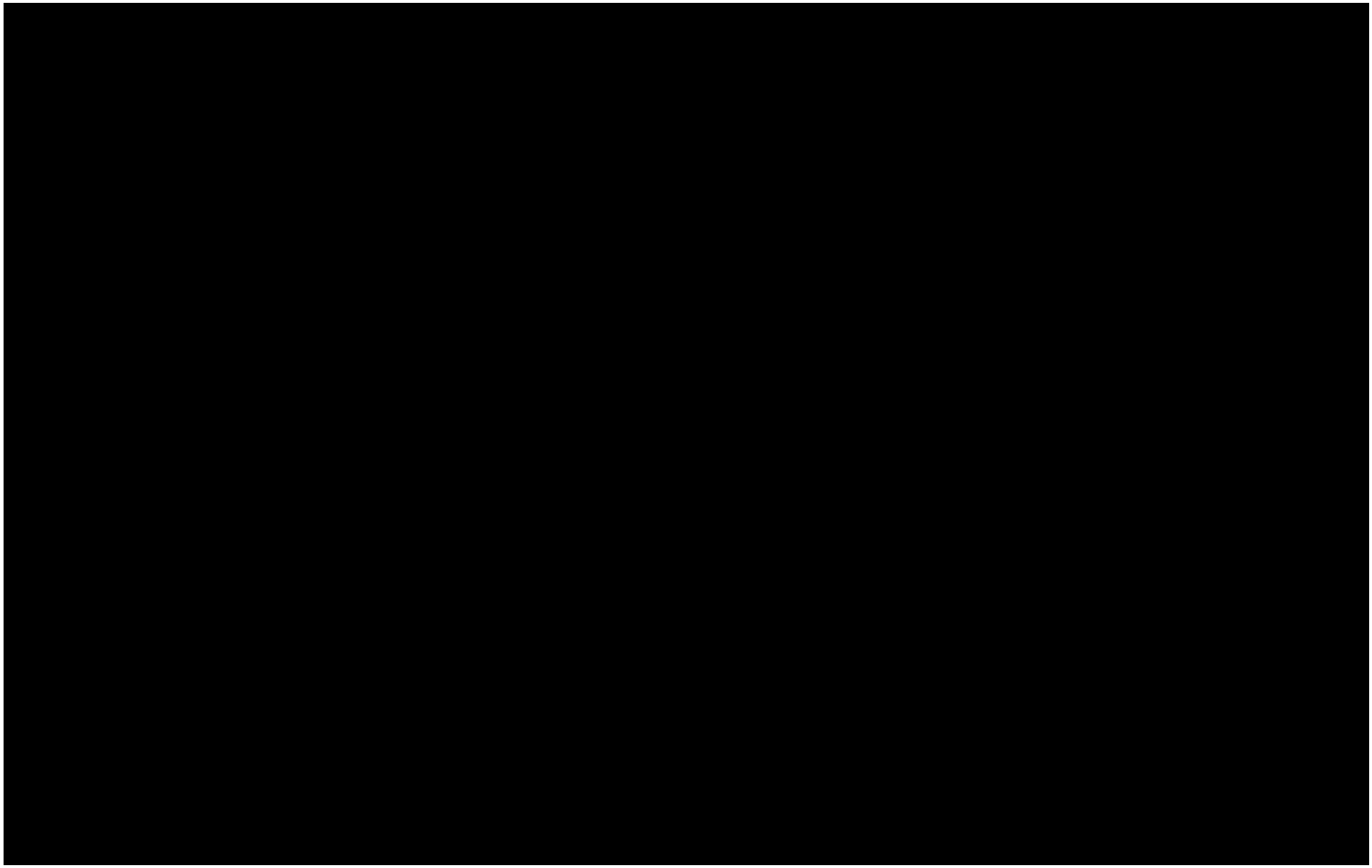
Up to 175 participants will be enrolled and 140 participants will be randomized at up to 15 US sites.

4.2 Study Objectives and Endpoints

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

Each study objective is presented with corresponding endpoints below:

Objectives	Endpoints
Primary • To evaluate the effectiveness of JUVÉDERM VOLBELLA XC injectable gel in adult participants seeking correction of infraorbital hollowing	**Primary Endpoint** • Responder rate on the AIHS at Month 3 after the last treatment. (A responder is defined as participants who show at least 1-point improvement from baseline on the AIHS in both infraorbital areas based on EI assessment. Baseline is defined as the EI assessment at screening.) **Secondary Endpoints** • Responder rate on the GAIS at Month 3 by EI and participant. (A responder is a participant who has Improved or Much Improved on GAIS.) • Participant responses on the FACE-Q Appraisal of Lower Eyelids questionnaire
• To evaluate the safety of JUVÉDERM VOLBELLA XC injectable gel in adult participants seeking correction of infraorbital hollowing	[redacted]



5. Statistical Methodology and Study Endpoints

5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This SAP will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included as an appendix to the CSR.

5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using SAS Version 9.3 or newer.

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Periods

- Participants will receive treatment at the outset of the study (treatment group) or have treatment delayed until Month 3 (control group). The delayed treatment for control group is optional and referred to as “Optional Treatment”.
- Participants in the treatment group may receive optional touch-up treatment at Day 30 or optional repeat treatment at the completion of Month 12.
- Participants in the control group may receive optional touch-up treatment at Day 30 after optional treatment.
- Analysis periods are defined in Table 5-1 below.

Table 5-1 Analysis period definition

Randomi-zation Group	Period	Treatment Group Label	Start Date	End Date
Treatment	CP	VOLBELLA	Initial treatment date	The date of effective assessment for Month 3. • If multiple assessments fall into Month 3 window, the date of the assessment included in the Month 3 analysis will be used as end date. • For participants who exit before Month 3, the end date is study exit date. • For participants with missing assessment at Month 3, the target day for Month 3 (Day 91) will be the end date.
	TP (12-Month)	VOLBELLA	Initial treatment date	Study exit date or date prior to repeat treatment, whichever is earlier
	Repeat Treatment Period	VOLBELLA	Repeat treatment date	Study exit date
Control	CP	Control	Randomization date	For participants who do not receive optional treatment: • If multiple assessments fall into Month 3 window, the date of the assessment included in the Month 3 analysis will be used as end date. • For participants who exit before Month 3, the end date is study exit date. • For participants with missing assessment at Month 3, the target day for Month 3 (Day 91) will be the end date. For participants who receive optional treatment: • The day before optional treatment
	TP (9-Month)	VOLBELLA Post-Control	Optional initial treatment date	Study exit date

5.1.1.1.2 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 5-2 Analysis Populations

Population	Definition	Study Treatment
mITT	• Participants who were randomized to study treatment (treatment group), received at least 1 study device treatment, and had baseline and at least 1 post-treatment assessment of the primary effectiveness variable • Participants who were randomized to the control group and have baseline and at least 1 follow-up assessment of the primary effectiveness variable	Randomized assignment
Safety	• Participants who were randomized to study treatment (treatment group) and received at least 1 study device treatment • Participants who were randomized to the control group	Actual received[a]
VIT Population	• Participants who were randomized and received VOLBELLA treatment at the beginning of the Control Period	Actual received
VRT Population	• Participants in the VIT population who received VOLBELLA repeat treatment	Actual received
VOT Population	• Participants who were randomized to control group and received VOBELLA optional treatment after the Control Period	Actual received

[a] If a randomized control participant does not receive the optional treatment, the actual received treatment will be assigned as control treatment.

Effectiveness analyses in the CP will be performed on the mITT population using the "as-randomized" assignment for each participant (i.e., if a participant randomized to the control group is treated inadvertently at the start of the study, the assessments for that participant will nonetheless be included in the control group analysis). Effectiveness analyses in the TP (12-Month) and Repeat Treatment Period will be performed on the VIT and VRT populations, respectively.

Safety analyses in the CP will be conducted on the safety population using the actual received treatment. Safety analyses in the TP (12-Month), Repeat Treatment Period, and TP (9-Month) will be performed on the VIT, VRT, and VOT populations, respectively.

5.1.1.1.3 Study Treatments

The following treatment groups are defined for this study:

- Study Treatment: JUVÉDERM VOLBELLA XC injectable gel
- Control Treatment: No-treatment

5.1.1.1.4 Statistical Methodology

When indicated, 95% 2-sided CIs and 2-sided p-values will be presented. Individual endpoint analyses may specify exceptions (additions or deletions) to these general definitions.

Descriptive statistics will be presented for key outcome measures. Categorical variables will be summarized with frequency and relative frequency. Continuous variables will be summarized by number of participants, mean, median, standard deviation, 1st and 3rd quartiles, minimum, and maximum. Where appropriate, 2-sided 95% CIs for population mean, or population proportion, will be provided as part of the descriptive summary. 2-sided p-values will be presented when indicated.

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

5.1.1.1.5 Missing Data

Missing data handling conventions for the primary endpoint is specified and summarized as follows:

Table 5-3 Missing Data Handling by Endpoint Type

Parameter type	Timing	Missing Data Handling
Responder	Month 3 (treatment period for treatment group and control period for the control group)	• All participants included (mITT population) • Multiple imputation with 5 imputed datasets is applied to participants with no Month 3 values using the below model: Month 3 AIHS = β_0+β_1Baseline AIHS + β_2Month 1 AIHS. This is performed by treatment group and by side (left and right).
Responder	Month 3 (treatment period for treatment group and control period for the control group)	• All participants included (mITT population) • LOCF for participants with no Month 3 values

Note: Missing baseline will be replaced with the average of all non-missing baseline values of all participants.

5.1.1.1.6 Site Pooling

The impact of investigational sites on the primary effectiveness analysis at Month 3 will be evaluated by including investigational site, treatment assignment, and their interaction as predictor variables in a multivariable logistic regression analysis with response status on the AIHS as the dependent variable. The interaction between site and treatment will be considered significant if the p-value of this interaction is less than 0.10. Investigational sites with few enrolled participants may be pooled with other sites based on participant enrolled, geographical region, or other site characteristics.

5.1.1.2 Demographics

5.1.1.2.1 Analysis Populations

Number of participants in each analysis population (described in Section 5.1.1.1.1) will be provided using all randomized or treated participants.

5.1.1.2.2 Participant Disposition

Study disposition including number of participants screened, randomized, treated, received touch-up treatment, repeat treatment, completed, discontinued from the study, as well as eCRF-reported reasons for discontinuation will be summarized using all screened participants.

5.1.1.2.3 Protocol Deviations

Protocol deviations will be defined in a separate document, including significance classification. Significant protocol deviations will be summarized using all randomized or treated participants.

5.1.1.2.4 Demographics

Demographics including age, sex, race, ethnicity will be summarized for the Safety Population in total and by treatment group.

5.1.1.2.5 Baseline Characteristics

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

- Weight (kg), height (cm), and BMI (kg/m2)
- Sun exposure (hours per day)

- Fitzpatrick skin phototype (each phototype, and by phototype groups, ie, I and II, III and IV, V and VI)
- Smoking history (status, tobacco product, frequency, and duration in months)
- Transient puffiness

5.1.1.2.6 Medical and Surgical History

Medical and surgical history as well as physical findings reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1 or newer. Participants who report medical and surgical history events that are ongoing at screening and not ongoing at screening will be summarized separately for the Safety population.

5.1.1.2.7 Prior and Concomitant Medications

Medications will be coded using the WHO Drug Dictionary, version MAR2017 or newer. Prior and concomitant medication will be presented in a data listing using the Safety population.

Table 5-4 Medication

Parameter	Description
Prior medications	Medications taken before the study treatment start date and time for the treatment group and before randomization date and time for the control group, regardless of medication end date
Concomitant medications	Medications taken on or after the study treatment start date and time for the treatment group and after randomization date for the control group, regardless of medication end date

If a medication's start date and stop date are missing or the start date is before the first study treatment start date and stop date is missing or after the first study treatment start date for treatment group or after randomization date for control group, the medication will be considered as both prior and concomitant medications.

5.1.1.3 Effectiveness Analyses

Effectiveness analyses in the CP will be based on the mITT Population. Effectiveness analyses in the TP (12-Month) and Repeat Treatment Period will be performed on the VIT and VRT populations, respectively. Effectiveness assessments are defined as follows:

Table 5-5 Effectiveness Assessments

Assessment/Term	Description
AIHS	Assessed by the EI 0 - None 1 - Mild 2 - Moderate 3 - Severe 4 - Extreme
GAIS	Assessed by participant and EI based on 5-point GAIS 2 - Much improved 1 - Improved 0 - No change -1 -Worse -2 - Much worse
FACE-Q appraisal of lower eyelids	Participant responses to the following question on a scale 1-Not at all 2-A little 3-Moderately 4-Extremely Questions include if they are bothered by Excess fat under eyes Excess skin under eyes Puffiness under eyes How noticeable are the lines under eyes Crepey (wrinkled) skin under eyes How old the area under the eyes makes them look How tired the area under the eyes makes them look
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Baseline assessments for applicable effectiveness endpoints defined as follows:

Table 5-6 Effectiveness Endpoint Baseline Definitions

Endpoint	Description
• AIHS (EI)	Baseline refers to the evaluation at screening
• FACE-Q Appraisal of Lower Eyelids module [redacted]	Baseline refers to the evaluation at randomization or initial treatment

5.1.1.3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the responder rate at Month 3 after the last treatment. A responder is defined as a participant who shows at least 1-point improvement from baseline on the AIHS in both infraorbital areas based on EI assessment. Baseline is defined as the EI assessment at screening.

For the primary effectiveness analysis, a 2-sided, Fisher's exact test at the 5% level will be used to test whether the responder rate at Month 3 in the treatment group is significantly greater than that in the control group at Month 3 in the control period. The 95% CI by Wald test will be provided.

The primary effectiveness analysis will be performed on the mITT population using multiple imputation, as specified in Section 5.1.1.1.5. Sensitivity analysis will be performed using as-observed and LOCF data, as described in Section 5.1.1.1.5.

Descriptive analysis on the responder rates in the TP (12-Month) for the VIT population will also be provided. The responder rate from the treatment group at Month 3 will also be summarized by the primary injection instrument used (needle or cannula) and by median volume injected.

5.1.1.4 Secondary Effectiveness Endpoint

The secondary effectiveness analyses will include the responder rates with 95% CIs for the treatment group based separately on the EI and participant assessments of GAIS, where a "responder" is a participant who shows improvement in the overall aesthetic assessment in the infraorbital area (Improved or Much Improved on GAIS) at the Month 3 Visit, and participant responses on the validated Appraisal of Lower Eyelids module of the FACE-Q questionnaire. A 2-sided paired t-test at the 5% level will be performed to demonstrate that the mean overall satisfaction score at Month 3 visit is statistically greater than that at baseline for the treatment group.

The secondary effectiveness analysis for Satisfaction with validated Appraisal of Lower Eyelids module of the FACE-Q questionnaire will be conducted only if the primary endpoint is met. No additional multiplicity adjustment or gatekeeping multiple comparisons procedures are needed.

5.1.1.5.1 Study Treatment Exposure

Study treatment exposure will be measured by volume injected at each treatment. Summary of volume injected will be provided by side of the face at initial, touch-up, and repeat treatments as well as the combination of the initial and touch-up treatments.

5.1.1.6 Administration of Study Treatment

Variables related to administration of treatment listed below will be summarized for safety population by treatment group and by side of the face if appropriate at initial, touch-up and repeat treatment as follows:

- Pretreatment anesthesia type (ice, topical, and local)
- Planes of injection [redacted]
- Injection technique [redacted]
- Injection instrument (needle, cannula, or both)
- Primary injection instrument used (needle or cannula)
- Injection ease (0 [Difficult] to 10 [Easy] scale)
- Product moldability (0 [Stiff] to 10 [Moldable] scale)

5.1.1.6.1 Adverse Events

An AE will be considered a TEAE if:

- The AE began on or after the date of the first dose of study intervention; or
- The AE was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first dose of study intervention; or
- For the control group, AE began on or after the date of randomization; or
- For the control group and prior to the initial treatment, if AE was present before randomization, but increases in severity on or after randomization date, the AE is considered as TEAE.

An AE will be considered a treatment-emergent SAE if it is a TEAE that additionally meets any SAE criteria.

AEs and encompassing abnormalities, reported as occurring after the Screening Visit, will be coded using MedDRA version 20.1 or newer. A listing for all TEAEs in the treatment and control groups will be presented. AEs that occur before initial treatment for the treatment group and randomization for the control group will be listed. Additionally, unique participants reporting AEs as well as the number of events in the following AE categories will be summarized for treatment participants, control participants after optional treatment, and all treated participants as follows:

Table 5-7 AE Summaries

Endpoint	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • TEAEs • Treatment-related TEAEs • Treatment-related TEAEs at injection site • Treatment-related TEAEs not at injection site • SAEs • Treatment-related SAEs • Treatment-related SAEs at injection site • Treatment-related SAEs not at injection site • Discontinued due to TEAE • Deaths	• CP • TP (12-Month) • Repeat Treatment Period • TP (9-Month)	Categorical counts, Event descriptive
TEAEs	• Overall Summary and by SOC, PT		Categorical counts, Event descriptive
TEAEs	• Overall summary and by SOC, PT and severity		Categorical counts, Event descriptive
Treatment-related TEAEs	• Overall summary and by SOC, PT		Categorical counts, Event descriptive
	• Overall summary and by SOC, PT and severity		
	• Summary by duration, time to onset, severity, causality, treatment required, and outcome		

Note: SOCs and PTs will be sorted in descending frequency in the treatment group, then control group.
AEs for control group before and after optional treatment are summarized separately.

For participants who receive repeat treatment, their AEs reported during the first months in the initial treatment period will be summarized and presented in parallel with AEs reported during the repeat treatment period.

Overall summary by severity for TEAEs and treatment-related TEAEs will also be summarized by the primary injection instrument used (needle vs cannula).

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.

Time to onset for TEAEs will be computed as

AE start date - reference date + 1,

where the reference date is initial treatment date for TEAEs occurring on or after initial treatment but before touch-up treatment and the reference date is touch-up treatment date for TEAEs occurring on or after touch-up treatment but before repeat treatment.

Duration for TEAEs will be computed as AE end date – AE start date + 1. If AE end date is not available, duration for TEAEs will not be computed.

5.1.1.7 ISR

ISRs recorded in participant diaries after each treatment (initial, touch-up, and repeat) will be summarized during that treatment by pre-defined symptoms.

Table 5-8 ISR Analyses

Endpoint	Description	Timing	Methodology
ISR severity	Maximum reported severity.	Initial, Touch-up, Repeat	Categorical counts
ISR duration	Duration from first instance of the ISR to the last instance of the ISR within the treatment period, where last instance means no further symptoms until the end of the 30-day diary collection period	Initial, Touch-up, Repeat	Categorical counts

ISR severity and ISR durations analyses described in Table 5-8 will also be summarized by the primary injection instrument used (Needle vs Cannula).

If a participant reported more than one “Other” ISR, the participant will be counted once in the summary for that treatment. If the incidence of any particular category of “Other” ISRs is greater than 5%, then the severity and duration analyses described in Table 5-8 will be performed for that specific category of the “Other” ISR.

[redacted]

[redacted]

5.1.1.9 Vital Signs

Vital signs will be provided in a listing.

5.1.1.10 Pregnancy Test Analyses

Urine pregnancy test is performed (for female participants of childbearing potential) at screening, randomization, prior to every treatment (initial, touch-up, and repeat), and study exit. Participants with a positive result will be presented in a listing.

5.1.1.11 Interim Analyses

No interim analysis is planned for this study.

5.1.2 Determination of Sample Size

[redacted]

[redacted]

Table 5-10 Sample Size Assumptions

Parameter	Assumption/Estimate
Primary endpoint	[redacted]
Risk difference	
A	
Sides	
Power	
N per group	
N total	

5.2 Changes in the Conduct of the Study or Planned Analyses

The primary analysis was changed from as-observed to multiple imputation so that all participants in the mITT will be used for statistical inference.

5.2.1 Changes in the Conduct of the Study

Not applicable.

5.2.2 Changes to Analyses Prior to Database Lock

Not applicable.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

Treatment day for effectiveness, ISR, and AE are defined as follows:

Table 6-1 Analysis Day Definitions

Term	Description
Effectiveness: Effectiveness Day	JUVÉDERM VOLBELLA XC and control (only the control participants receiving optional treatment): Relative to the last treatment date (either the initial treatment, if no touch-up is performed, or the touch-up treatment, repeat treatment) • Effectiveness Day = analysis date - last treatment start date + 1 o Effectiveness Day 1 = last treatment start date Control (before receiving optional treatment): Relative to the randomization date • Effectiveness Day = analysis date - randomization date +1 • Effectiveness Day 1 = randomization date
Safety (including AE and ISR): Safety Day	JUVÉDERM VOLBELLA XC and treated control (only the control participants receiving optional treatment): Relative to treatment date (initial and touch-up) Safety Day = analysis date - treatment date + 1 Safety Day 1 = treatment date Control (before receiving optional treatment): Relative to the randomization date • Safety Day = analysis date - randomization date +1 • Safety Day 1 = randomization date JUVÉDERM VOLBELLA XC Only: Relative to the repeat treatment date (after repeat treatment) • Safety Day = analysis date - repeat treatment date + 1 • Safety Day 1 = repeat treatment date

6.2 Analysis Visit Windows

All scheduled and unscheduled visits with complete dates will be assigned visit windows and used for analysis. However, if a scheduled visit with incomplete date is available with no other visits with complete date during the visit window, then the visit with incomplete date may be used for analysis and the nominal visit will be used as the visit window (eg, if the only assessment collected for Month 3 visit window is on a Month 3 eCRF with incomplete date, then those data will be used for the Month 3 assessments).

If there are multiple visits occurring within a single visit window with relevant data, the visit closest to the target day will be used in the analysis of the corresponding visit windows. If 2 visits are equal distance to the target day and are the same type of visit, then the later visit will be used.

Analysis visit windows for effectiveness endpoints and safety are defined as follows.

6.2.1 Effectiveness

The analysis visit windows for effectiveness endpoints are defined as follows:

Table 6-2 **Effectiveness Analysis Visit Definitions for Treatment Group and Control Group during Treatment Period**

Scheduled Visit for Effectiveness Measure	[redacted]
Screening[a]	
Touch-up Treatment[b]	
Last Treatment[c]	
Month 1	
Month 3	
Month 6	
Month 9	
Month 12	
Repeat Treatment[d]	
Month 1 Repeat	

[a] Participants may have scree
[b] Not all participants will receive touch-up treatment
[c] Initial treatment if touch-up is not performed, otherwise touch-up treatment
[d] Not all participants will receive repeat treatment

Table 6-3 **Effectiveness Analysis Visit Definitions for Control Group during Control Period**

Scheduled Visit	[redacted]
Randomization Day	
Month 1	
Month 3	

6.2.2 Safety

No analysis visit windows are required for TEAEs and ISRs. Nominal visit will be used for summarizing Snellen visual acuity, ocular motility, and Tyndall effect.

6.3 Missing/Incomplete Date Conventions

Dates may be imputed with year, month, and day values under certain scenarios:

Table 6-4 Imputation Scenarios

Scenario	Complete			Imputable
	Year	Month	Day	
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	No[a]
4	Yes	—	—	Yes
5	—	Yes	Yes	No[a]
6	—	Yes	—	No[a]
7	—	—	Yes	No[a]
8	—	—	—	Yes

[a] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

Table 6-5 Initial Imputed Date Algorithm

Available Year (YYYY)	Available Month (MM)			
	Missing	< Target Month	= Target Month	> Target Month
Missing	Target Date	—		
< Target Year	YYYY-12-31	YYYY-MM-LD		
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	YYYY-MM-01		

LD = last day of the month; MM = available start date month; YYYY = available start date year.

6.3.1 Missing/Incomplete AE Start Date

Imputation of dates with missing day and/or month is only applied to TEAEs. If adequate information is available, no imputation is needed. TEAE start dates with missing day or month will be imputed as following:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan or the initial treatment date if they have the same year, whichever is later (because TEAE onset is not expected prior to administration of study treatment)
- If day is missing but the month and year are available, then the imputed day will be the first day of the month or the initial injection date if they have the same month and year, whichever is later.

6.3.2 Missing/Incomplete AE/Medication End Date

Imputation of dates with missing day and/or month is only applied to TEAEs when AE duration is calculated. If adequate information is available, no imputation is needed. TEAE end dates with missing day or month will be imputed as following:

- If day and month are missing but year is available, then the imputed day and month will be 31 Dec or the study exit date if they have the same year, whichever is earlier

If day is missing but the month and year are available, then the imputed day will be the last day of the month or the study exit date if they have the same month and year, whichever is earlier.

6.4 Safety Endpoint Conventions

6.4.1 Adverse Events

6.4.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

Table 6-6 Missing AE Intensity and Relationship Imputation Algorithms

Missing Value	Imputation	Timing
Intensity	Mild	Screening Period, Pretreatment Period,
	Severe	Treatment Period
Relationship	—	Screening Period, Pretreatment Period
	Related	Treatment Period

6.4.1.2 Character Values

Character values (eg, < 5, negative) will be reviewed prior to database lock and converted to numeric values for analysis as appropriate. These conversions will be documented in the ADaM specifications.

6.5 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in endpoint derivation. In instances where imputed values will be presented, imputed values will be flagged. Actual rules will be fully defined in the table, figure, and data listing specification document.

7. SAP Version History

SAP Version History Summary		
SAP Version	**Approval Date**	**Change**
1	May 1, 2018	Not Applicable
2	Mar 11, 2019	• Clarify safety population definition • Change ISR days to ISR duration • Clarify prior and concomitant medication definition • Editorial changes
3		• Defined analysis periods • Add VIT population • Add VRT population • Add VOT population • Changed primary endpoint analysis from as-observed to multiple imputation • Editorial changes
		• Removed change from baseline analysis for assessment of dark circles and individual FACE-Q items
		• Included the FACE-Q – Appraisal of Lower Eyelids questionnaire in the Appendix