NCT02833077

Study ID: VOLUMA-006

Title: A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM VOLUMA® XC injectable gel for chin augmentation

Statistical Analysis Plan Date: 28 Feb 2017

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 chin augmentation

Draft 1.0: 2017-02-28

Study Number:	VOLUMA-006
Development Phase:	Pivotal
Product Name:	JUVÉDERM VOLUMA XC Injectable
Study Statistician:	[redacted].
Sponsor:	Allergan, Inc. 2525 Dupont Drive, Irvine, CA 92612

2. Table of Contents

2.1 List of Tables

[redacted]

[redacted]

[redacted]

[redacted]

3. List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
3D	3-dimensional
ACRS	Allergan Chin Retrusion Scale
ADE	Adverse Device Effect
AE	Adverse Event
CFR	Code of Federal Regulations
CI	Confidence Interval
eCRF	Electronic Case Report Form
EI	Evaluating Investigator
DFU	Directions For Use
FDA	Food and Drug Administration
[redacted]	[redacted]
GAIS	Global Aesthetic Improvement Scale
HA	Hyaluronic Acid
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISO	International Organization for Standardization
ISR	Injection Site Response
ITT	Intent-to-treat
IWRS	Interactive Web Response System
mITT	modified Intent-To-Treat
PP	Per-Protocol
PT	Preferred Term
SADE	Serious Adverse Device Effect
SOC	System Organ Class
TI	Treating Investigator
UADE	Unanticipated Adverse Device Effect
US	United States

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the effectiveness and safety data outlined and/or specified in the protocol of Study VOLUMA-006 (Amendment 4 version dated 2017-03-01). This SAP will be approved prior to database lock.

4.1 Study Design Summary

[redacted]

[redacted]

[redacted]

[redacted]

4.1.2 Number of Participants

Up to 224 subjects will be enrolled at up to 15 sites.

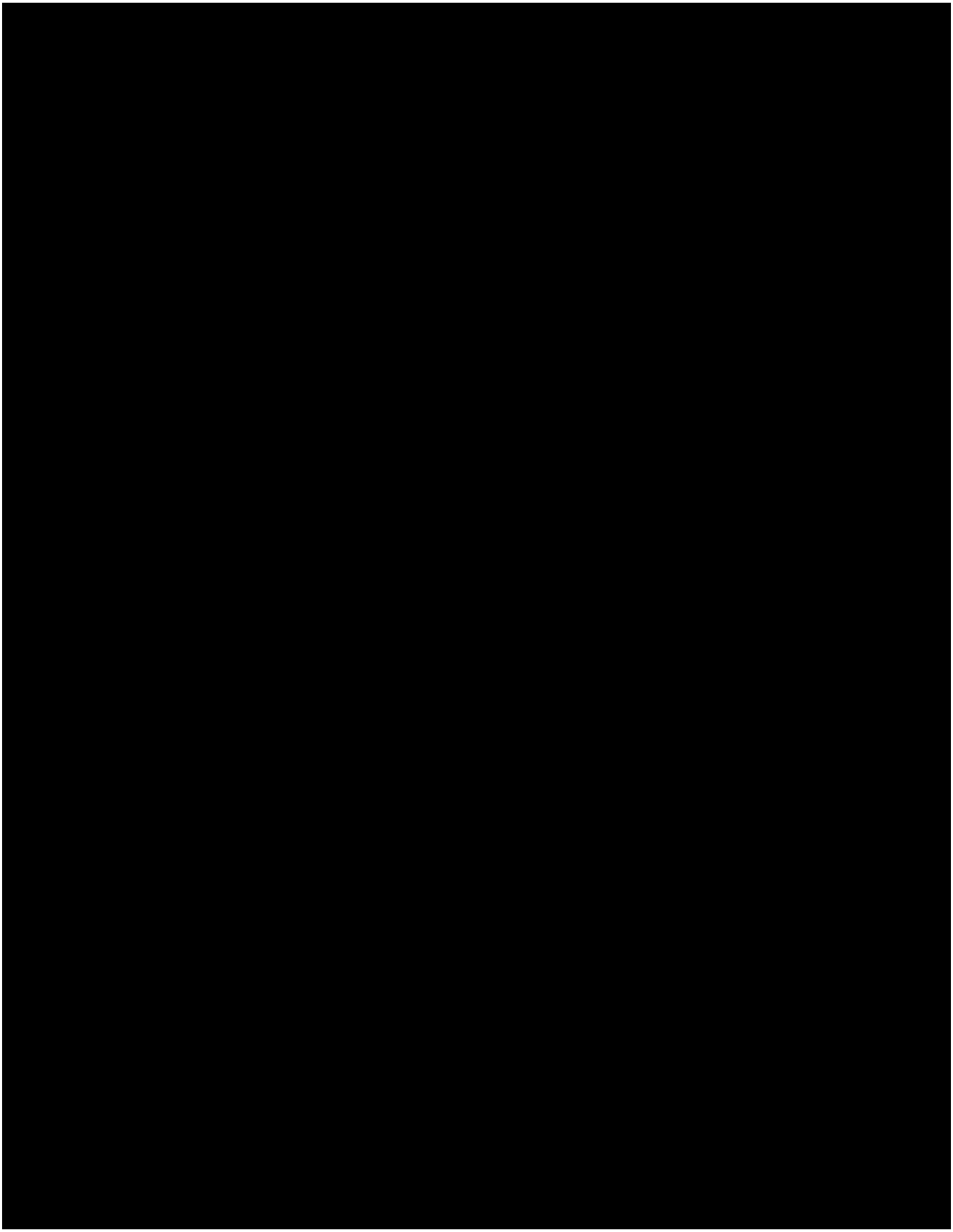
4.2 Study Objectives and Endpoints

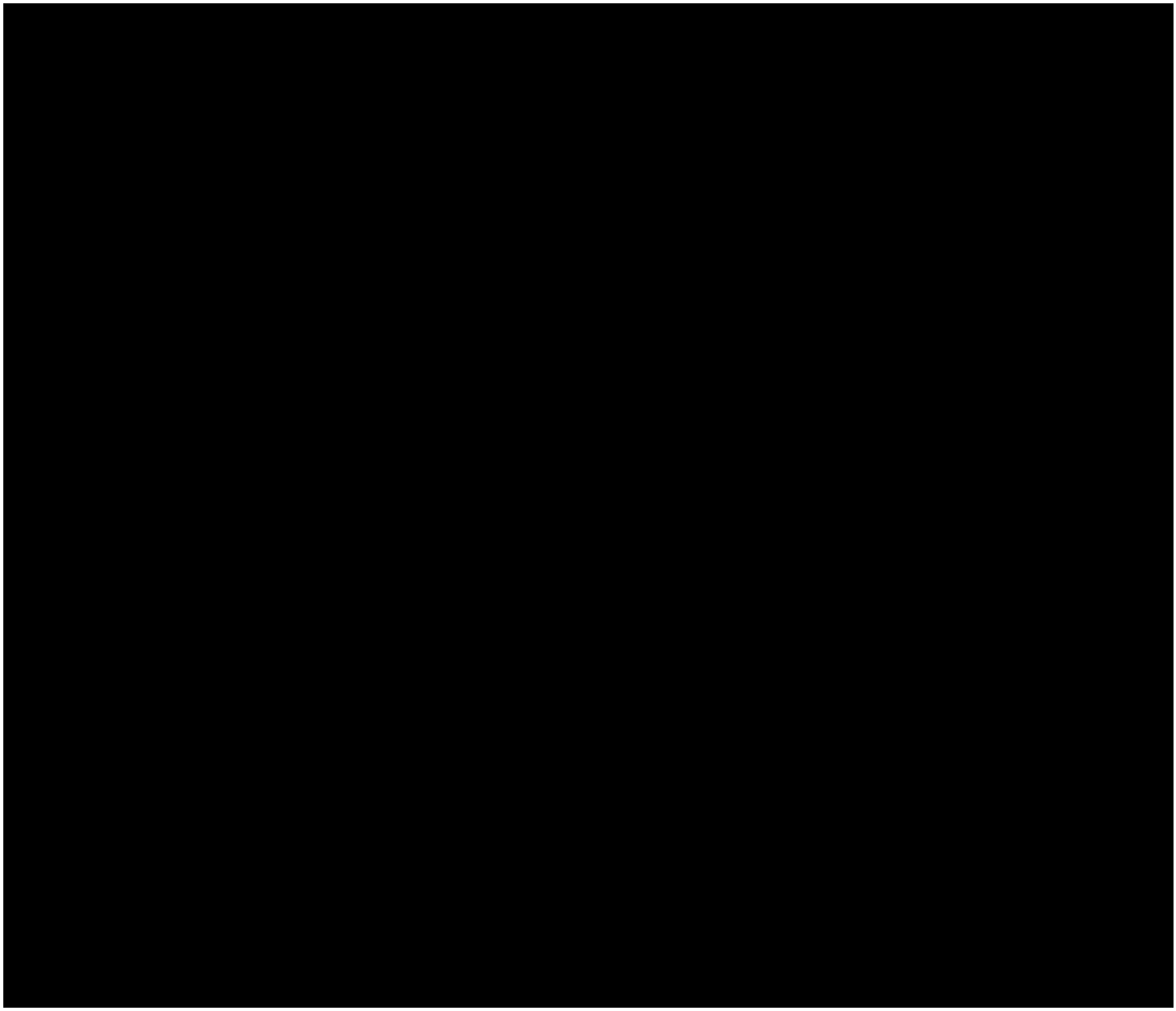
The objectives of this study are to evaluate the safety and effectiveness of JUVÉDERM VOLUMA XC injectable gel in augmentation of chin retrusion in adult subjects seeking improvement in chin volume deficit.

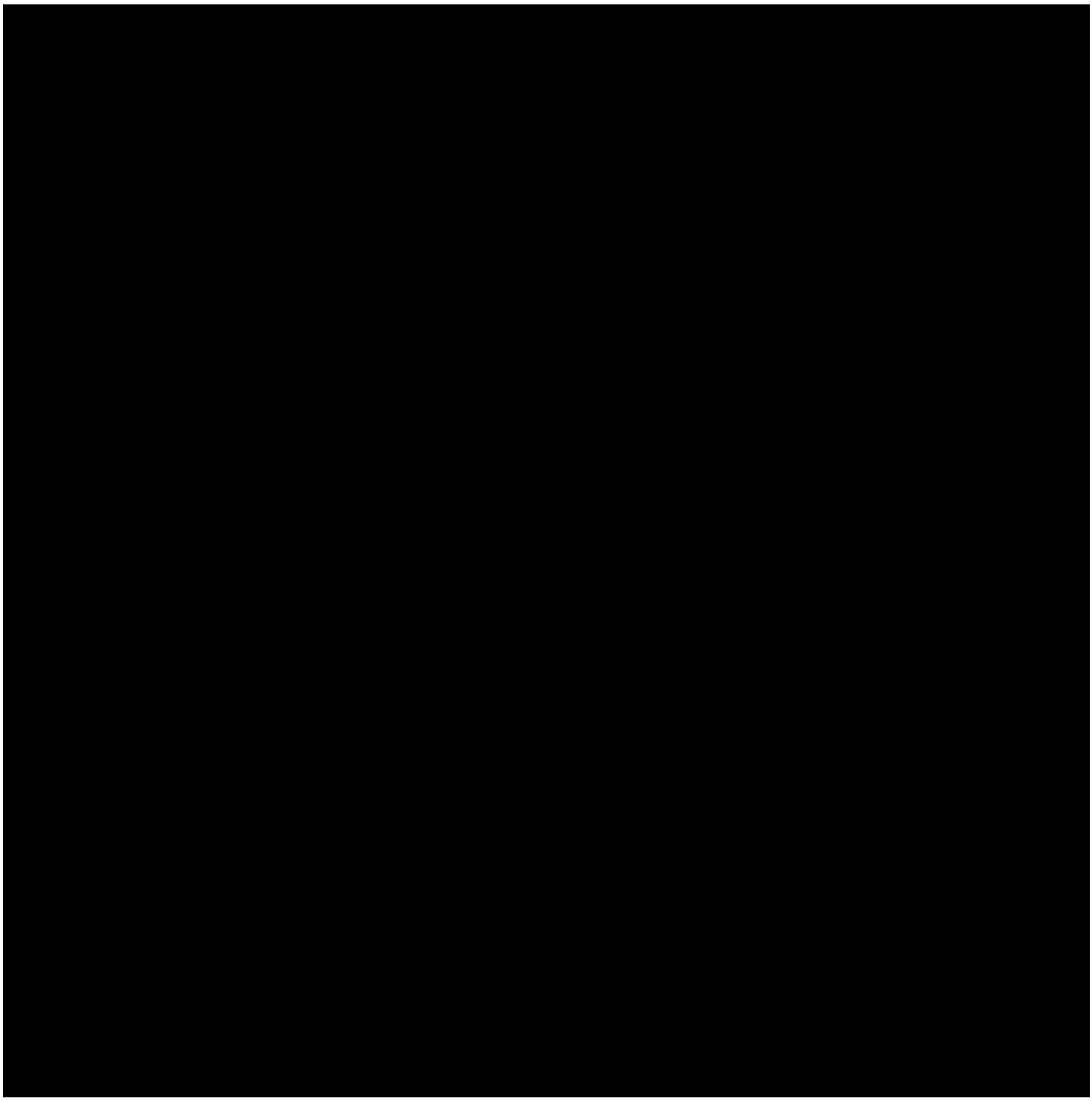
Each study primary objective, secondary objective, and other objectives are presented with corresponding endpoint(s) below:

Table 4-1 Study Objectives and Corresponding Endpoints

Objectives	Endpoints
• To evaluate and compare the effectiveness of JUVÉDERM VOLUMA XC injectable gel with no treatment control in augmentation of chin retrusion in adult subjects seeking improvement in chin volume deficit	Primary Endpoint : • Responder rate based on photo assessment of the Allergan Chin Retrusion Scale (ACRS) at month 6 Secondary Endpoints: • Change from baseline in overall scores of the Satisfaction with Chin module of the FACE-Q questionnaire at month 6 • Responder rate based on Evaluating Investigator (EI) assessment of global aesthetic improvement scale (GAIS) in the chin area at month 6 • Responder rate based on subject assessments of the GAIS in the chin area at month 6
• To evaluate the safety of JUVÉDERM VOLUMA XC injectable gel in augmentation of chin retrusion in adult subjects seeking improvement in chin volume deficit	[redacted]







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	Study Treatment
Intent-to-Treat (ITT)	All randomized subjects	Randomized assignment
Modified Intent-to-Treat (mITT)	• All subjects randomized to the treatment (treatment group) who receive at least 1 study treatment • All subjects randomized to the control group	Randomized assignment
Per-Protocol (PP) population	All mITT subjects who do not have any significant protocol deviations affecting the primary effectiveness endpoint	Randomized assignment
Safety	• All subjects randomized to the treatment (treatment group) who receive at least 1 study device treatment • All subjects randomized to the control group	Actual received

Unless specified otherwise, all effectiveness analyses will be performed on the mITT population using the "as-randomized" assignment for each subject (ie, if a subject randomized to the control group is treated inadvertently at the start of the study, the assessments for that subject will nonetheless be included in the control group analysis). The ITT and PP populations will be used to perform sensitivity analyses for the primary effectiveness variable. All safety analyses will be conducted using the safety population.

5.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Study Treatment: JUVÉDERM VOLUMA XC injectable gel
- Control Treatment: Delayed treatment

5.1.1.3 Statistical Methodology

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

Table 5-2 Statistical Methodology

Methodology	Description
Categorical counts	• Number and percent of subjects in individual categories ○ Subjects with ≥ 1qualifying event counted once per individual category ○ N included = participants with non-missing value for by visit analysis
Event descriptives	• Number and percentage of events in individual categories ○ Events counted individually for each instance • Percentage denominator = total number of events
Continuous descriptives	• N included, mean, standard deviation (SD), median, minimum, maximum • N included = subjects with non-missing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N included = subjects with non-missing values at both baseline and the specified postbaseline analysis visit
CFB Paired T	• Continuous descriptives for baseline, postbaseline, and CFB values ○ P-values from a 2-sided paired t-test comparing baseline and postbaseline values • N included = subjects with non-missing values at both baseline and the specified postbaseline analysis visit
Responder	• Categorical descriptives for responders and nonresponders ○ Include count and percent along with exact binomial 95% CI ○ P-values from 2-sided Fisher's exact test • N included = with non-missing values at both baseline and the specified postbaseline analysis visit

5.1.1.4 Missing Data

General missing data handling conventions are specified and summarized as follows:

Table 5-3 Missing Data Handling by Endpoint Type

Endpoint type	Timing	Missing Data Handling
Responder	Month 6 (no-treatment control period)	• All subjects included (ITT population) • Multiple imputation with 5 imputed datasets is applied to subjects with no postbaseline values using the below model: Month 6 ACRS = β_0+β_1Baseline ACRS + β_2Month 1 ACRS + β_3Month 3 ACRS where ACRS score is based on photo assessment.
Responder	Month 6 (no-treatment control period)	▪ All subject included (ITT population) ▪ Last observation carried forward (LOCF) for subjects with no postbaseline values

The above missing data handling conventions will only be used for sensitivity analysis of the primary effectiveness endpoint.

5.1.1.5 Site Pooling

The impact of investigational sites on the primary effectiveness analysis at Month 6 will be evaluated by including investigational site, treatment assignment, and their interaction as

predictor variablies in a multivariate logistic regression analysis with response status on the ACRS as the dependent variable. Investigational sites with few enrolled subjects may be pooled with other sites based on subjects enrolled, geographical region, or other site characteristics. The interaction between site and treatment will be considered significant if the p-value of this interaction is less than 0.05.

5.1.2 Demographics

5.1.2.1 Analysis Populations

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

Table 5-4 Analysis Population Summaries

Endpoint	Description	Timing	Methodology
All Consented	Distribution of all randomized, Randomized but Discontinued Before Treatment, Not Randomized (with Reason for Randomization Failure)	Screening period	Listing
Not Randomized	List of not randomized subjects with randomization failure reasons	Screening period	Listing
ITT, mITT, PP and Safety populations	Distribution in total and 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 (i.e., screening and treatment periods), along with eCRF-reported discontinuation reasons from each respective analysis period. A subject in the treatment group is considered a completer if s/he completes the month 12 visit without receiving repeat treatment or completes the month 1 visit after receiving repeat treatment. A subject in the control group is considered a completer if s/he completes the month 6 visit without receiving optional treatment or completes the month 6 visit after receiving optional treatment. Subject disposition will be summarized as follows:

Table 5-5 Subject Disposition Summaries

Endpoint	Description	Timing	Methodology
Study disposition	Distribution in the randomized subjects in total and by treatment group	Month 6 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 follows:

Table 5-6 Protocol Deviation Summary

Endpoint	Description	Timing	Methodology
Important protocol deviations	Important protocol deviation will be listed	—	Categorical counts/ Listing

5.1.2.4 Demographics

Demographics will be summarized for mITT population in total and by treatment group as follows:

Table 5-7 Demographic Summaries

Endpoint	Description	Timing	Methodology
Age	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Sex, race, and ethnicity	○ Sex ○ ○ Female ○ ○ Male ○ Race ○ ○ White ○ ○ Black or African American ○ ○ Asian ○ ○ American Indian or Alaska Native ○ ○ Native Hawiaan or Other Pacific Islander • 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 and by treatment group for the mITT population as follows:

Table 5-8 Baseline Characteristics Summaries

Endpoint	Timing	Methodology
• Sun exposure (hours per day) • Duration of Smoking	Latest assessment prior to randomization	Continuous descriptives
• Fitzpatrick Skin Phototype o I, II, III, IV, V, VI • Smoking history	Latest assessment prior to randomization	Categorical counts

5.1.2.6 Medical History

Medical history, encompassing abnormalities, surgeries, and cosmetic procedures reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1 or newer. Unique subjects who report medical history events will be presented as subject listing for the Safety Population.

Table 5-9 Medical History

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 World Health Organization (WHO) Drug Dictionary, version March 2014 or newer. Unique subjects who reported medications (Anatomical Therapeutic Chemical (ATC) 4 class and PT) will be presented as subject listing for the Safety Population.

Table 5-10 Medication

Endpoint	Description	Timing	Methodology
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	Screening Period prior to treatment/randomization	Listing
Concomitant medications during control period	Medications taken on or after the study treatment start date and time for the treatment group and after randomization date and time but before optional treatment date time (at month 6) for the control	Control Period	Listing

Endpoint	Description	Timing	Methodology
	group, regardless of medication end date		
Concomitant medications during treatment period	Medications taken on or after the study treatment start date and time for both control and treatment groups, regardless of medication start date	Treatment 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	Initial, Touch-up, Combined initial and touch-up, Repeat	Treament 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 Administration of Study Treatment

Endpoint	Description	Timing	Methodology
• Pretreatment Anesthesia type • Planes of injection • Injection technique • Needle/cannula used • Injection ease • Product moldability	Initial, Touch-up, Repeat (Repeat for Treatmemt Group only)	Treatment period	Categorical counts
Pretreatment Anesthesia duration	Initial, Touch-up, Repeat (Repeat for Treatmemt Group only)	Treament period	Continuous descriptives

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
Chin retrusion based on photo assessment	Assessed by EI using the 5-point ACRS (see Appendix A). The EI will assess 2D profile images of the left side of the chin rendered by the Canfield image analysis technician from the 3D images.
Chin retrusion based on live assessment	EI's live ACRS assessment
Global Aesthetic Improvement Scale (GAIS)	Assessments by subject and EI based on 5-point GAIS (see Appendix B)
Satisfaction with Chin module	Assessed by subject response on the Satisfaction with Chin module of the validated FACE-Q questionnaire (see Appendix C)
[redacted]	[redacted]

Baseline assessments for applicable effectiveness endpoints are defined as follows:

Table 5-2 Effectiveness Endpoint Baseline Definitions

Endpoint	Description	Timing
• Chin retrusion based on photo assessment	Baseline refers to the photo evaluation by EI at randomization (or screening if no usable assessment is available at randomization)	Randomization/ Screening
• Chin retrusion based on live assessment	Baseline refers to the joint live evaluation by EI and TI at randomization (or screening if no usable assessment is available at randomization)	Randomization/ Screening
• Satisfaction with Chin module	Baseline refers to the evaluation at screening	Screening
[redacted]	[redacted]	[redacted]

5.1.3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint will be met if the responder rate at month 6 for the treatment group is statistically greater than that for the control group at month 6 and the observed responder rate at month 6 for the treatment group is greater than 50%. A responder is a subject who shows clinically significant improvement, i.e., ≥ 1-point decrease, on the ACRS from baseline based on EI assessment of 2D renderings of the chin profile.

The primary effectiveness analysis is summarized in Table 5-15.

Table 5-15 Primary Effectiveness Analyses

Endpoint	Description	Timing	Methodology
Primary: Responder analysis based on photo ACRS	• Superiority of the treatment group over no-treatment control group • Responder rate of treatment group is greater than 50%	Month 6	Responder

The primary effectiveness analysis will be performed on the mITT population without any missing data imputation. Sensitivity analysis will be performed using ITT and PP populations as well as using missing data handling conventions as decribed in Section 5.1.1.1.4. Additionally, sensitivity analysis will be performed on mITT subjects with a baseline ACRS photo score of 2 or 3.

5.1.3.2 Secondary Effectiveness Endpoint

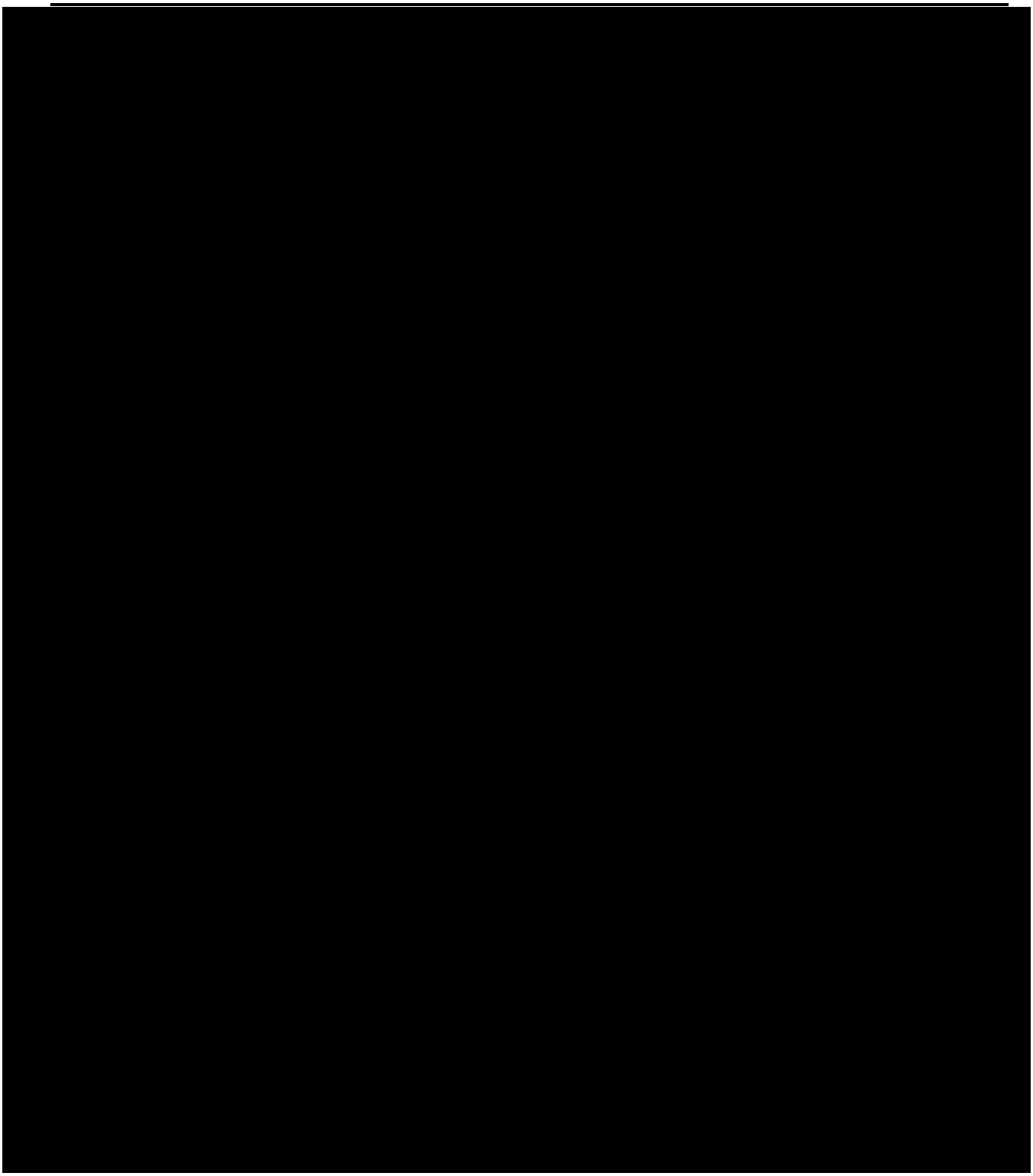
The secondary effectiveness analysis is summarized in Table 5-16.

Table 5-16 Secondary Effectiveness Analyses

Endpoint	Description	Timing	Methodology
Secondary 1: Responder analysis based on GAIS (by EI and by subject)	Summary for treatment group	Month 6	Categorical
Secondary 2: Satisfaction with Chin module using overall score	Comparison of baseline vs. postbaseline for treatment group using 2-sided paired t-test	Month 6	CFB Paired T

A responder on GAIS is a subject who shows improvement in the overall aesthetic assessment in the chin area (corresponds to a response of “Improved” or “Much Improved” on GAIS).

The secondary effectiveness analysis for Satisfaction with Chin 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.



5.1.4 Safety Analyses

Safety analyses will be based on the Safety Population.

5.1.4.1 Study Treatment Exposure and Compliance

See section 5.1.1.2.8.

5.1.4.2 Adverse Events

The following adverse event (AE) terms are defined:

Table 5-18 AE Terms

Term	Description
Treatment-emergent Adverse Event (TEAE)	Treatment group: An event that initially occurs or increases in severity on or after the treatment start date. Control group: An event that initially occurs or increases in severity on or after randomization date.

AEs and encompassing abnormalities, reported as occurring after the Screening Visit, will be coded using MedDRA version 18.1 or newer. A listing for all TEAEs in the treatment and control groups will be presented. Additionally, unique subjects reporting AEs as well as the number of events in the following AE categories will be summarized for treatment subjects, control subjects after optional treatment, and all treated subjects as follows:

Table 5-3 AE Summaries

Endpoint	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • Treatment-emergent AEs (TEAEs) • Treatment-related TEAEs • Treatment-related TEAEs at injection site • Treatment-related TEAEs not at injection site • All Serious AEs (SAE) • Treatment-related SAE • Discontinued due to TEAE • Deaths	Treatment period	Categorical counts, Event descriptives
TEAEs	• Overall summary and by SOC, PT and severity	Treatment period	Categorical counts, Event descriptives
Treatment-related TEAEs	• Overall summary and by SOC, PT and severity • Overall summary by severity, duration, time to onset, resolution, and treatment required	Treatment period	Categorical counts, Event descriptives
SAEs	Overall summary and by PT	Treatment Period	Listing
AEs leading to discontinuation	Overall summary and by PT	Treatment Period	Listing

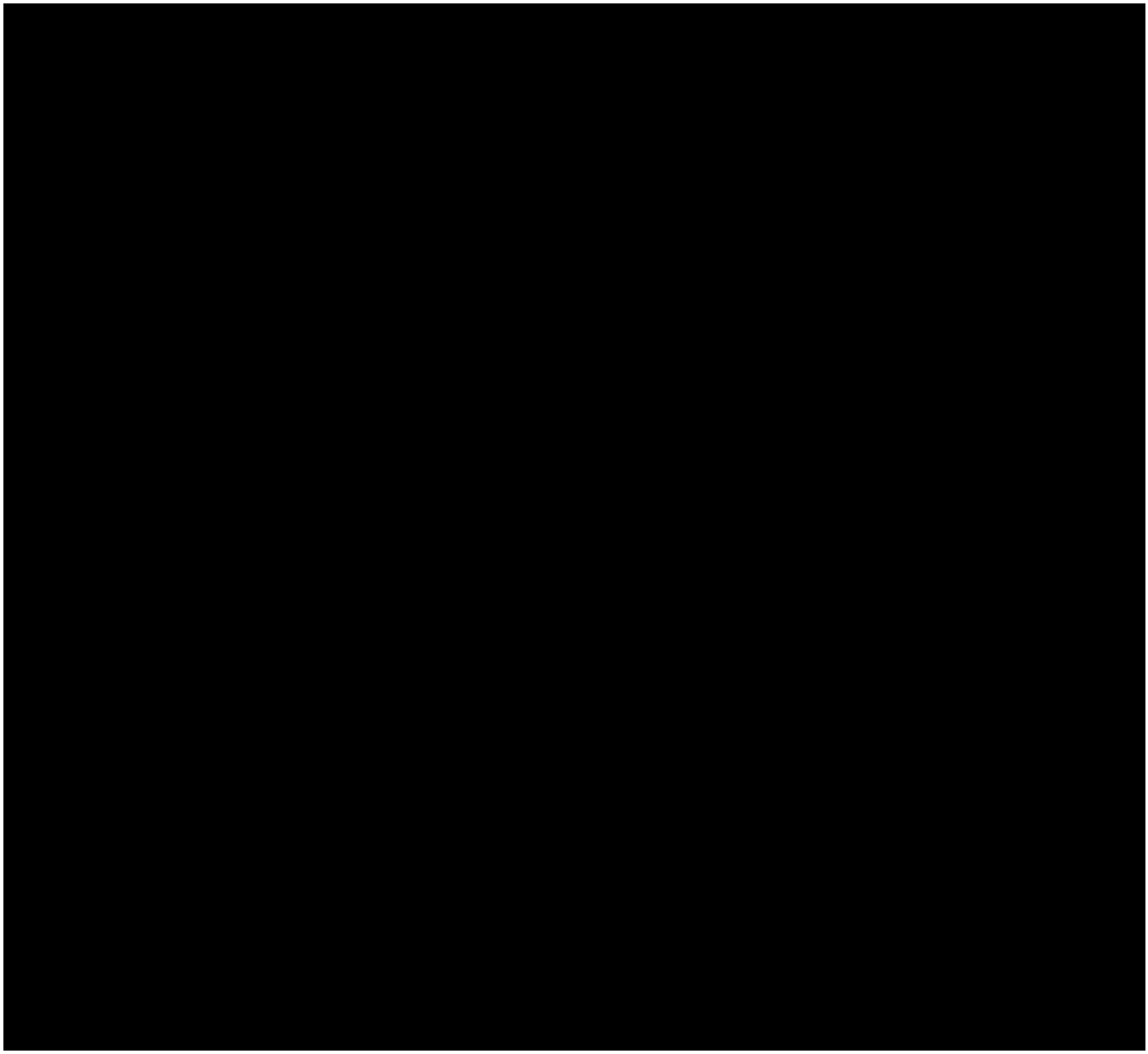
Note: SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the treatment group.
AEs for control group before and after optional treatment are summarized separately.

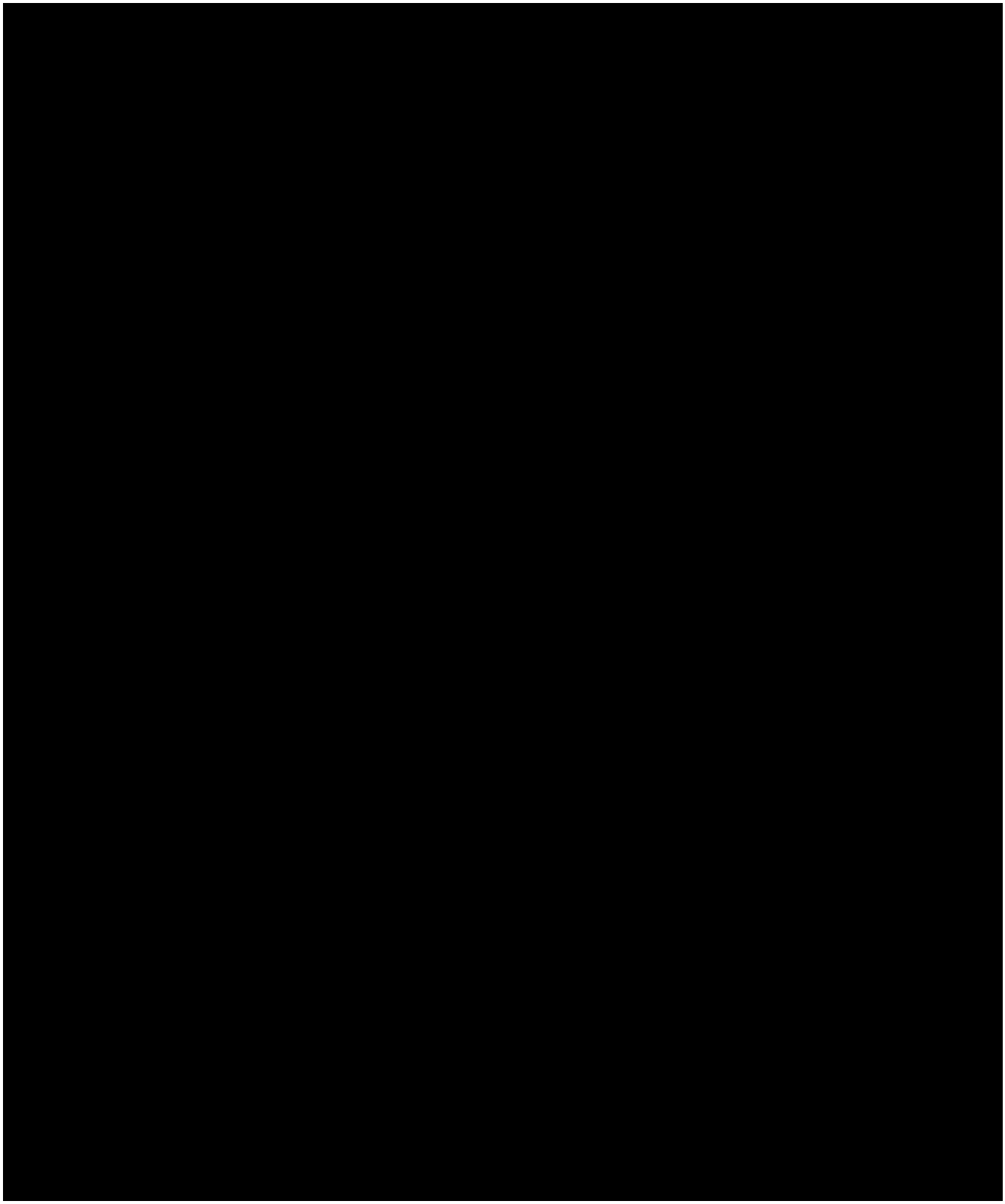
Time to onset for TEAEs will be computed as

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.





5.1.6 Interim Analyses

No interim analysis will be performed.

5.2 Determination of Sample Size

The sample size assumptions and estimate are summarized as follows:

Table 5-4 Sample Size Assumptions

Parameter	Assumption / Estimate
Primary endpoint	Chin retrusion assessment responder
Risk difference[1]	40 (80% Voluma vs 40% Control)
SD	NA
α	5%
Sides	2
Power	>99%
N per group	120 in Voluma group, 40 in control group
Screen Fail Rate	15%
Drop-out Rate	15%
N total	224

[1] Based on literature/previous study VOLUMA-002 and relevant details.

5.3 Changes in the Conduct of the Study or Planned Analyses

Prior to database lock, there were no changes in study conduct or planned analyses (except per protocol analysis) from what was described in the protocol and detailed in the SAP. No unplanned analyses were conducted, and the planned analyses were conducted following database lock.

6. Data Handling and Analysis Conventions

6.1 Analysis Days

Treatment Day for effectiveness, [redacted] and AE are defined as follows:

Table 6-1 Analysis Day Definitions

Term	Description
Effectiveness [redacted] Effectiveness Day	Treatment Group and Control Group (only the control subjects receiving optional treatment): Relative to the last treatment date (either the initial treatment, if no touch-up is performed, or the touch-up treatment) o 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 o Effectiveness Day = analysis date –randomization date +1 o Effectiveness Day 1 = randomization date
Safety (including AE [redacted] Safety Day	Treatment Group and Treated Control (i.e., only the control subjects receiving optional treatment): Relative to treatmentdate (initial and touch-up) Safety Day = analysis date – initial treatment date + 1 Safety Day 1 = initial treatment date Control (before receiving optional treatment): Relative to the randomization date o Safety Day = analysis date – randomization date +1 o Safety Day 1 = randomization date Treatment Group 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 (e.g., if the only assessment collected for Month 6 visit window is on a Month 6 CRF with incomplete date, then those data will be used for the Month 6 assessments).

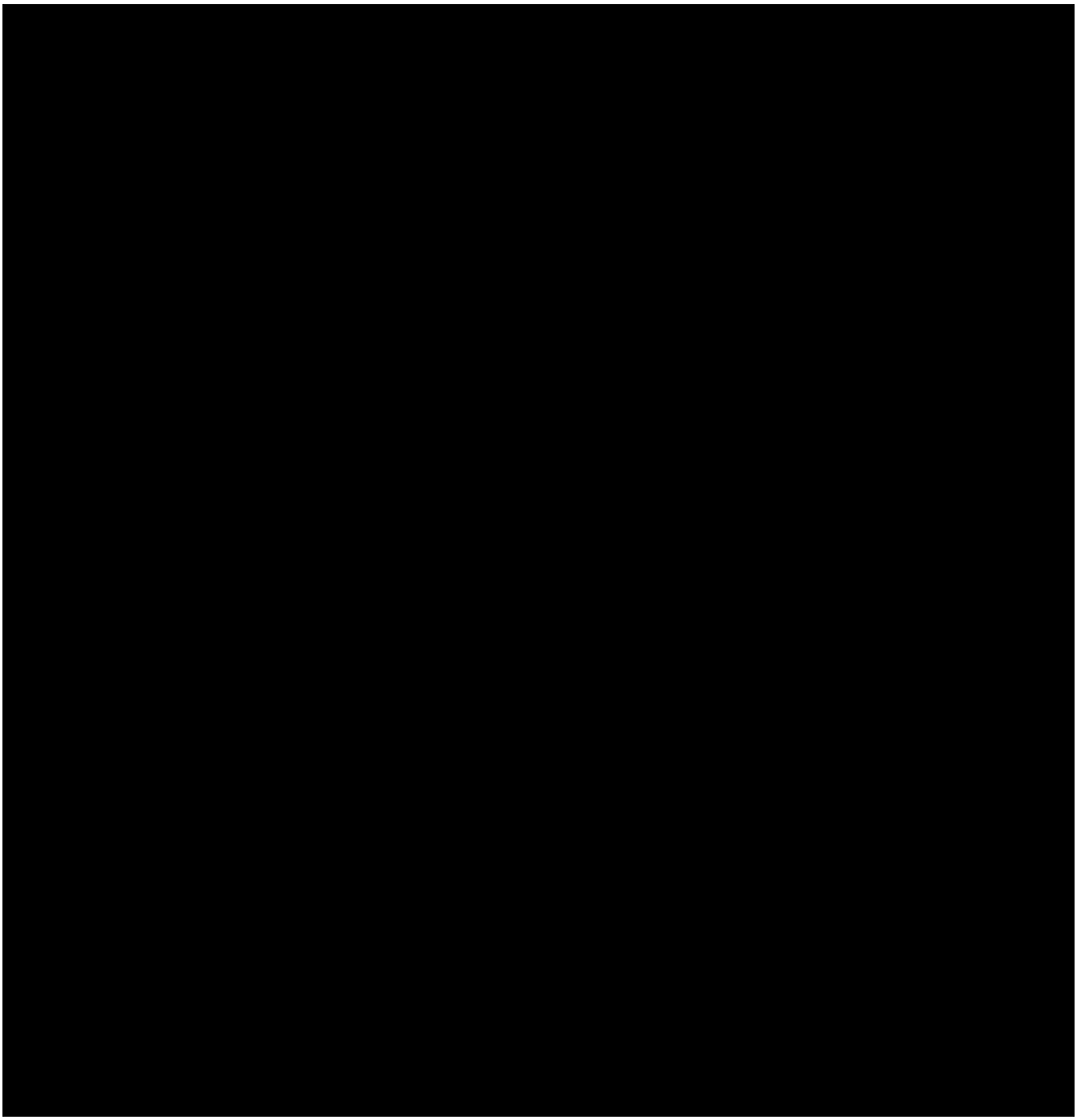
If there are multiple visits occurring within a single visit window with relevant data, the visit closest to the target day will be used in the analysis of the corresponding visit windows. If 2

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:



[redacted]

6.2.2 Safety

No analysis visit windows are required for TEAEs [redacted]. Analysis visit windows will only be used for summarizing [redacted]. For the treatment group, refer to table 6.2 for analysis visit windows [redacted] For the control group in the control period (i.e., no treatment period) refer to table 6.3 and for the control group in the treatment period refer to table 6.2.

6.3 Missing/Incomplete Date Conventions

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 End 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 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 exitdate 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 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.

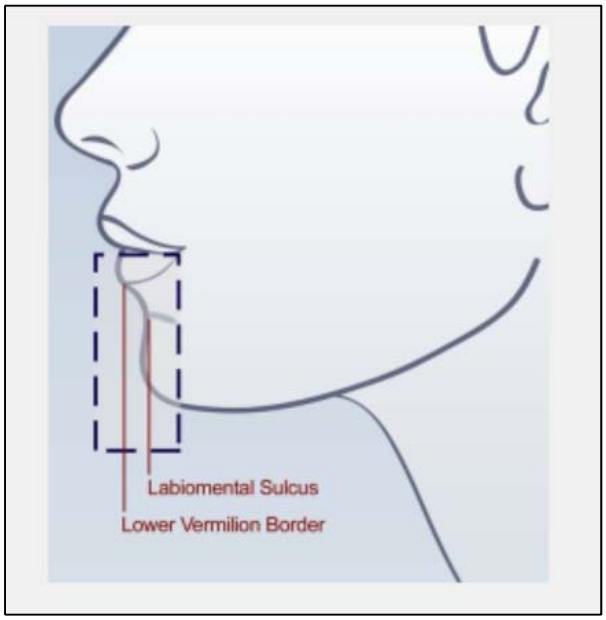
Appendix A: Allergan Chin Retrusion Scale

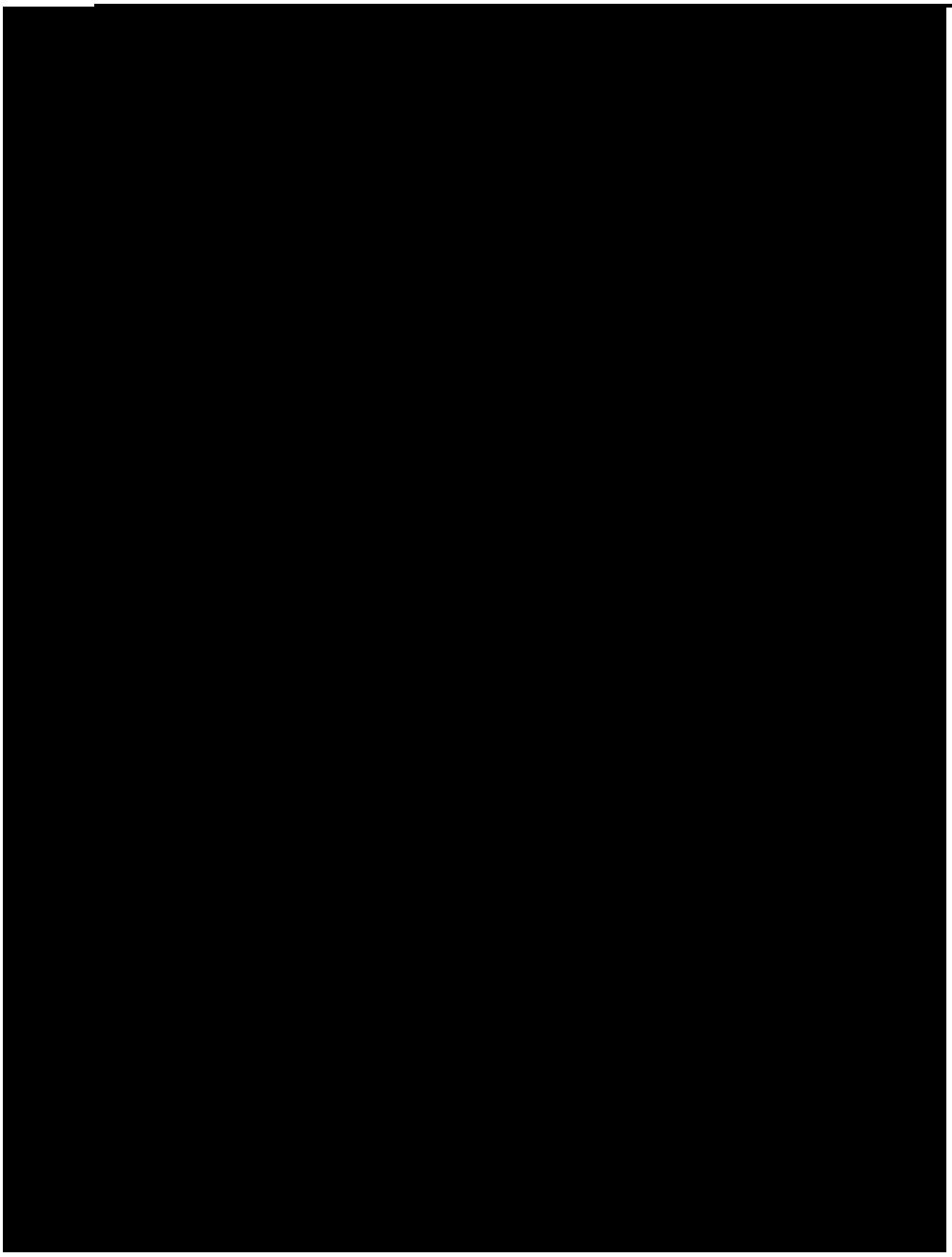
Table 1: Allergan Chin Retrusion Scale (ACRS)

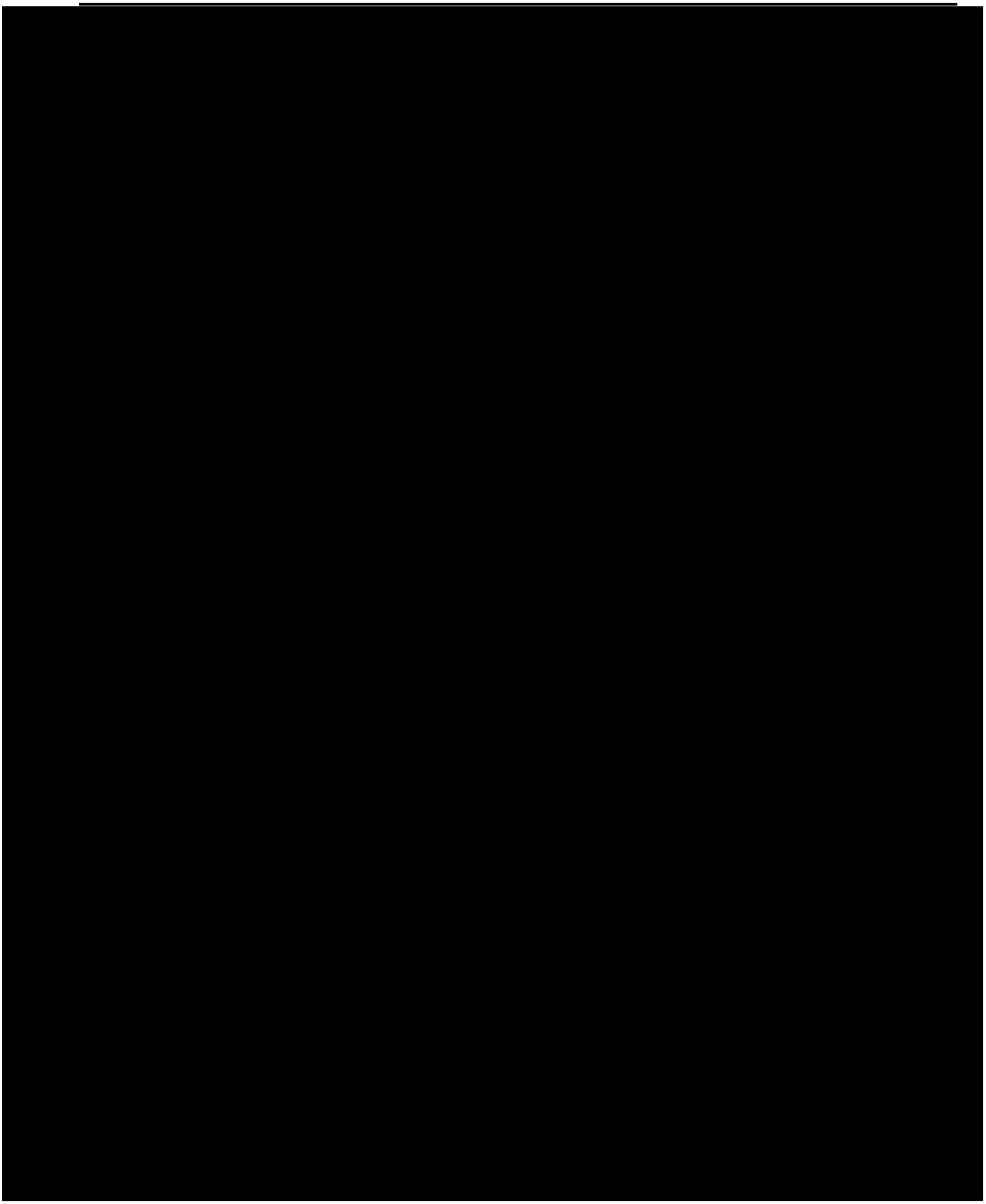
Score	Grade	Description
0	None	No chin retrusion; Chin midpoint* at or in front of the lower vermilion border vertical line
1	Minimal	Minimal chin retrusion; Chin midpoint* is between the labiomental sulcus vertical line and lower vermilion border vertical line
2	Moderate	Moderate chin retrusion; Chin midpoint* at labiomental sulcus vertical line
3	Severe	Sever chin retrusion; Chin midpoint* slightly behind labiomental sulcus vertical line
4	Extreme	Extreme chin retrusion*; Chin midpoint significantly behind labiomental sulcus vertical line

* Chin midpoint: the midpoint between the labiomental sulcus and the inferior point of the chin

Figure 1: Lines Used in the ACRS Descriptiors







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Statistical Analysis Plan

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