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Study ID: 1650-801-008

Title: A Multicenter, Single-blind, Randomized, Controlled Study of the Safety and Effectiveness of JUVÉDERM VOLUMA® XC Injectable Gel for Cheek Augmentation Using Cannula

Statistical Analysis Plan Date: 13 July 2018

1. Title Page

STATISTICAL ANALYSIS PLAN

A Multicenter, Single-Blind, Randomized, Controlled Study of the Safety and Effectiveness of JUVÉDERM VOLUMA® XC Injectable Gel for Cheek Augmentation Using Cannula

V2.0: 2018-07-12

Study Number:	1650-801-008
Development Phase:	Post-market
Product Name:	JUVÉDERM VOLUMA® XC injectable gel
Sponsor:	Allergan 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
AE	Adverse event
BMI	Body mass index
BOCF	Baseline observation carried forward
Cannula	JUVÉDERM VOLUMA® XC injectable gel using cannula
CI	Confidence interval
eCRF	Electronic case report form
EI	Evaluating Investigator
ISR	Injection site response
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MFVDS	Mid-Face Volume Deficit Scale
MI	Multiple imputation
mITT	Modified intent-to-treat
PP	Per-protocol
PT	Preferred term
Needle	JUVÉDERM VOLUMA® XC injectable gel using needle
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TI	Treating Investigator
TEAE	Treatment-emergent adverse event
TR-TEAE	Treatment-related treatment-emergent adverse event

4. Introduction

This statistical analysis plan (SAP) details the statistical analyses of the effectiveness and safety data described in the protocol of study 1650-801-008 (original dated 19Oct2017). 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-blind, randomized, within-subject, controlled, paired-comparison study of the safety and effectiveness of VOLUMA XC injectable gel using a cannula versus needle for cheek augmentation to correct age-related volume deficit in the mid-face.

Subjects eligible for study enrollment should have cheeks that are either moderate for both cheeks, significant for both cheeks or severe for both cheeks, as assessed by the EI using the 6-point photonumeric Mid-Face Volume Deficit Scale (MFVDS), ranging from 0-5 (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = significant, 5 = severe).

Eligible subjects will be randomized to undergo treatment with cannula in the right or left cheek and with needle in the other cheek (ie, treatment groups will be "cannula left and needle right" or "needle left and cannula right). Prior to randomization, the subjects' demographic information and cosmetic, medical, surgical and dental history will be recorded. Physical measurements and vital signs will be collected, and a urine pregnancy test will be conducted for women of childbearing potential.

The Treating Investigator (TI) and subject will not be blinded to treatment assignment. The Evaluating Investigator (EI) is to remain blinded to treatment assignments for each cheek throughout the duration of the study. Hence, this is considered to be a single-blind study, although some measurement variables are unblinded (eg, injection ease rated by the treating investigator and procedural pain rated by the subject).

Immediately after treatment, subjects will rate procedural pain (pain during injection) separately for the right and left cheeks on an 11-point scale, [redacted] The subject will complete a daily safety diary for 30 days after the treatment session beginning on the day of treatment. Subjects will

return 1 month after treatment, and the TI will evaluate the treatment areas for localized reaction and will review the safety diary with the subject and discuss reported symptoms.

Subjects will attend follow-up visits for safety and effectiveness at Months 1 and 3 after treatment. Safety and effectiveness assessments will be performed at posttreatment follow-up visits. The EI will rate subjects on the MFVDS for each cheek, the TI (or designee other than EI) will record any adverse events (AEs), and subjects will complete the Satisfaction with Cheeks module of the FACE-Q questionnaire. At the month 3 visit, a urine pregnancy test will be performed for female subjects of childbearing potential. Subjects will be exited from the study at the Month 3 visit after study procedures are completed.

4.1.2 Number of Subjects

Up to 75 subjects will be screened at up to 7 sites in order to have an estimated 60 subjects treated.

4.2 Study Objectives and Endpoints

The objective of this study is to evaluate the safety and effectiveness of VOLUMA XC injectable gel using cannula in subjects seeking correction of age-related volume deficit in the mid-face.

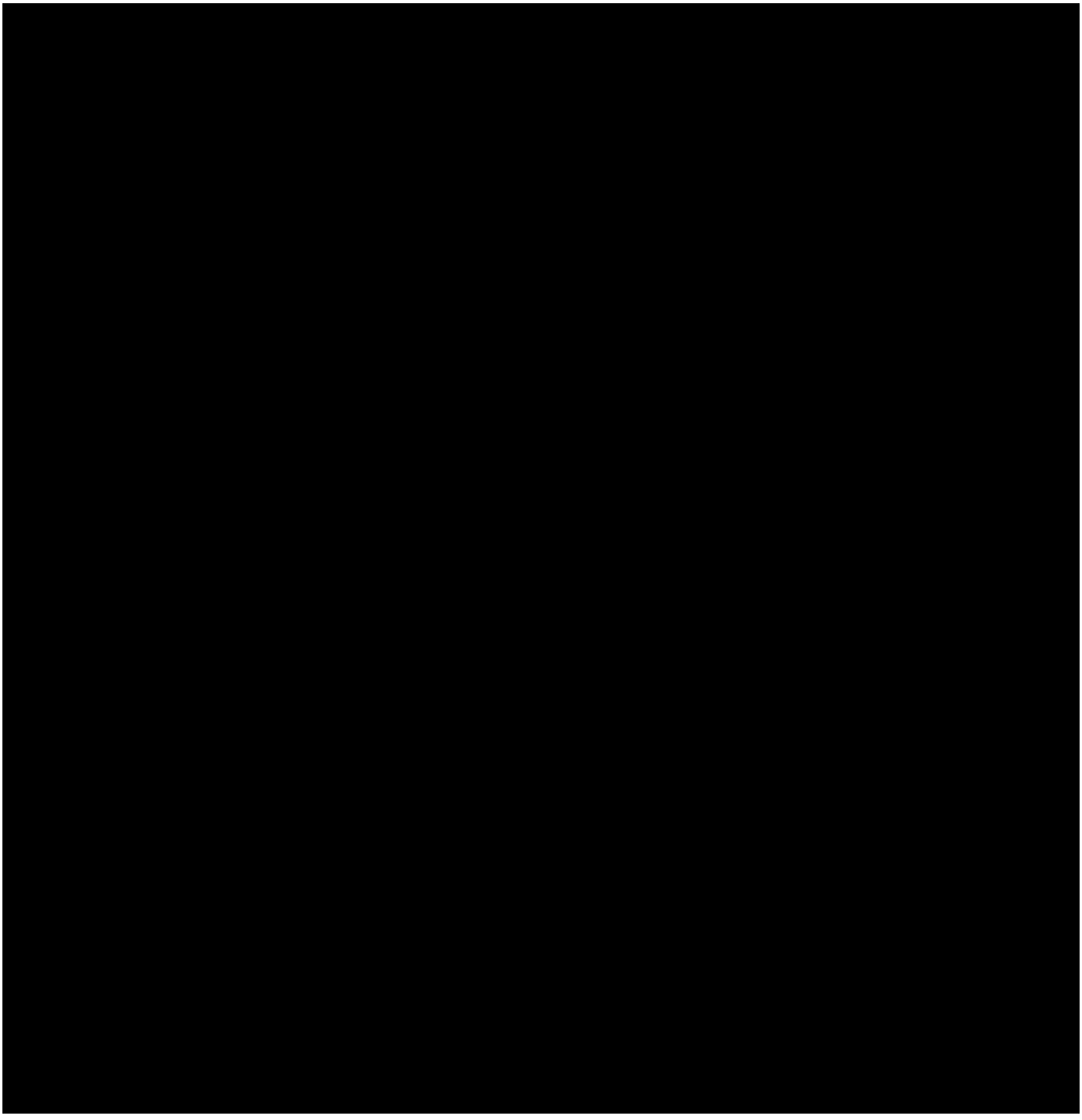
The study primary objective, secondary objective, and other objectives are presented with corresponding endpoint(s) below:

Table 4-1 Study Objectives and Corresponding Endpoints

Objectives	Endpoints
• To evaluate the safety and effectiveness of cannula versus needle for the correction of age-related volume deficit in the mid-face.	Primary Endpoint : • MFVDS response distribution by treatment, based on EI assessment on a 6-point scale of ordinal categories, from 0 to 5 (none, minimal, mild, moderate, significant, severe), for baseline and change from baseline to month 1 (primary endpoint) [redacted] Secondary Endpoints: • MFVDS responder rates by treatment, based on EI assessments on a 6-point scale of ordinal categories, from 0-5 (none, minimal, mild, moderate, significant, severe), with responders defined as ≥1 grade improvement from baseline, for month 1 (primary measurement time) [redacted] • Subject's FACE-Q Satisfaction with Cheeks, at the subject level rather than by treatment (because the questions are asked regarding the face rather than the treatment sides), for the

	FACE-Q Rasch transformed score (0-100), which is converted from the sum score (range 5-20) across 5 items (symmetric, smooth, attractive, contour, and fullness), with each item scored on an ordinal scale from 1 to 4 (very dissatisfied, dissatisfied, satisfied, very satisfied); the FACE-Q Rasch score will be summarized for baseline and change from baseline to month 1 (primary measurement time) [redacted] [redacted] Safety Assessments • AEs, separately for AEs at cheeks, not at cheeks and combined • Procedural Pain, based on subject assessment on an 11-point scale, [redacted] response distribution by treatment, and paired treatment comparison of each subject's difference score (-10 to +10) • Injection Site Responses (ISR), based on subject's 30-day diary, overall and for each of 10 categories (redness, pain after injection, tenderness to touch, firmness, swelling, lumps/bumps, bruising, itching, discoloration and other), response distribution by treatment, separately for presence, severity (none, mild, moderate, severe), number of ISR days (none, 1-3, 4-7, 8-14 and 15 or more), and total duration (none, 1-3, 4-7, 8-14 and 15 or more days).

4.3 Schedule of Activities



5. Statistical Methodology and Study Endpoints

5.1 Statistical and Analytical Plans

Statistical analyses will be conducted using [redacted]

5.1.1 Common Conventions

5.1.1.1 Analysis Populations

The analysis populations will consist of subjects as defined below:

Table 5-1 Analysis Populations

Population	Definition	Analysis Treatment
Screened	All screened subjects who signed the informed consent	—
Intent-to-Treat (ITT)	All randomized subjects	Actual treatment received
Modified Intent-to-Treat (mITT)	All randomized subjects who received treatment with cannula on 1 cheek and treatment with needle on the contralateral cheek	Actual treatment received
Per Protocol (PP)	All mITT subjects who did not have any significant protocol deviations that could affect the primary endpoint and who received each assigned treatment on the assigned side. A significant deviation that occurred after the primary endpoint would not lead to exclusion from the PP analysis.	Actual treatment received (identical to as randomized, by PP definition)
Safety	All randomized subjects who received ≥ 1 study treatment	Actual treatment received

Analyses of safety variables will be performed on the safety population. Unless specified otherwise, all other analyses will be performed on the mITT population. The PP population will be used to perform PP sensitivity analyses for the primary and secondary effectiveness variables.

Analyses will be based on treatment received, regardless of randomization assignment (ie, "as treated" rather than "as randomized"), in order to prevent bias towards study success (non-inferiority) that would be due to randomization errors that reverse the direction of the paired comparison. In addition, the mITT population will be used to do an "as randomized" sensitivity analysis for the primary effectiveness variable. That will not be necessary for the PP population, since it will exclude subjects who were not treated as randomized.

5.1.1.2 Study Treatments

The following paired-comparison treatments are defined for this study:

- Study Treatment: JUVÉDERM VOLUMA® XC injectable gel using cannula
- Control Treatment: JUVÉDERM VOLUMA® XC injectable gel using needle

5.1.1.3 Statistical Methodology Types

The methodologies defined below apply as specified to individual endpoints defined in this SAP.

[redacted]

5.1.1.4 Missing Data

If there are any mITT subjects with missing scores for the primary effectiveness endpoint, the following 2 missing-data handling methods are pre-specified to use for missing-data sensitivity analysis of the primary effectiveness endpoint. For each method, there will be no missing baseline MFVDS, because protocol inclusion criteria 2 requires a score of 3, 4 or 5.

Table 5-3 Missing Data Handling by Endpoint Type

Endpoint type	Timing	Missing Data Handling
Categorical Response	Month 1	• All subjects included (mITT population) • Multiple imputation (eg, via SAS procedure MI) within treatment, with 5 imputed datasets, will be applied to subjects with missing post-baseline MFVDS scores, using the following model: Month 1 MFVDS = β_0+β_1 Baseline MFVDS + β_2 Month 3 MFVDS [redacted]
Categorical Response	Month 1	▪ All subject included (mITT population) ▪ Baseline observation carried forward (BOCF) for subjects with missing post-baseline MFVDS values.

5.1.1.5 Site Pooling

The impact of investigational sites (not investigator, but site) on the primary effectiveness analysis at Month 1 will be evaluated by ANOVA modeling of the treatment difference in MFVDS score change from baseline as a function of investigational site. Investigational sites with fewer than 6 enrolled subjects will be pooled with other such sites.

5.1.2 Demographics and other Baseline Descriptions

5.1.2.1 Analysis Populations Distributions

The distribution of subjects within the analysis populations will be summarized as follows:

Table 5-4 Analysis Population Summaries

Population	Description	Timing	Methodology
Screened	Distribution of All Randomized, Randomized but Discontinued Before Treatment, Unrandomized, Reason not Randomized	Screening period	Categorical counts
Unrandomized	List unrandomized subjects with reasons not randomized	Screening period	Listing
ITT, mITT, PP and Safety	Distribution in total and, for the safety population, if not all treated subjects receive each of the paired treatments, by treatment group	After randomization	Categorical counts

5.1.2.2 Subject Disposition

Subject disposition encompasses the distribution of subjects who enter, complete, and discontinue during each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Subject disposition will be summarized as follows:

Table 5-5 Subject Disposition Summaries

Endpoint	Description	Timing	Methodology
Study disposition	Distribution in the randomized (ITT) subjects in total	Month 1 and final	Categorical counts

5.1.2.3 Protocol Deviations

Protocol deviations will be defined in a separate document, including importance classification. Protocol deviations will be summarized as a data listing, as follows:

Table 5-6 Protocol Deviation Summary

Endpoint	Description	Timing	Methodology
Significant protocol	Significant protocol deviation will be listed	—	listing

Endpoint	Description	Timing	Methodology
deviations			

5.1.2.4 Demographics

Demographics will be summarized for the mITT population in total as follows:

Table 5-7 Demographic Summaries

Endpoint	Description	Timing	Methodology
Age	Age (years) at informed consent date	Informed consent	Continuous descriptives
Age group	• < 40 years • 40-65 years • ≥ 66 years (none expected)	Informed consent	Categorical counts

Sex, race, and ethnicity	• eCRF categories
	• Race group
	  ○ White
	  ○ Black or African American
	  ○ Asian
	  ○ American Indian or Alaskan Native
	  ○ Native American or Native Pacific Islander
	  ○ Other
	• Ethnicity
	  ○ Hispanic or Latino
	  ○ Not Hispanic or Latino
		Screening Period	Categorical counts

5.1.2.5 Baseline Characteristics

Baseline characteristics will be summarized in total for the mITT population and, if it differs, the safety population as follows:

Table 5-8 Baseline Characteristics Summaries

Endpoint	Description	Timing	Methodology
Baseline characteristics	• Height (m) • Weight (kg) • Body mass index (BMI) ○ Weight (kg) / height $(m)^2$ • Body mass index (BMI) category (<18.5, 18.5-<25, 25-<30, ≥30) • Fitzpatrick skin phototype (I, II, III, IV, V and VI)	Latest assessment prior to randomization	Continuous descriptives

5.1.2.6 Medical History

Medical history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0 or newer. Unique subjects who report medical history events will be presented in a subject data listing for the ITT population.

Table 5-9 Medical History Summary

Endpoint	Timing	Methodology
Abnormalities and surgeries occurring before the Screening Visit	Screening Period	Listing

5.1.2.7 Prior and Concomitant Medications

Medications will be coded using the MedDRA, version 20.0 or newer. The MedDRA system organ class (SOC) and preferred term (PT) will be displayed for the indication, and the preferred name will be displayed as assigned to the 11-digit drug code from the WHO Drug Dictionary Enhanced (DDE). Unique subjects who reported medications will be presented in a subject data listing for the ITT population.

Table 5-10 Medication Summaries

Endpoint	Description	Timing	Methodology
Prior medications	Medications taken before the study treatment start date and time, regardless of medication end date	Screening Period, prior to treatment	Listing
Concomitant medications	Medications taken on or after the study treatment start date and time, regardless of medication start date	Treatment Follow-up period	Listing

5.1.2.8 Exposure to Study Treatment

Treatment exposure related variable will be summarized for safety population by treatment group as follows.

Table 5-11 Exposure to Study Treatment

Endpoint	Description	Timing	Methodology
Volume injected	By cannula, by needle, and combined across cannula and needle separately for each of cannula and needle cheeks	Treatment period	Continuous descriptives

5.1.2.9 Administration of Study Treatment

Variables related to administration of treatment will be summarized for safety population by treatment group as follows.

Table 5-12 Exposure to Study Treatment

Endpoint	Description	Timing	Methodology
• Pretreatment anesthesia type and duration • Planes of injection • Injection technique • Needle/cannula used • Number of injections Injection ease	Separately for each of cannula and needle cheeks. Also, combined across cannula and needle for anesthesia type and number of injections.	Treatment	Categorical Counts. For injection ease: responder descriptives with paired-comparison difference and CI

5.1.3 Effectiveness Analyses

Effectiveness analyses will be based on the mITT Population.

The following effectiveness assessments are defined:

Table 5-13 Effectiveness Assessments

Assessment	Description
Cheek severity by MFVDS	Assessed by EI based on 6-point MFVDS (see Appendix A).
FACE-Q Satisfaction with Cheeks	Assessed by subjects based on 4-point FACE-Q for 5 items (see Appendix B).

Baseline assessments for applicable effectiveness endpoints defined as follows:

Table 5-14 Effectiveness Endpoint Baseline Definitions

Endpoint	Description	Timing
Cheek severity by MFVDS	Baseline refers to the last evaluation prior to treatment	Screening Day -30
FACE-Q Rasch Score	Baseline refers to the last evaluation prior to treatment	Screening Day -30

5.1.3.1 Primary Effectiveness Analysis

For the primary effectiveness analysis of change from baseline at Month 1 in EI-assessed overall MFVDS, the mean paired difference between treatment with cannula and treatment with needle,

and its 95% CI based on the paired t-test will be calculated. If the upper confidence limit is less than 0.5, statistical non-inferiority will be concluded.

[redacted]

Table 5-15 Primary Effectiveness Analyses

Endpoint	Description	Timing	Methodology
MFVDS change from baseline to month 1	Compare mean difference in the MFVDS change from baseline score between cannula and needle at Month 1, [redacted]	Baseline and change from baseline to months 1 [redacted]	Continuous descriptives with paired-comparison CI

5.1.3.2 Secondary Effectiveness Analysis

The following analyses will be performed for secondary effectiveness variables:

- Within-treatment overall MFVDS responder rates at Month 1 (and 95% CI) for the cannula side and, separately, for the needle side will be displayed, with support from paired-comparison response categories [redacted]

- FACE-Q Satisfaction with Cheeks module (subject self-assessment) change from baseline at Month 1 Visit will be summarized with descriptive statistics. For secondary effectiveness, this will be done for the Rasch transformed score. The 5 component item scores will be summarized under other effectiveness analysis.

To control the overall type I error rate at 5%, treatment comparison for the secondary MFVDS responder variable will not be deemed significant unless the comparison for the primary effectiveness variable is statistically significant. No significance testing of FACE-Q will be done.

Table 5-16 Secondary Effectiveness Analyses

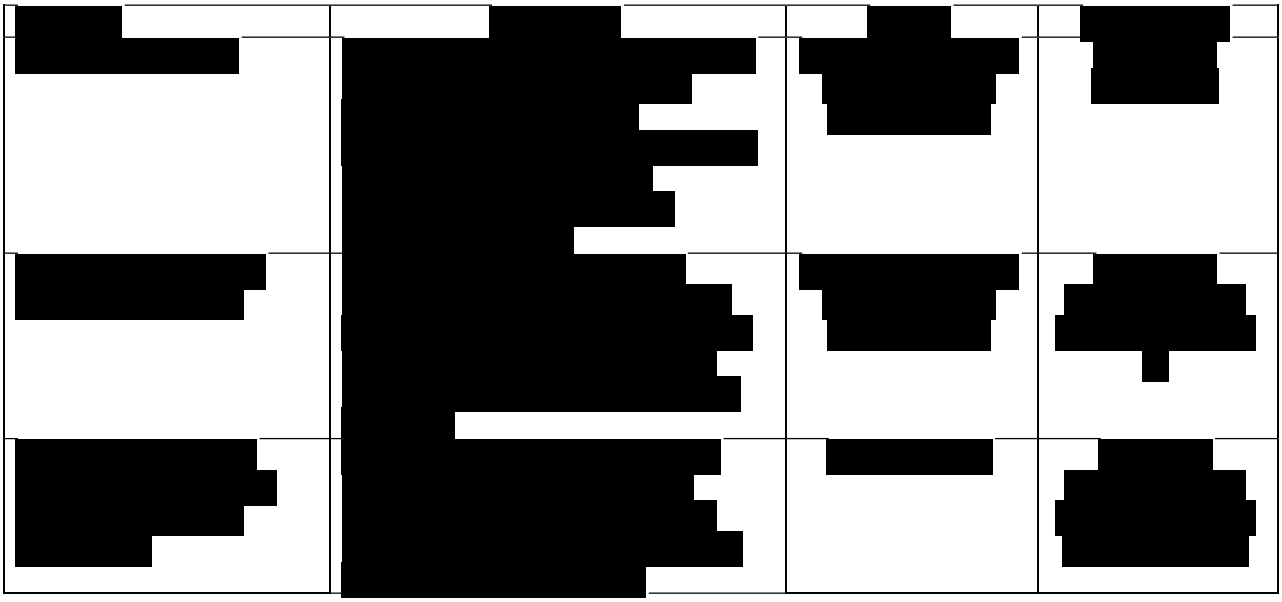
Endpoint	Description	Timing	Methodology
Responder rate based on MFVDS change from baseline scores of ≥ 1	non-inferiority of cannula to needle with respect to responder rates at 1 month, with tertiary support at month 3	Months 1 [redacted]	Responder descriptives with paired-comparison difference and CI
FACE-Q Rasch scores	subject level (rather than by treatment) response distribution, for Rasch transformed scores on 0-100 scale	Baseline and change from baseline to months 1 [redacted]	Continuous descriptives

The sum of the FACE-Q 5-item scores for a subject's visit will be set to missing if more than 2 items have missing scores. If only 1 or 2 items have missing scores, the sum score will be calculated by prorating (ie, by 5/4 or 5/3, respectively) the sum of the non-missing scores and rounding the result to the nearest integer. (This is essentially imputation by mean substitution.) Following is a conversion look-up table for mapping the sum of the FACE-Q 5-item scores to its Rasch transformed score.

Sum Score	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Rasch Score	0	13	20	25	30	35	40	44	50	55	63	70	77	83	91	100

[redacted]

[redacted]



5.1.4 Safety Analyses

Safety analyses will be based on the Safety Population.

Baseline assessments for applicable safety endpoints defined as follows:

Table 5-18 Safety Endpoint Baseline Definitions

Endpoint	Description	Timing
• Vital signs	eCRF- or (standardized) vendor-provided assessments	Latest non-missing assessment on/before treatment start date

5.1.4.1 Study Treatment Exposure and Compliance

See Section 5.1.2.8.

5.1.4.2 Adverse Events

The following AE terms are defined:

Table 5-19 AE Terms

Term	Description
Treatment-emergent AE (TEAE)	An AE that initially occurs or increases in severity on or after the treatment start date.
Treatment-related TEAE (TR-TEAE)	A TEAE that is related to study treatment in the judgment of the investigator.

AEs, encompassing abnormalities and surgeries reported as occurring after the Screening Visit, will be coded using MedDRA version 20.0 or newer. A listing of all TEAEs will be presented. Also, unique subjects reporting AEs as well as number of events in the following AE categories will be summarized by treatment group and in total for the Safety Population as follows (ie, AEs at cheeks, AEs not at cheeks and all AEs combined). The overall summary tables of AE categories and the summary tables for TEAEs and TR-TEAEs that are grouped by SOC, PT and severity will be included within a CSR-appendix set of tables. The other AE summary tables listed will be generated within a supplemental set of tables.

Table 5-20 AE Summaries

Endpoint	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • Treatment-emergent AEs (TEAEs) • Treatment-related TEAEs • All Serious AEs (SAE) • Treatment-related SAE • Discontinued due to TEAE • Deaths	Treatment	Categorical counts
TEAEs	• by SOC and PT • by SOC, PT, and severity (mild, moderate, severe) • by SOC, PT, and duration (≤ 7 days, 8-14 days, 15-30 days, > 30 days) • non-serious and occur ≥ 5%, by SOC and PT	Treatment	Categorical counts
TR-TEAEs	• by SOC and PT • by SOC, PT, and severity	Treatment	Categorical counts
SAEs[1]	Overall summary and by PT	Treatment	Listing
AEs leading to discontinuation[1]	Overall summary and by PT	Treatment	Listing

[1] Subjects who report ≥ 1 AE in the AE category and all AEs for those subjects will be listed.
SOCs will be sorted alphabetically; PTs will be sorted in descending frequency across treatments (cannula and needle).

5.1.4.3 Injection Site Responses

ISRs recorded in subject diaries after treatment will be summarized by pre-defined symptoms.

Table 5-21 ISR Analyses

Endpoint	Description	Timing	Methodology
ISR incidence	Incidence of occurrence. Response distribution for cannula, needle, cannula only, needle only.	30 days post treatment	Categorical counts
ISR severity	Maximum reported severity. Response distribution for cannula, needle, cannula only, needle only.	30 days post treatment	Categorical counts
Number of ISR days	Number of days with ISR reported during the 30-day diary period. Response distribution for cannula, needle, cannula only, needle only.	30 days post treatment	Categorical counts
ISR total duration	Total duration from first instance of the ISR to the last instance of the ISR within the treatment period, where last instances means no further report to the end of the 30-day diary period. Response distribution for cannula, needle, cannula only, needle only.	30 days post treatment	Categorical counts

5.1.4.4 Vital Signs and Physical Exam

Vital signs will be presented in a data listing for the Safety Population.

Physical measurements taken at screening (height and weight) will be summarized by descriptive statistics.

Table 5-22 Physical Examination Analyses

Endpoint	Description	Timing	Methodology
Physical measurement	Summary of height, weight, and BMI	Screening	Continuous descriptives

5.1.4.5 Pregnancy Test Analyses

Urine pregnancy tests are taken at screening, treatment, and Month 3 exit visits. Subjects with a positive result will be summarized in a data listing.

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

5.1.6 Interim Analyses

No interim analysis is planned.

[redacted] [redacted]

[redacted]

[redacted]

5.3 Changes in the Conduct of the Study or Planned Analyses

The PP definition in the study protocol was enhanced (see Table 5-1) to specifically exclude subjects who did not receive each assigned treatment on its assigned side for this paired-comparison study. The intent is that such cases would be identified as significant protocol deviations, but, in case they are not, the enhanced definition specifically excludes them from the PP population. Also, the study populations defined in the protocol were expanded (see Table 5-1) to include the screened population and the ITT population, because those definitions are needed for some of the data listings.

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
Treatment Day	Relative to the treatment date • Day = analysis date – treatment date + 1 o Day 1 = treatment date
Safety Day (including AE and ISR)	Relative to the treatment date • Day = analysis date – treatment date + 1 o Day 1 = 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.

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.

If a subject's visit falls into the analysis window for a visit other than its nominal visit, but is not selected by the above decision rules, and if the subject had no other visits to represent its nominal visit, then that visit will used for analysis of its nominal visit (eg, a month 1 visit that falls into the month 3 window will instead be used for month 1 analysis if the subject has another visit that is selected for month 3 analysis).

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. If treatment does not occur on the same day as randomization, the treatment date will be the reference date for post-treatment analysis.

Table 6-2 Effectiveness Analysis Visit Definitions

Analysis Visit (Derived)	Target Day of the Visit	Window

Analysis Visit (Derived)	Target Day of the Visit	Window
Screening	-30	< randomization
Day 1	Day 1	Randomization to Treatment Day
Month 1	Day 31	Treatment Day [2, 61] post-treatment
Month 3	Day 91	Treatment Day [62, 121] post-treatment
> Month 3	Not analyzed	Treatment Day > 121 post-treatment

6.2.2 Safety

Analysis visit windows do not apply to TEAEs and ISRs; they are by definition post-treatment.

6.3 Missing/Incomplete Date Conventions

In general, there will be no substitution of missing time or date. However, any partial information will be utilized to its full extent wherever sensible. For example, a medication may be classified as a prior medication if the partial information of the medication ending date with only month and year permits a determination that the medication ended prior to the treatment date of study treatment.

Partial dates occurring when calculation of study day is germane to the study outcome will be handled as follows, but only for purposes of summary tables; data will be displayed in the data listings as recorded:

If the year is missing, then the date will be treated as missing.

In general, if either the month or the day is missing, then the closest date to study treatment will be used. That is, an event occurring the year before treatment will use December and/or the last day of the month. An event occurring the year after treatment will use January and/or the first day of the month. Following are rules specific to AEs and concomitant medications.

All AEs with missing onset dates will be identified and the missing dates will be imputed as follows for analysis.

(1) For AE onset date: If day and month are missing, but year is available (../../yy), then the imputed day and month will be 01/01/yy. However, if the treatment date is during the same year, the onset date will instead be set to the treatment date. If the day is missing but the month and year are available (mm/../yy), then the imputed day will be mm/01/yy. However, if the treatment

date is during the same month and year, the onset date will instead be set to the treatment date. If an imputed date is prior to the screening visit, it will be reset to the screening date.

(2) For AE stop dates: If day and month are missing, but year is available (../../yy), then the imputed day and month will be 12/31/yy. However, if the exit date is during the same year, the stop date will instead be set to the study exit date. If day is missing, but the month and year are available (mm/../yy), then the imputed day will be the last day of the month mm in the year yy. However, if the study exit date is during the same month and year, the stop date will instead be set to the study exit date.

(3) If the AE onset month, day, and year are missing (../../..), then the treatment date will be used as the AE onset date. If the treatment date is missing, the randomization date will be used instead. If the randomization date is also missing, the screening date will be used instead.

(4) If the AE has stopped, but the stop month, day, and year are missing (../../..), then the exit date will be used as the AE stop date. If the AE is indicated to be ongoing, the stop date will remain missing.

Concomitant medication and prior medication will be calculated using the following decision rules: (1) if the stop date of taking medication is prior to the treatment date, then it will be counted as prior medication; (2) if the start date of taking medication is on or after the treatment date, then it will be counted as concomitant medication; (3) if the start date of taking medication is prior to the treatment date and the stop date is on or after the treatment date, then it will be counted as both prior medication and concomitant medication; (4) if still unresolved, it will be counted as a concomitant medication.

6.4 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. References

1. Newcombe, RG. "Improved confidence intervals for the difference between binomial proportions based on paired data", Statistics in Medicine, 17, 2635-2650 (1998).

2. May, WL and Johnson, WD. "The validity and power of tests for equality of two correlated proportions", Statistics in Medicine, 16, 2127-2136 (1997).

3. Fleiss, JL. Statistical Methods for Rates and Proportions, 2nd edn, Wiley, New York, 1981.

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