NCT03425253

Study ID: CMO-MA-FAS-0513

Title: A Prospective, Open-label Study to Evaluate Sequential Treatment with BELKYRA® and Juvéderm® VOLUMA™ with Lidocaine for Overall Improvement in Jawline Contour

Statistical Analysis Plan Version 3.0 Date: 21Feb2020

Allergan
Biostatistics
Statistical Analysis Plan

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Version 3.0
Date: 21-February-2020

Prepared by: [redacted]

Approved by: [redacted]

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Summary of Changes

Version Number	Version Date	Author	Changes Made
1.0	14-Jan-2019	[redacted]	Initial Version
2.0	29-Aug-2019	[redacted]	Changes from V1.0 to V2.0 include: • Revisions to section 6.2.3.3 - Image Analysis • Revisions to section 7.4 - Other Safety Analysis • [redacted]
3.0	21-Feb2020	[redacted]	Changes from V2.0 to V3.0 include: • Addition of section 6.3 - SubGroup Analyses • [redacted]

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the data analyses as outlined in the study protocol dated on March 21, 2018 and titled "A Prospective, Open-label Study to Evaluate Sequential Treatment with BELKYRA® and Juvéderm® VOLUMA with Lidocaine (VOLUMA) for Overall Improvement in Jawline Contour".

This SAP should be reviewed in conjunction with the study protocol. In case of any discrepancies in the statistics section between the protocol and the SAP, the SAP will supersede the protocol, as the SAP is intended to be more precise and specific. Any amendment to the SAP will be made prior to database lock. Any additional analyses performed but not described in the final SAP or deviations from the final SAP will be documented in the clinical study report.

This study is a Phase IV, post-marketing study sponsored by Allergan. It is a prospective, open-label, multi-center, interventional, drug and medical device study to evaluate the combined effectiveness of sequential BELKYRA treatments of convexity or fullness associated with submental fat and VOLUMA to restore volume along the mandible in enhancing the overall contour of the jawline. This post-marketing study includes an exploratory endpoint for a Biopsy Sub-study to evaluate histological changes from baseline to after the final BELKYRA treatment.

Approximately 50 male and female subjects will be treated in the study, out of which approximately 10 subjects are expected to participate in the Biopsy Sub-study. Data collection on participants may continue from a minimum of 12 weeks and up to approximately 64 weeks, depending on the number of BELKYRA injections needed and participation in the Biopsy Sub-study.

There will be no interim analysis. One final analysis is planned for this study. The final analysis will be performed upon the completion of the study. Database lock will be executed for the final analysis.

2. Primary Study Objectives and Design

2.1 Study Design

This Phase IV trial is a prospective, open-label, multi-center, interventional, drug and medical device, post-marketing study. Each subject will act as his/her own control. Subjects will attend a minimum of 6 and maximum of 18 visits.

Approximately 50 male and female subjects will be treated. Approximately 10 of them are expected to participate in the Biopsy Sub-study.

All subjects will sign an informed consent form (ICF) at the Screening Visit (Visit 1). Eligible subjects will undergo treatment with BELKYRA injected into subcutaneous pre-platysma fat tissue in the submental area (Visit 2.1/Day 0). Seven days after the initial BELKYRA treatment (Visit 3.1), the subject will return to the clinic for a safety evaluation. Eight weeks after BELKYRA treatment, the submental profile will be evaluated by the investigator and the subject. If further BELKYRA intervention is required to achieve the desired result, subjects may receive up to 5 optional BELKYRA treatments (Visits 2.2 to 2.6), for a maximum of 6 treatments including the initial required treatment. Subjects who receive optional BELKYRA treatments will be contacted by telephone 7 days after treatment for safety evaluation (Visits 3.2 to 3.6). The submental profile will be assessed as described 8 weeks after each BELKYRA treatment, and a decision made if further BELKYRA treatments are desired.

When the investigator and the subject agree that no further BELKYRA intervention is required to achieve the desired result, the subject may receive VOLUMA treatment (Visit 4). Fourteen days after VOLUMA treatment, subjects will return to the clinic (Visit 5) and the investigator will assess whether a VOLUMA touch up treatment is to be performed. All subjects will attend a final exit visit (Visit 6) which is 4 weeks after the last VOLUMA treatment (Visit 4 if no touch-up done or Visit 5, if touch-up was performed).

Subjects will have the option of participating in a Biopsy Sub-study. Participation in the sub-study is voluntary and will not affect the subject's eligibility to participate in the main study. Biopsy samples will be collected from the submental region at 2 time points: Visit B1 will occur at least 4 weeks before the first BELKYRA treatment (at Visit 2.1); Visit B2 will occur 8 weeks after the last BELKYRA treatment and at least 4 weeks prior to VOLUMA treatment (at Visit 4). Histological changes from baseline to after final BELKYRA treatment(s) will be evaluated.

[redacted]

2.2 Primary Objective

The primary objective of the study is to evaluate the combined effectiveness of sequential BELKYRA treatments on submental fat (SMF) and VOLUMA on restoring mandible volume to enhance the overall contour of the jawline.

2.3 Secondary Objectives

- To evaluate the investigator's and subject's assessment of aesthetic improvement of the lower face and jawline.

[redacted]

3. Analysis Populations and Data Conventions

3.1 Analysis Populations

To adequately describe the statistical analyses, three analysis populations are defined as follows:

- Full Analysis Set (FAS): Consists of all subjects who received BELKYRA.
- Evaluable Set (ES): Consists of the FAS subjects who received both BELKYRA and VOLUMA and a post-treatment efficacy assessment at Visit 6 (Exit Visit).
- Safety Analysis Set (SAS): Consists of all subjects who consented to participation. Includes subjects who are defined as FAS subjects and those subjects who underwent biopsy procedure but did not receive the BELKYRA treatment. This population will be used for safety analyses.

Unless specified otherwise, the FAS will be used for summary of subject disposition, demographics, baseline characteristics, and for efficacy analyses of endpoints that are

assessed up to the end of BELKYRA treatment; the Evaluable Set will be used for the efficacy analyses of endpoints that are assessed at the final study visit, and the Safety Analysis Set will be used for safety analyses.

Note that in the context of the SAP (including the TFL mockup shells), subjects in the safety analysis set are called safety subjects, and subjects in the evaluable set are called evaluable subjects. Also, the terms of full analysis set, safety analysis set and evaluable set mentioned in the protocol are used interchangeably with full analysis population, safety analysis population and evaluable population respectively.

[redacted]

3.3 Data Conventions

3.3.1 Study Day

For each subject, the reference start date (also referred to as Day 0 per the protocol) is the date when the subject receives his/her first injection of BELKYRA treatment at Visit 2.1. Study day will be calculated using visit date and the reference start date as follows: (1) study day = (visit date – reference start date + 1), for any visit date ≥ reference start date. (2) study date = (visit date – reference start date), for any visit/time point date < reference start date.

3.3.2 Imputation for Missing Measurement or Assessment Data

There is no imputation for missing values for post-baseline measurements or assessments. All data summaries and analyses of post-baseline data will be conducted using observed cases.

3.3.3 Imputation for Missing or Partially Missing Dates

Any partial or missing dates occurring between the enrollment date and the exit date will be queried to obtain the full date prior to imputation.

3.3.3.1 For assigning treatment-emergent AEs (TEAEs), and prior and concomitant medications

The followings rules will be applied for partial or missing start dates:

- If the day is missing, the first day of the given month will be used unless the month and year are the same as the month and year of enrollment, in which case the date of enrollment will be used. Note that the enrollment date for the subjects of the biopsy sub-study is at Visit B1, instead of Visit 2.1.
- If the day and month are missing, the 1st of January will be used unless the year is the same as the year of enrollment, in which case the date of enrollment will be used.
- If the whole date is missing, the date of enrollment will be used.

3.3.3.2 For calculating durations of treatments, adverse events (AEs), and medications

The followings rules will be applied for partial or missing start dates:

- If the day is missing, the 15th day of the given month will be used unless the month and year are the same as the month and year of enrollment, in which case the date of enrollment will be used.
- If the day and month are missing, the 1st of July will be used unless the year is the same as the year of enrollment, in which case the date of enrollment will be used.
- If the whole date is missing, the date of enrollment will be used.

The followings rules will be applied for partial or missing end dates:

- If the day is missing, the 15th day of the given month will be used unless:
  - the month and year are the same as the month and year of date of last contact, in which case the date of last contact will be used.
  - the imputed date is earlier that the start date, in which case the start date will be used.
- If the day and month are missing, the 1st of July will be used unless:
  - the year is the same as the year of last contact, in which case the date of last contact will be used.
  - the imputed date is earlier that the start date, in which case the start date will be used.
- If the whole date is missing, the date of last contact will be used.

Under those circumstances where missing data components will make the imputation of missing values problematic for calculating relevant time intervals, decisions will be made on a case by case basis for the pertinent analysis.

No other dates will be imputed.

3.3.4 Study End Date for Individual Subject

Study end date for individual subject is defined as the date of his/her exit visit. Note that a subject who exits early from the study for whatever reasons will be invited to attend exit visit for data collection.

3.3.5 Other Conventions

Summary statistics (used interchangeably with the term “descriptive statistics”) for continuous data include sample size (N), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using sample size (N), frequency and percentages of patients. In calculating the percentage, unless specified otherwise, the count of subjects “at risk” will be used as denominator. Ordinal variables will be handled as categorical variables in terms of presenting summary statistics.

Subject’s demographic and baseline characteristics, including height, weight, Fitzpatrick skin type and Allergan Jowl Fat Rating Scale (AJFRS) will be collected at Visit 1 (Screening) and the value at Visit 1 (Screening) will be used as baseline value. For efficacy parameters, such as Allergan Loss of Jawline Definition Scale (ALJDS), CR (Clinician-Reported) and PR (Patient reported) Submental Fat Rating Scale (SMFRS) scores, Submental Skin Laxity Grade (SMSLG) score, FACE-Q™ satisfaction with lower face and jawline score; FACE-Q™ appraisal of neck; and FACE-Q™ appraisal of area under chin, baseline value is defined as the assessment outcome taken at Visit 1 (Screening). [redacted]).

Change from baseline is calculated as ‘visit value minus baseline value’. Percentage change from baseline is calculated as change from baseline divided by baseline value, then multiplied by 100. If baseline value is zero, percentage change from baseline will be undefined or not evaluable (NE). If baseline value is missing, percentage change from baseline will be missing.

Data will be pooled across clinical sites/centers for all analyses.

The International System of Units (Système international d'unités or SI) is the current international standard metric system. The SI units will be used for the reporting in all Tables/Figures/Listings for this study.

All statistical analysis and reporting will be performed using [redacted].

4. Subject Disposition and Exit Status

4.1 Screening Log Data

Subject eligibility criteria (including both inclusion and exclusion criteria) and date of informed consent will be listed for all the subjects screened. Note that date of informed consent will be included in the subject disposition listing.

4.2 Disposition and Withdrawals

The number of subject enrolled and the number and percentage of subjects completed and discontinued together with the reasons for discontinuation will be summarized for FAS. The number and percentage of subjects included, and reasons for exclusion, from each of the analysis sets will be presented as well.

Subject disposition (including date of and reasons for early discontinuation from study) will be listed for the FAS.

5. Demographics and Other Baseline Characteristics

5.1 Demographics

All subject demographic and baseline characteristic data will be summarized using descriptive statistics for the full analysis population and/or the evaluable population whenever appropriate.

Age (years) captured at screening visit will be summarized as a continuous variable. Other continuous variables to be presented include weight, height and body mass index. Categorical or ordinal variables to be presented include sex, race, AJFRS on right and left sides, and Fitzpatrick skin type.

All demographic data will be listed.

5.2 Prior Medications and Therapies

Prior medications/therapies are defined as any medication/therapy which is administered any time prior to the first BELKYRA treatment at Visit 2.1 (Day 0) regardless of when the medication stops.

Partial or missing medication start dates will be handled as per Section 3.3.3 of the SAP.

Prior medications/therapies will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the latest World Health Organization (WHO) Drug Dictionary Enhanced WHODDE. Medications/therapies will be summarized by ATC class (level 2) and subclass preferred term (PT) for all patients in the safety population.

Summary tables will show the frequency count and percentage of patients with at least 1 usage of medication/therapy on the subclass level within each ATC class, sorted alphabetically. Percentages will be calculated using the number of patients in the safety population as the denominator.

All prior medications/therapies will be listed.

5.3 Concomitant Medications and Therapies

Concomitant medication/therapy is defined as any medication/therapy which is administered any time on or after the initial BELKYRA treatment at Day 0, regardless of when the medication starts or stops. An episode of medication can be classified into both of prior and concomitant medication/therapy based on how the start and stop date of the medication are relative to the first BELKYRA treatment visit.

Partial or missing medication start and end dates will be handled as per Section 3.3.3.

Any concomitant medication will be recorded collected at each visit, including the medication name, dose, unit, frequency, route of administration, indication, and medication start and end dates.

Concomitant medications/therapies will be coded by the ATC classification system according to the latest WHODDE. Medications will be summarized by ATC class (level 2) and subclass (PT) for all subjects in the safety population.

Summary tables will show the frequency count and percentage of patients with at least 1 usage of medication on the subclass level within each ATC class, sorted alphabetically. Percentages will be calculated using the number of patients in the safety population as the denominator.

All concomitant medications/therapies will be listed.

5.4 Medical History

Descriptions of medical history findings will be coded using latest Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized for the safety population by the number and percentage of patients within each system organ class (SOC) and PT, sorted descending by overall frequency.

Medical history will be listed for all patients in the safety population. Medical history data listings will be sorted by patient number, start date, SOC, PT and verbatim term.

6. Efficacy Analyses

For this post-marketing study, efficacy data are collected at three critical time points, namely, Baseline (prior to Visit 2.1/Day 0), Visit 4 (end of BELKYRA treatment, prior to VOLUMA treatment), and final study visit (Exit Visit 6; end of VOLUMA treatment). The three critical time points will be referenced in most of the statistical analyses for this study. [redacted]

Efficacy analyses will be conducted to evaluate the combined effectiveness of sequential treatments with BELKYRA and Juvéderm VOLUMA on the following parameters: Allergan Loss of Jawline Definition Scale (ALJDS), CR (Clinician-Reported) and PR (Patient reported) Submental Fat Rating Scale (SMFRS) scores, Submental Skin Laxity Grade (SMSLG) score, FACE-Q™ satisfaction with lower face and jawline score; FACE-Q™ appraisal of neck; and FACE-Q™ appraisal of area under chin, and investigator and subject [redacted]

Efficacy analyses to evaluate the effect of BELKYRA treatment will be conducted at

- Visit 4 (after last BELKYRA treatment) from baseline on ALJDS score, SMSLG score, FACE-Q™ satisfaction with lower face and jawline score; FACE-Q™ appraisal of neck score; FACE-Q™ appraisal of area under chin score.
- Visit 2.x (after each treatment of BELKYRA) from baseline on CR and PR SMFRS scores;
- Visit B2 (after the last BELKYRA treatment) from Visit B1 (before the first BELKYRA treatment) for histological changes in the submental tissue

[redacted]

All efficacy analyses will be based on the evaluable population (for combined effectiveness assessments); and on the full analysis population (for BELKYRA treatment evaluation).

6.1 Collection of Efficacy Measurements and Derivation of Efficacy Variables

The following measurements and variables are of the efficacy interests. Data on Submental convexity or fullness and Jawline contour assessments, including ALJDS (investigator and independent reviewer), CR-SMFRS, PR-SMFRS, SMSLG and FACE-Q™ Satisfaction with lower face and jawline score/Appraisal of Neck/Appraisal of Area under Chin are collected at baseline (Visit 2.1/Day 0), Visit 4 (end of BELKYRA treatment, prior to VOLUMA treatment), and final study visit (Visit 6; end of VOLUMA treatment). [redacted]).

- Measurement: ALJDS by investigator and by independent reviewer;
  Variables: Change on ALJDS from baseline (numeric variable on the value of right side; and value of left side); and having had at least 1-point improvement from baseline (binary variable). Improvement is defined as having had negative change from baseline.

- Measurement: CR-SMFRS;
  Variables: Change on CR-SMFRS from baseline (numeric variable). Improvement is defined as having had negative change from baseline.

- Measurement: PR-SMFRS;
  Variables: Change on PR-SMFRS from baseline (numeric variable). Improvement is defined as having had negative change from baseline.

- Measurement: SMSLG;
  Variables: Change on SMSLG from baseline (numeric variable). Improvement is defined as having had negative change from baseline.

- Measurement: FACE-Q™ lower face and jawline;
  Variables: Change on FACE-Q™ lower face and jawline from baseline (numeric variable on combined scores). Improvement is defined as having had positive change from baseline.

- Measurement: FACE-Q™ Neck;
  Variables: Change on FACE-Q™ Neck from baseline (numeric variable on combined scores). Improvement is defined as having had positive change from baseline.

- Measurement: FACE-Q™ Chin;
  Variables: Change on FACE-Q™ Chin from baseline (numeric variable on combined scores). Improvement is defined as having had positive change from baseline.

[redacted]

[redacted]

6.2 Efficacy Analyses

6.2.1 Primary Efficacy Analysis

The primary endpoint will be the responder rate for jawline improvement on the ALJDS, which is defined as the proportion of subjects who show ≥ 1-point improvement from baseline on the ALJDS at the final study visit (after last VOLUMA™ treatment received), as assessed by the Investigator. It will be summarized by the number and percentage of subjects together with exact 95% confidence interval. The analysis of primary efficacy endpoint will be based on evaluable population.

6.2.2 Secondary Efficacy Analyses

Secondary efficacy endpoints include followings:

6.2.2.1 Allergan Loss of Jawline Definition Scale (ALJDS)

- Change from baseline to last BELKYRA® treatment on ALJDS

- Change from baseline to final study visit in jawline definition based on Independent Reviewer assessment using the ALJDS and photographic images

6.2.2.2 FACE-Q Questionnaires

- Change from baseline to final study visit on the FACE-Q™ Satisfaction with Lower Face and Jawline module at the final study visit.
- Change from baseline to final study visit on the FACE-Q™ Appraisal of Neck
- Change from baseline to final study visit on the FACE-Q™ Appraisal of Area Under Chin

6.2.2.3 Clinician-Reported and Patient-Reported Submental Fat Rating Scale (CR-SMFRS and PR-SMFRS)

Change from baseline to final study visit for CR-SMFRS and PR-SMFRS scores.

6.2.2.4 Submental Skin Laxity Grade (SMSLG) Score

The change from baseline in ALJDS, CR-SMFRS, PR-SMFRS, and SMSLG will be analyzed using paired t-test (or Wilcoxon signed-rank test if normality assumptions are not met). Descriptive statistics and 95% confidence intervals will be presented. As exploratory endpoints, CR- and PR SMFRS will be summarized at each Belkyra treatment visit beside those mentioned three critical visits'

For FACE-Q™ satisfaction with lower face and jawline score, appraisal of neck, and appraisal of area under chin, descriptive statistics of the Rasch transformed scale score will be provided. The Rasch transformed scale score, ranging from 0 (worst) to 100 (best), is derived for the responses for each of the three FACE-Q™ items. The change from baseline in Rasch transformed scale score will be analyzed using paired t-test and 95% confidence intervals will be presented.

The distribution-free 95% CI for the estimate of median (or median change) will be calculated using SAS® procedure Proc Univariate.

[redacted]

[redacted]

[redacted]

6.2.3.2 Biopsy Sub-study

Subjects who consent to participate in the optional Biopsy Sub-study will have a biopsy sample collected at least 4 weeks prior to the first BELKYRA treatment at Visit B1. A second biopsy sample will be collected 8 weeks following the last BELKYRA treatment at Visit B2. Biopsy samples, approximately 2 mm, will be excised from the submental area approximately 1.5 cm from the submental crease and 1.5 cm left and right of midline.

- Objective: Evaluate changes from baseline to last BELKYRA® treatment based on histological evaluation of the submental tissue biopsies.
- Analysis: For each biopsy sample, mean levels of pro-collagen I, collagen I, collagen III, and elastin will be evaluated. For each subject, changes in expression from baseline to after final BELKYRA® treatment will be calculated for each marker. The mean change across all subjects for each marker will be determined. Statistical comparisons from baseline to after final BELKYRA® treatment (based on mean change) may be performed to determine the significance of these observations.

Refer to Appendix I for Analysis Plan of Biopsy Data

6.2.3.3 Image Analysis

Standardized facial photographic images using the VECTRA M3 camera system will be captured at the investigative sites prior to each study treatment (BELKYRA and VOLUMA), within 60 minutes of VOLUMA treatment and at the end of study visit. Once the images are submitted to and received at Canfield Scientific, the images will be staged into its digital monitoring system (DMS) and available for review by the Clinical Services Project Management Team (CSPMT). The CSPMT member assigned to monitor the study will review all the images for photographic quality.

All images selected for analysis will be assigned a random tracking number by the CSPMT which will blind the Image Analysis Technicians (IATs) to information such as Subject Secondary Identifier, Visit Name, Image Date, and/or Treatment Group.

Image Analysis (IA) using Canfield Scientific software or scripts will be performed on two dimensional (2D) and three dimensional (3D) images by the IAT(s) on a rolling basis. to provide left and right jawline and submental volume, submental surface area, submental strain, and submental direction movement as well as facial angle measurements on the frontal view image. The 3D image analysis data will measure major and minor strain, displacement in the x, y, and z-directions, and surface area within the submental area of interests (AOI); while the 2D image analysis data will measure subject's two facial angles and submental angle.

Descriptive statistics will be provided for the 3D and 2D image analysis data.

Refer to Appendix II for Analysis Plan of Imaging Data

6.3 SubGroup Analyses

As males and females may have differing expectations and perceptions of aesthetic improvement, assessment outcomes of efficacy data will be analyzed by gender.

7. Safety Analyses

All safety analyses will be based on the safety population. Safety will be assessed primarily in terms of the frequency count and the binominal incidence rate of the AEs of interest. The binomial incidence rate for a given event of interest during a certain period is defined as the number of unique patients who have experienced the event of interest in the period divided by the number of patients in the safety population, then multiplied by 100. Note that, for the calculation of the incidence rate, the numerator will be counted at subject level. Specifically, if a subject has experienced the event(s) of interest (at a given summarization level) more than once during the period, he/she will be counted only once into the numerator. The total number of events will also be presented. The 95% confidence intervals (CIs) for binomial incidence rate per the Clopper and Pearson exact method (via SAS procedure Proc Freq) will also be calculated and presented.

7.1 Exposure to Study Treatment(s)

Treatment duration in days will be calculated as: (Date of the last treatment session – Date of the first treatment + 1) for study drugs BELKYRA and/or VOLUMA. Treatment duration will be summarized using descriptive statistics. The number of the sessions of BELKYRA and VOLUMA treatment administered over the study period will be summarized using

descriptive statistics. The total injection volume (mL) of BELKYRA and VOLUMA will be calculated and summarized, as well as treatment specific injection volumes.

Partial or missing start/end dates will be handled as per Section 3.3.3.2.

All treatment data will be listed.

7.2 Adverse Events

Adverse events (AE) will be coded using MedDRA v20.1 or later to give a PT and a SOC term for each event.

An AE is defined as any untoward medical occurrence in a clinical investigational patient administered a pharmaceutical (investigational) product or any undesirable physical, psychological or behavioral effect experienced by a subject during his/her participation in a study, in conjunction with the use of the device and which does not necessarily have to have a causal relationship with this treatment.

All AEs will be included in by-subject AE listings. A separate listing will be created with all the distinct levels of SOC and PT, and the verbatim investigator description reported in the study. Sorting will be by earliest observed SOC, PT within SOC and then verbatim description.

A treatment-emergent adverse event (TEAE) is a post-baseline AE where (i) there is no pre-treatment AE of the same MedDRA primary SOC and PT; or (ii) the maximum severity during the post-baseline period is greater than the maximal severity of any pre-treatment AE of the same MedDRA primary SOC and PT during the enrollment visit. Note that the post-baseline period of the study starts upon the initiation of the BELKYRA treatment at Visit 2.1/Day 0.

Partial or missing AE start dates will be handled as per Section 3.3.3.1.

An overall summary of frequency count and the binomial incidence rate with associated 95% CIs will be presented to describe the incidents of TEAEs. Note that 95% CIs of the binomial incidence rate will be presented for the overall summary analyses of TEAEs, but not for the by-visit analyses. Percentages and corresponding 95% CIs will be displayed to 1 decimal place.

Each type of AE will be tabulated by SOC and PT within SOC. The SOC and PT within SOC will be sorted by descending frequency. Number of subjects with percentage and number of events will be presented based on SOC and PT.

The incidence of all TEAEs by SOC and PT will be presented for the following categories:

- Any TEAE
- Any TEAE related to BELKYRA
- Any TEAE related to VOLUMA
- Any TEAE related to anesthesia
- Any TEAE related to study procedure
- Any TEAE related to BELKYRA/VOLUMA and leading to discontinuation of treatment with BELKYRA/VOLUMA
- Any TEAE by maximum severity

The following listing will be provided:

- Listing of all TEAE

7.3 Serious Adverse Events

A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. While an unanticipated adverse device effect (UADE) is any device-related SAE that meets one or more of the criteria listed in the Sec. 9.1.3 of the Protocol in page 49.

An overall summary of frequency count and the binomial incidence rate with associated 95% CIs will be presented to describe the incidents of treatment emergent SAEs. Note that 95% CIs presented are for the overall summary analyses of SAE, but not for the by-visit analyses. Percentages and corresponding 95% CIs will be displayed to 1 decimal place.

The incidence of all treatment-emergent SAEs by SOC and PT within SOC will be presented for the following categories:

- Any SAE
- Any SAE related to BELKYRA
- Any SAE related to VOLUMA
- Any SAE related to anesthesia
- Any SAE related to study procedure

- Any SAE related to BELKYRA/VOLUMA treatment and leading to discontinuation of treatment
- Any SAE by maximum severity

7.4 Other Safety Analysis

Injection Site Reactions (ISR) following treatment with dermal fillers (VOLUMA) will be analyzed using the AE terms captured in the patient diary (i.e. ISR Diary).
ISR events will be tabulated by PT and sorted by descending frequency. If a subject has multiple occurrences (start and stop) of an event associated with a specific SOC and PT, a patient will only be counted once in the incidence count. The total number of events will also be presented.

An overall summary of frequency count and the binomial incidence rate with its associated 95% CIs will be presented to describe ISRs.

The 95% CIs for the binominal incidence rate will be calculated using the Clopper and Pearson exact method.

7.5 Pregnancy

All positive results of pregnancy tests will be listed.

7.6 Subgroup Analyses for Safety Variables

Not applicable.

8. Pharmacokinetic, Biomarker, Genomic, or Immunogenicity Data Analyses

Not applicable.

9. Health Outcomes Data Analyses

There are no health outcomes analyses planned for this study.

10. Interim Analyses

There is no interim analysis planned for this study.

11. Data Collected but not Analyzed

Not Applicable.

12. References

[redacted]

Allergan's Study Protocol

Study Number	Study Title
CMO-MA-FAS-0513	A Prospective, Open-label Study to Evaluate Sequential Treatment with BELKYRA® and Juvéderm® VOLUMA™ with Lidocaine for Overall Improvement in Jawline Contour

13. Appendices