NCT03519204

Study ID: VOLBELLA-005

Title: A randomized, multicenter, no-treatment-controlled study of the safety and effectiveness of JUVÉDERM® VOLBELLA® with Lidocaine for lip enhancement in Chinese adults

Statistical Analysis Plan Date: 16-July-2018

1. Title Page

STATISTICAL ANALYSIS PLAN

A randomized, multicenter, no-treatment-controlled study of the safety and effectiveness of JUVÉDERM® VOLBELLA® with Lidocaine for lip enhancement in Chinese adults

Study Number:	VOLBELLA-005
Development Phase:	Pivotal
Product Name:	JUVÉDERM® VOLBELLA® with Lidocaine injectable gel
[redacted]	[redacted]
Sponsor:	Allergan Information Consulting (Shanghai) Co., Ltd. Suite 5605 56F, 1266 West Nanjing Road Jingan District Shanghai, China, 200040

2. Table of Contents

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2.1 List of Tables

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3. List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
3D	3-dimensional
AE	Adverse event
ATC	Anatomical therapeutic chemical
CFB	Change from baseline
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic case report form
EI	Evaluating Investigator
EKG	Electrocardiogram, electrocardiographic
ISR	Injection Site Response
ITT	Intent-to-treat
[redacted]	[redacted]
LFS	Lip Fullness Scale
LOCF	Last observation carried forward
MedDRA	Medication Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TI	Treating Investigator
TP	Treated period
UCP	Untreated control period
WHO	World health organization

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 final protocol of Study VOLBELLA-005 (Amendment 2 dated 2015-07-29). This SAP will be approved prior to database lock.

4.1 Study Design Summary

4.1.1 Overall Design

This is a randomized, multicenter, no-treatment-controlled study of the safety and effectiveness of JUVÉDERM® VOLBELLA® with Lidocaine for lip enhancement in Chinese adults. Subjects will be randomized at a 3:1 ratio either to have treatment with VOLBELLA with Lidocaine at the outset of the study (VOLBELLA with Lidocaine group, also referred to as the treatment group, or VOLBELLA group) or to have treatment delayed by 3 months (no-treatment control group, also referred to as the control group). Subjects with Lip Fullness Scale (LFS) score of Minimal, Mild, or Moderate as assessed by Evaluating Investigator (EI) will be enrolled in the study based on inclusion criteria. Randomization will be stratified by baseline LFS score (ie, LFS score rated as Minimal, Mild, or Moderate at the randomization visit by EI).

Treatment and safety assessments of a subject throughout the study will be performed by the same Treating Investigator(TI) (maximum 2 TIs per site), and effectiveness assessments will be performed by the same EI. The EI will remain blinded to treatment assignments throughout the duration of the study.

For subjects randomized to the treatment group, the study treatment will be on the same day as randomization (or within 30 days after screening). Subjects may undergo an optional touch-up treatment at the day 30 visit after initial treatment, if the TI assesses that optimal correction was not achieved. Routine follow-up visits for safety and effectiveness will occur at 1, 3, and 6 months after the last treatment (initial or touch-up treatment, whichever is last). Long-term safety data will be collected by telephone call at 9 and 12 months after the last treatment.

Meanwhile, subjects randomized to the no-treatment control group will attend study visits at months 1 and 3 of the no-treatment control period. After the completion of the control period, control group will receive optional treatment and optional touch-up treatment. Routine follow-up visits will occur at 1, 3, and 6 months. Safety follow-up phone call will be at 9 months.

At initial treatment visit, the TI will inject the treatment into the vermilion body, vermilion border (including the Cupid's bow), and philtral columns, as needed for lip enhancement. The

subject will rate procedural pain on an 11-point scale immediately after receiving the injections, and the TI will assess the ease of injection and the product moldability. Subjects will complete a safety diary for 30 days and will receive a safety follow-up telephone call at 3 days after each initial and touch-up treatment. [redacted]

4.1.2 Number of Subjects

Up to 176 subjects will be randomized at up to 9 Chinese sites.

4.2 Study Objectives and Endpoints

The objective of this study is to evaluate the safety and effectiveness of VOLBELLA with Lidocaine for lip enhancement in a Chinese population.

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

Table 4-1 Study Objectives and Corresponding Endpoints

Objectives	Endpoints
• To evaluate and compare the effectiveness of Volbella with no-treatment control in lip enhancement among Chinese population	**Primary Endpoint** • Responder at Month 3 (Subject showing ≥ 1-point improvement (increase in fullness)) in LFS score compared with baseline as assessed by EI **Secondary Endpoint(s)** • Responder at Month 3 (Subject showing ≥ 1-point improvement (increase in fullness)) in LFS score compared with baseline as assessed by subject • Change from baseline to month 3 in overall lip volume as measured from 3D images • Percentage change from baseline to month 3 in lip surface area as measured from 3D images
• To evaluate the safety of Volbella in lip enhancement among Chinese population	**Safety Assessments** • Study treatment exposure • Adverse events (AE) • Injection site responses (ISR) • Procedural pain • Clinical laboratory values (routine hematology and blood chemistry testing and urinalysis)

	• Vital sign • Physical measurement • EKG • Urine pregnancy test

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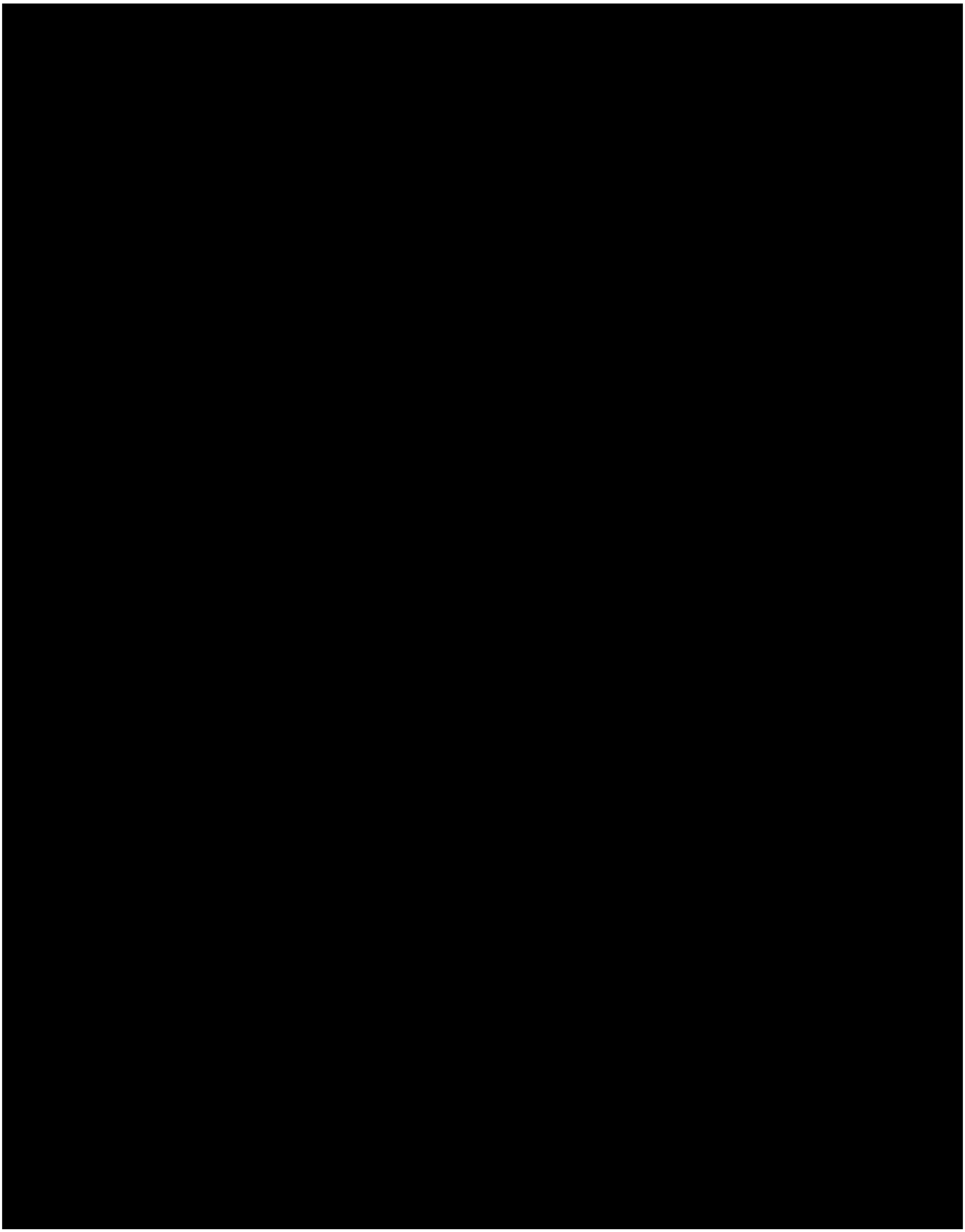
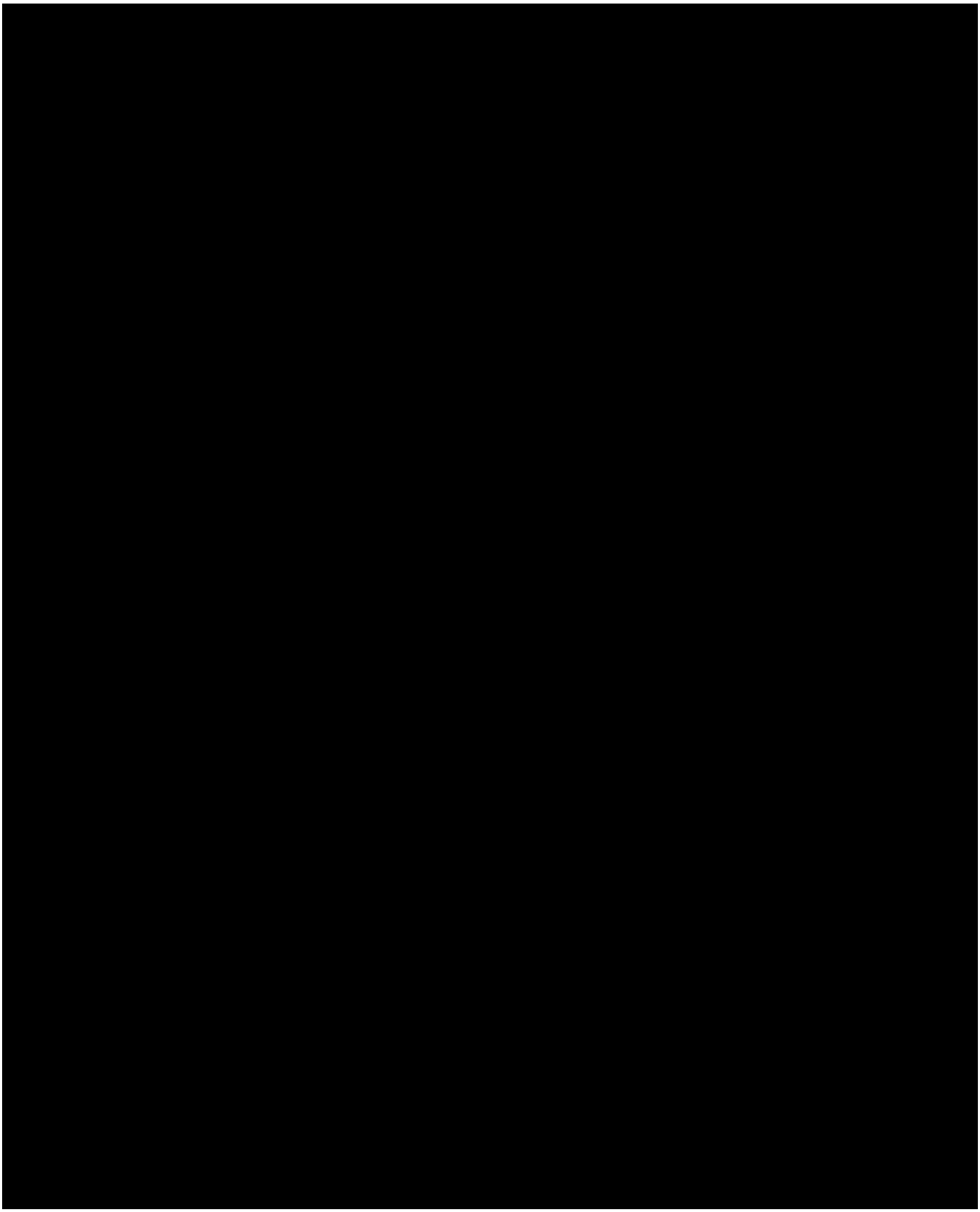
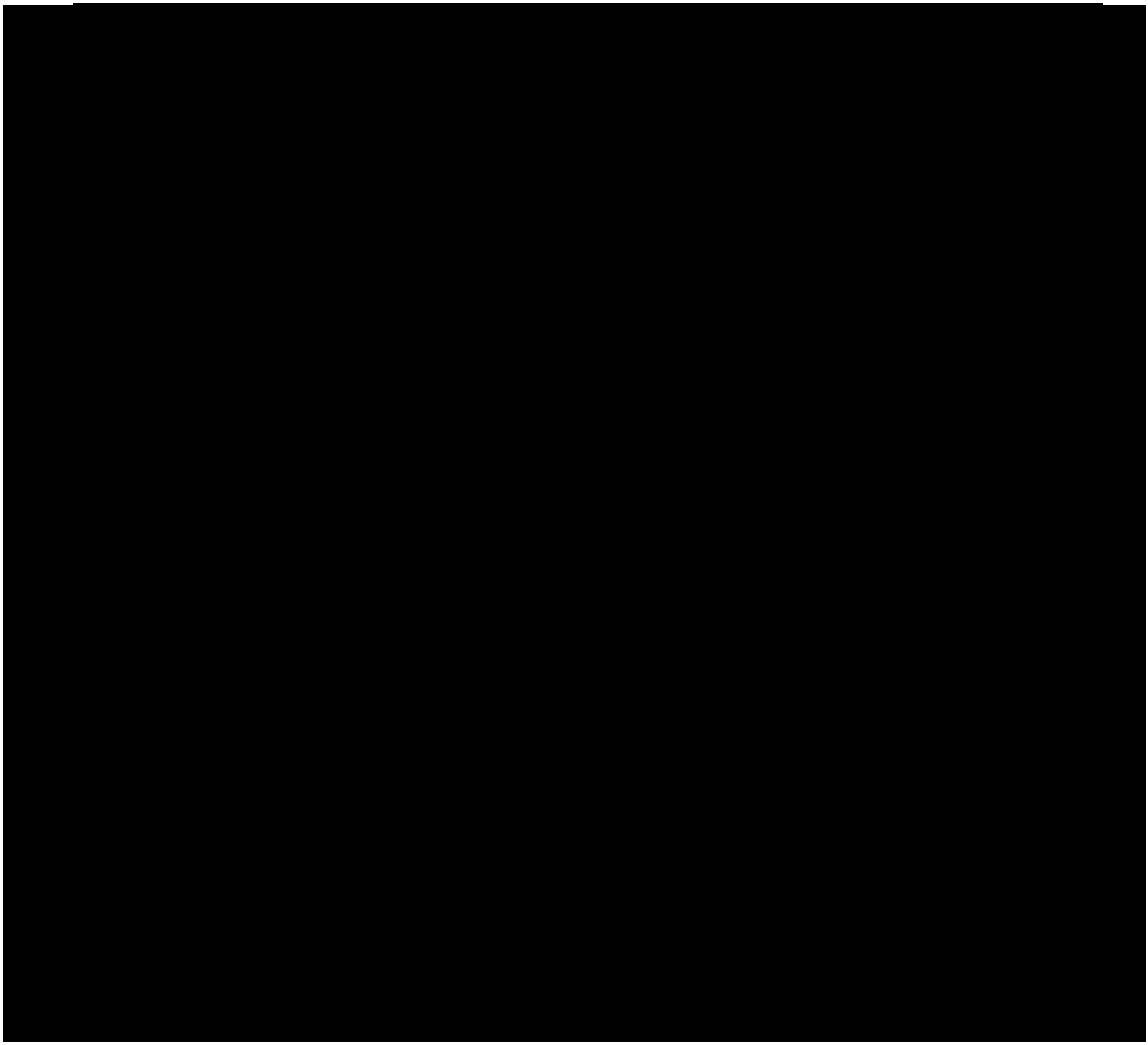
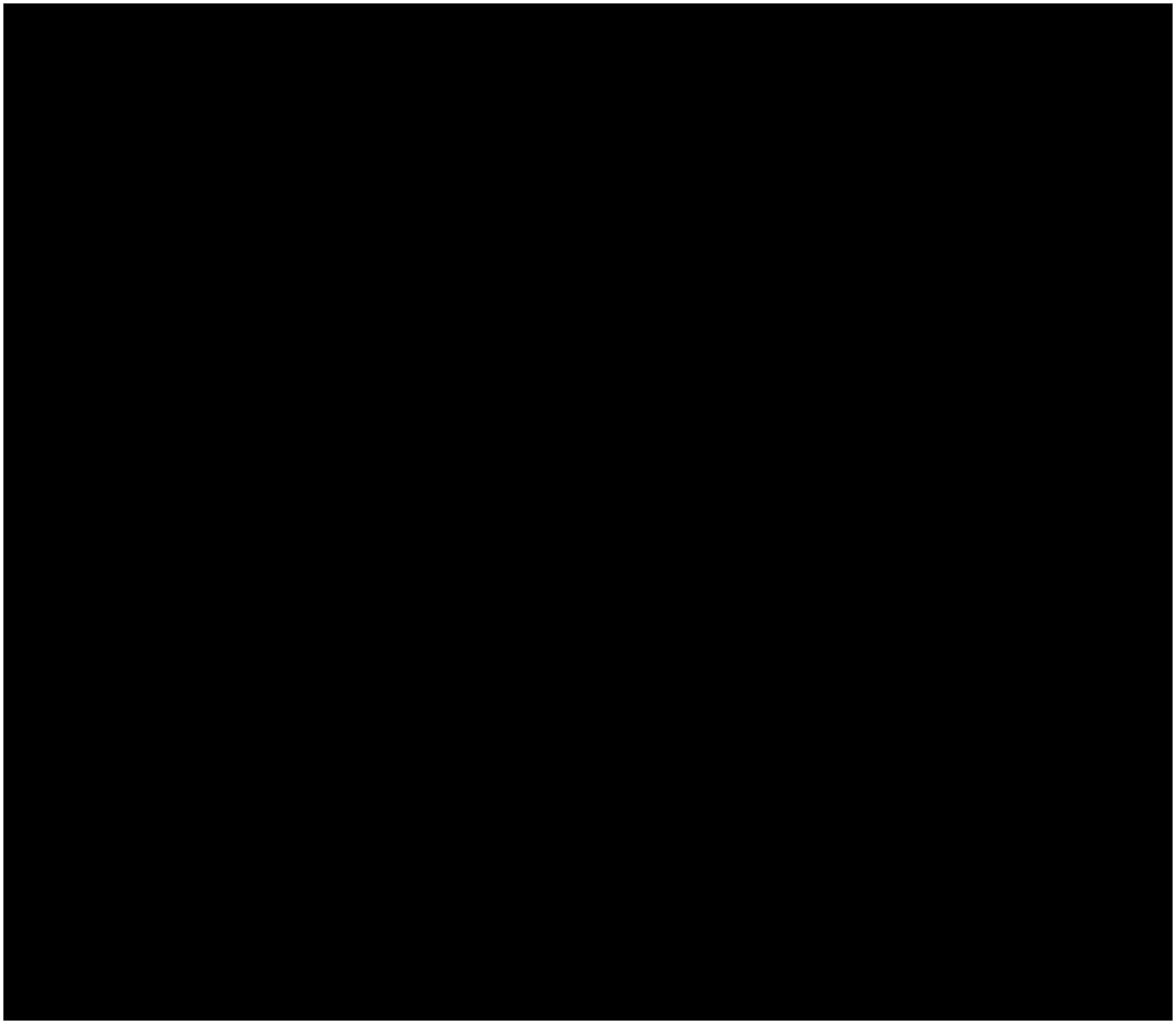








5. Statistical Methodology and Study Endpoints

5.1 Statistical and Analytical Plans

Subjects will receive treatment at the outset of the study (treatment group) or have treatment delayed by 3 months (control group). The analysis based on period up to Month 3 is referred to as "Untreated Control Period" (UCP). After the control group receives treatment, safety and effectiveness data will be collected. The analysis period based on treatment group and control group after treatment will be referred to as "Treated Period" (TP).

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

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
Modified Intent-to-Treat (mITT) population	• All subjects who are randomized to study treatment (treatment group) and receive at least 1 study device treatment and have baseline and at least 1 post-treatment assessment of the primary variable • All subjects who are randomized to the no-treatment control group and have baseline and at least 1 follow-up assessment of the primary variable	As treated
Per-protocol (PP) population	All mITT subjects who have baseline LFS score of Minimal, Mild, or Moderate, have Month 3 LFS assessments, and do not have any significant protocol deviations affecting the primary effectiveness endpoint	As treated
Safety population	• All subjects randomized to the treatment (treatment group) who receive at least 1 study treatment • All subjects randomized to the control group	As treated

Subjects will be analyzed as treated. All effectiveness analyses will be performed using the mITT population. Additional sensitivity analyses for the primary effectiveness analysis will also be performed using PP population. All safety analyses will be performed using the safety population.

5.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Study treatment: VOLBELLA with Lidocaine injectable gel
- Control Treatment: No-treatment control

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 of subjects in individual categories o Subjects with ≥ 1qualifying event counted once per individual category • N included = subjects with non-missing value for by-visit analysis
Categorical descriptives	• Number and percentage of subjects in individual categories o Subjects with ≥ 1qualifying event counted once per individual category • N included = subjects with non-missing value for by-visit analysis
Event descriptives	• Number and percentage of events in individual categories o Events counted individually for each instance • Percentage denominator = total number of events
Continuous descriptives	• N included, mean, standard deviation (SD), Q1, median, Q3, 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 2-sample t-test	• Continuous descriptives for baseline, postbaseline, and CFB values • For comparing VOLBELLA group vs. no-treatment control group during UCP (Volbella minus control) o Mean differences o P-values and 95% CI from 2-sample t-test • N included = subjects with non-missing values at both baseline and the specified postbaseline analysis visit
CFB Wilcoxon test	• Continuous descriptives for baseline, postbaseline, and CFB values • For comparing VOLBELLA group vs. no-treatment control group during UCP (Volbella minus control) o Mean differences o P-values and 95% CI from Wilcoxon rank-sum test • N included = subjects with non-missing values at both baseline and the specified postbaseline analysis visit
Responder exact test	• Categorical descriptives for responders • Exact binomial 95% CI of percentages within group • For comparing VOLBELLA group vs. no-treatment control group during UCP (VOLBELLA minus control) o Responder rate difference o 95% exact unconditional confidence interval o P-value from 2-sided Fisher's exact test • N included = with non-missing values at both baseline and the specified postbaseline analysis visit
Responder exact 95% CI within group (treatment group only)	• Categorical descriptives for responders • Exact binomial 95% CI of percentages within group • N included = with non-missing values at both baseline and the specified postbaseline analysis visit
Responder CMH	• Categorical descriptives for responders

Methodology	Description
test	• Responder rate differences for VOLBELLA group vs. no-treatment group during UCP • P-values from Cochran-Mantel-Haenszel test stratified by baseline characteristic comparing VOLBELLA group vs. no-treatment group during UCP • 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 summarized as follows:

Table 5-3 Missing Data Handling by Endpoint Type

Endpoint type	Timing	Missing Data Handling
Responder	Month 3 UCP	• All subjects included (mITT population) • Multiple imputation with 5 imputed datasets is applied to subjects with Month 3 LFS missing using the below model: Month 3 LFS = β_0 + β_1 Baseline LFS + β_2 Month 1 LFS
Responder	Month 3 UCP	• All subject included (mITT population) • Last observation carried forward (LOCF) for subjects with Month 3 LFS missing, baseline value will be carried forward if no postbaseline value before Month 3 Last observation will be carried forward regardless of schedule/ unscheduled visit or analysis window flag.

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

5.1.1.5 Site Pooling

No site pooling will be done. All analyses will also be presented by investigational site. No inferential statistics will be presented for by site analyses.

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

Endpoint	Description	Timing	Methodology
All Screened	List of all screened	Screening and Baseline screening	Listing
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, 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 subjects in total and by treatment group	Month 3, final	Categorical descriptives

5.1.2.3 Protocol Deviations

Protocol deviations will be defined in a separate document, including significance classification. Protocol deviations will be presented as follows:

Table 5-6 Protocol Deviation Summary

Endpoint	Description	Timing	Methodology
Significant protocol deviations	Number (%) of subjects with significant protocol deviations	During study period	Categorical counts

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
	  o Male
	  o Female
	• Race
	  o Asian
	• Ethnicity
	  o Chinese
		Screening	Categorical counts

5.1.2.5 Baseline Characteristics

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

Table 5-8 Baseline Characteristics Summaries

Endpoint	Description	Timing	Methodology
LFS score as assessed by EI	Number (%) of subjects in each category (Minimal, Mild, Moderate, Marked, Very Marked)	Screening	Categorical descriptives

LFS score as assessed by Subject	Number (%) of subjects in each category (Minimal, Mild, Moderate, Marked, Very Marked)	Randomization	Categorical descriptives
[redacted]	[redacted]	[redacted]	[redacted]
Fitzpatrick skin phototype	Number (%) of subjects in each category (I, II, III, IV, V, VI, as well as I/II, III/IV, V/VI)	Screening	Categorical descriptives
Exposure to Sunlight (hrs per day)	Exposure to Sunlight (hrs per day)	Screening	Continuous descriptives
Smoking status	Number (%) of subjects in each category, current, former, and never smoke	Screening	Categorical counts
Duration of smoking (in years)	Duration of smoking (in years)	Screening	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 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	Description	Timing	Methodology
Abnormalities and surgeries	Abnormalities and surgeries occurring before the Screening Visit	Screening	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
Treatment Group	Prior medications	Medications taken before the study treatment regardless of medication end date	Screening	Listing
	Concomitant medications during UCP	Medications taken on or after the study treatment and before Safety Day 91 (at month 3), regardless of medication start date or end date (For treatment group, concomitant medications during UCP consist a subset of concomitant medications during TP.)	UCP	Listing
	Concomitant medications during TP	Medications taken on or after the study treatment regardless of medication start date	TP	Listing
Control Group	Prior medications	Medications taken before randomization regardless of medication end date	Screening	Listing
	Concomitant	Medications taken after randomization and before	UCP	Listing

Endpoint		Description	Timing	Methodology
	medications during UCP	optional treatment (at month 3), regardless of medication start date or end date		
	Concomitant medications during TP	Medications taken on or after the study treatment regardless of medication start date	TP	Listing

5.1.2.8 Exposure to Study Treatment

Treatment exposure related variable will be summarized for safety population by treatment group (treatment group and treated control group), treatment (combined initial and touch-up, initial, touch-up), and treatment area as in Table 5-11. For treated control group, data after receiving initial treatment at Month 3 are included.

Table 5-11 Exposure to Study Treatment

Endpoint	Description	Timing	Methodology
Volume injected • Total • Upper Lip • Lower Lip Philtral Columns	Summarize by treatment group, treatment, and treatment area	Initial, Touch-up	Continuous descriptives
Treatment sites • Total • Upper Lip o Vermilion body o Vermilion border • Lower Lip o Vermilion body o Vermilion border • Philtral Columns	Summarize by treatment group, treatment, and treatment area	Initial, Touch-up	Categorical counts

5.1.2.9 Administration of Study Treatment

Variables related to administration of treatment will be summarized for safety population by treatment group (treatment group and treated control group), treatment (initial, touch-up), and treatment area as in Table 5-12. For treated control group, data after receiving initial treatment at Month 3 are included.

Table 5-12 Administration of Study Treatment

Endpoint	Description	Timing	Methodology
Pretreatment Anesthesia • Pretreatment Anesthesia type	Ice, Topical, Injectable, Other	Initial, Touch-up	Categorical counts
Pretreatment Anesthesia duration (minutes) • Pretreatment Anesthesia duration	Anesthesia duration is computed as injection time minus start of anesthesia administration time. Summarize by treatment group, treatment, and anesthesia type.	Initial, Touch-up	Continuous descriptives
Treatment administration • Injection technique • Planes of injection • Needle gauge length	Summarize by treatment group, treatment (initial or touch-up), and treatment area	Initial, Touch-up	Categorical counts

Endpoint	Description	Timing	Methodology
Pretreatment Anesthesia • Pretreatment Anesthesia type	Ice, Topical, Injectable, Other	Initial, Touch-up	Categorical counts
Pretreatment Anesthesia duration (minutes) • Pretreatment Anesthesia duration	Anesthesia duration is computed as injection time minus start of anesthesia administration time. Summarize by treatment group, treatment, and anesthesia type.	Initial, Touch-up	Continuous descriptives
• Massage used • Device/Needle problem or malfunction			
Characteristics of the product • Injection ease • Product moldability	Summarize by treatment group, treatment (initial or touch-up), and treatment area	Initial, Touch-up	Categorical counts

5.1.3 Effectiveness Analyses

All effectiveness analyses will be based on the mITT Population.

The following effectiveness assessments are defined as:

Table 5-13 Effectiveness Assessments

Assessment	Description
Lip fullness	Assessed by EI and subject based on the overall lip fullness using the 5-point LFS. (Vey Marked, Marked, Moderate, Mild, Minimal)
Overall lip volume	The volume of the overall lips as measured from 3D images.
Lip surface area	The lip surface area as measured from 3D images.
[redacted]	[redacted]
[redacted]	[redacted]

Baseline assessments for applicable effectiveness endpoints are defined as follows:

Table 5-14 Effectiveness Endpoint Baseline Definitions

Endpoint	Description	Timing
• Overall Lip fullness • Overall lip volume • Lip surface area • Philtral column definition	Baseline refers to the last evaluation prior to initial treatment for treatment group, and prior to randomization for control group	Screening/ Randomization
[redacted]	[redacted]	[redacted]

5.1.3.1 Primary Effectiveness Endpoint

The primary effectiveness analysis based on UCP is summarized in the following table. Subjects with baseline LFS score as assessed by EI of Minimal, Mild, or Moderate are enrolled in the study. A LFS (as accessed by EI) responder is defined as a subject with at least one grade improvement from baseline on 5-point LFS as assessed by EI.

Table 5-15 Primary Effectiveness Analyses

Endpoint	Description	Timing	Methodology
LFS Responder as assessed by EI	Superiority of VOLBELLA with Lidocaine over no-treatment control Number (%) of responders by treatment group (mITT population)	Month 3	Responder exact test

The primary effectiveness analysis will be performed based on the mITT population without any missing data imputation. For treatment subjects, assessments within window will be used. For control subjects who do not receive optional treatment, the assessments within month 3 window will be used. For control subjects who receive optional treatment, the assessments within month 3 window and before optional treatment will be used. Sensitivity analysis will be performed using missing data handling conventions as described in Section 5.1.1.4 as well as using PP population.

5.1.3.2 Secondary Effectiveness Endpoints

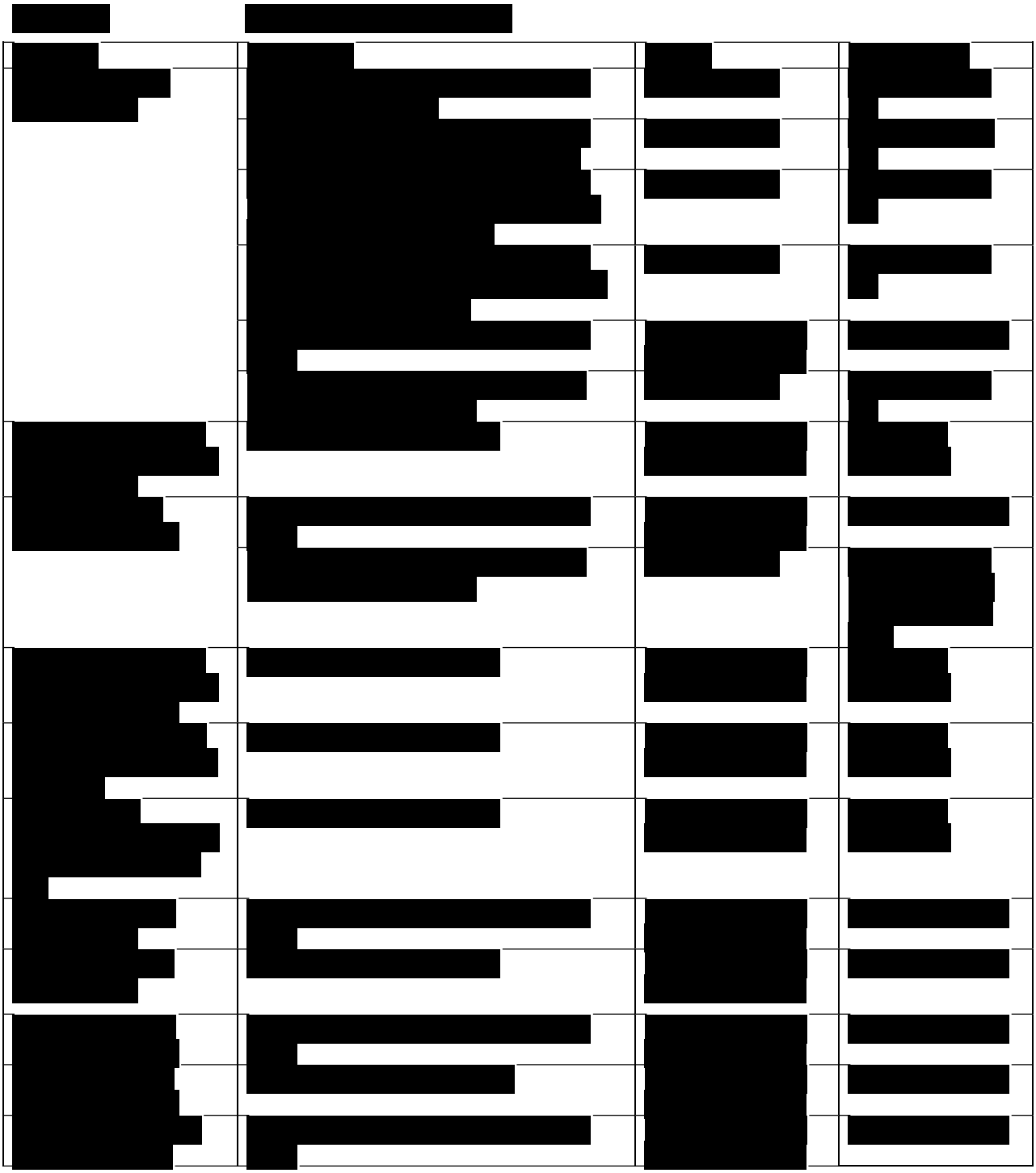
The secondary effectiveness analysis based on UCP is summarized in the following table.

Table 5-16 Secondary Effectiveness Analyses

Endpoint	Description	Timing	Methodology
LFS responder as assessed by subject	Number (%) of responders by treatment group	Month 3	Responder exact test within group (treatment group only)
Change from baseline in overall lip volume	Summary by treatment group	Month 3	CFB 2-sample t-test or Wilcoxon test
Percentage change from baseline in lip surface area	Summary by treatment group	Month 3	CFB 2-sample t-test or Wilcoxon test

[redacted]

[redacted]



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5.1.4 Safety Analyses

Safety analyses will be based on the Safety Population.

5.1.4.1 Study Treatment Exposure and Compliance

See Sections 5.1.2.8 and 5.1.2.9

5.1.4.2 Adverse Events

The following treatment emergent adverse event (TEAE) terms are defined:

Table 5-18 AE Terms

Term	Description	Timing
Treatment group	An event that initially occurs or increases in severity on or after the treatment and before safety day 91 (month 3) (For treatment group, TEAEs during UCP consist a subset of TEAEs during TP.)	UCP
	An event that initially occurs or increases in severity on or after the treatment	TP
Control Group	An event that initially occurs or increases in severity on or after randomization and before optional treatment at month 3	UCP
	An event that initially occurs or increases in severity on or after optional treatment at month 3	TP

AEs, encompassing abnormalities reported as occurring after the Screening Visit, will be coded using MedDRA version 18.1 or newer. A listing for all AEs in the treatment and control groups will be presented. Additionally, unique subjects reporting AEs as well as number of events in the following AE categories will be summarized for treatment subjects, control subjects after treatment, and all treated subjects as listed in Table 5-19. AEs during UCP will be listed only.

Table 5-19 AE Summaries

Endpoint	Description	Timing	Methodology

Overall summary	Treatment-emergent AEs (TEAEs)
	• Treatment-related TEAEs
	  o At injection site
	  o Not at injection site
	• All Serious AEs (SAEs)
	  o Treatment-related SAE
	  ▪ At injection site
	  ▪ Not at injection site
	• Discontinued due to TEAE
	• Deaths
		TP	Categorical counts, Event descriptives

TEAEs	• Overall summary and by SOC, PT, and severity	TP	Categorical counts, Event descriptives
Treatment-related	• Overall summary and by SOC, PT, and	TP	Categorical counts,

Endpoint	Description	Timing	Methodology
TEAEs	severity • Overall summary by duration, time to onset, outcome, and treatment required		Event descriptives
SAEs	Overall summary and by PT	TP	Listing
AEs leading to discontinuation	Overall summary and by PT	TP	Listing

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

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.

Duration for TEAEs will be computed as AE end date – AE start date + 1.

5.1.4.3 Injection Site Responses (ISR)

ISRs recorded in subject diaries after each treatment (initial, touch-up) will be summarized for that treatment by predefined symptoms.

Table 5-20 ISR Analyses

Endpoint	Description	Timing	Methodology
ISR severity	Maximum reported severity	Initial, Touch-up	Categorical counts
ISR duration	Duration from first instance of the symptom to the last instance of the symptom within the treatment period, where last instance means no further symptoms till the end of the 30-day diary period. Duration is derived as date of last ISR minus date of first ISR plus one.	Initial, Touch-up	Categorical counts
ISR	All ISR Diary analysis day will be derived using diary date minus last treatment date plus one.	Initial, Touch-up	Listing

5.1.4.4 Procedural Pain

Subject assessment of procedural pain (pain during injection) on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable) after initial treatment will be summarized.

Table 5-21 Procedural Pain Analyses

Endpoint	Description	Timing	Methodology

Endpoint	Description	Timing	Methodology
Procedural pain	Summary of pain scores as continuous scale	Initial	Continuous descriptive

5.1.4.5 Clinical Laboratory Assessments

Clinical laboratory assessments are taken at Screening, Month 1 and Month 6. Subjects with at least one abnormal finding will be listed for the Safety Population.

5.1.4.6 Vital Signs and Physical Measurement

Vital signs and physical measurement (height and weight) will be listed and summarized for the Safety Population.

Table 5-22 Physical Examination Analyses

Endpoint	Description	Timing	Methodology
Vital signs	Summary of blood pressure (systolic and diastolic in a sitting position), temperature, pulse, and respiratory rates	Month 1, 3 (UCP), Month 1, 3, 6 (TP)	Continuous descriptives
Physical measurement	Summary of height, weight, and BMI	Screening	Continuous descriptives

5.1.4.7 Electrocardiograms

Electrocardiograms (EKG) will be taken at Screening and initial treatment visit. Subjects with abnormal finding will be listed.

5.1.4.8 Pregnancy Test Analyses

Urine pregnancy test is taken at screening, initial, touch-up, and Month 6. Subjects with positive result will be presented as listing.

5.1.5 Subgroup Analyses

Subgroup analyses of the primary effectiveness endpoint will be performed by baseline lip LFS score and volume injected ($\leq$ median vs > median). All analyses will be repeated for each investigational site descriptively.

Table 5-23 Subgroup Analyses

Endpoint	Description	Timing	Methodology
LFS Responder as assessed by EI by baseline LFS score	Number (%) of responders by treatment group by baseline LFS score	Month 3	Categorical count
LFS Responder as	Number (%) of responders by	Month 3	Categorical count

Endpoint	Description	Timing	Methodology
assessed by EI by volume injected	treatment group by volume injected (≤ median, and > median)		
All analyses by investigational site	Summary by investigational site	As described in Table 5-15, 5-16, 5-17	As described in Table 5-15, 5-16, 5-17

5.1.6 Interim Analyses

Not applicable.

5.2 Determination of Sample Size

Up to 176 subjects will be randomized at up to 9 Chinese sites.

Table 5-24 Sample Size Assumptions

Parameter	Assumption / Estimate
Primary endpoint	Lip fullness assessment responder
Risk difference[1]	34.1% (79% Volbella vs 44.1% Control)
SD	NA
α	5%
Sides	2
Power	> 96%
N per group	111 in treatment group, 37 in no-treatment control group
Drop-out Rate	15%
N total randomized	176

[1] Based on interim data from Study JULIDO-002.

5.3 Changes in the Conduct of the Study or Planned Analyses

5.3.1 Changes in the Conduct of the Study

Prior to database lock, there were no changes in study conduct.

5.3.2 Changes to Analyses Prior to Database Lock

Cross table for overall lip fullness responders between subjects and Evaluating Investigators will not be provided.

6. Data Handling and Analysis Conventions

6.1 Analysis Days

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

Table 6-1 Analysis Day Definitions

Term	Description
Analysis day: Effectiveness Day	VOLBELLA Group Relative to the last treatment date (either the initial treatment, if no touch-up is performed,

Term	Description
	or the touch-up treatment) If analysis date >= last treatment date: • Effectiveness Day = analysis date – last treatment date + 1 • Effectiveness Day 1 = last treatment date If analysis date < last treatment date: • Effectiveness Day = analysis date – last treatment date • Effectiveness Day -1 = day before last treatment date <u>Control group before receiving treatment</u> Relative to the randomization date If analysis date >= randomization date: • Effectiveness Day = analysis date –randomization date +1 • Effectiveness Day 1 = randomization date If analysis date < randomization date: • Effectiveness Day = analysis date –randomization date • Effectiveness Day -1 = day before randomization date <u>Control group after receiving treatment</u> Relative to the last treatment date (either the initial treatment, if no touch-up is performed, or the touch-up treatment) If analysis date >= last treatment date: • Effectiveness Day = analysis date – last treatment date + 1 • Effectiveness Day 1 = last treatment date
Analysis day Safety Day	<u>VOLBELLA Group</u> Relative to the immediate prior treatment date (initial or touch-up) If analysis date >= initial treatment date: • Safety Day = analysis date – immediate prior treatment date + 1 • Safety Day 1 = immediate prior treatment date If analysis date < initial treatment date: • Safety Day = analysis date – immediate prior treatment date • Safety Day -1 = day before immediate prior treatment date <u>Control group before receiving treatment</u> Relative to the randomization date If analysis date >= randomization date: • Safety Day = analysis date –randomization date +1 • Safety Day 1 = randomization date If analysis date < randomization date: • Safety Day = analysis date –randomization date • Safety Day -1 = day before randomization date <u>Treated Control after receiving treatment</u> Relative to the immediate prior treatment date (initial or touch-up) If analysis date >= initial treatment date: • Safety Day = analysis date – immediate prior treatment date + 1 • Safety Day 1 = immediate prior treatment date

6.1.1 Missing/Incomplete Treatment End Date

Not applicable.

6.2 Analysis Visit Windows

6.2.1 Effectiveness

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

Table 6-2 Effectiveness Analysis Visit Definitions for Treatment Group

Analysis Visit	Target Day of the Visit	Analysis Visit Window
Screening [a]	N/A	Screening visit
Baseline	N/A	Randomization/Initial treatment visit
Touch-up treatment [b]	Day 30 After Initial Treatment	Day 30 after initial treatment visit
Last treatment [c]	Day 1	Day 1
Month 1	Day 31	Days [2, 61]
Month 3	Day 91	Days [62, 136]
Month 6	Day 181	>=Day 137

[a] Subjects may have screening and randomization on the same day. In such cases, only randomization visit is relevant.

[b] Not all subjects will receive touch-up treatment.

[c] Initial treatment if touch-up is not performed, otherwise touch-up treatment

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

Analysis Visit	Target Day of the Visit	Analysis Visit Window
Screening[a]	N/A	Screening visit
Baseline	Day 1	Randomization visit
Month 1	Day 31	Days [2, 61]
Month 3	Day 91	From Day 62 to study exit day if the subject didn't receive optional treatment, or to the day of optional treatment if the subject received optional treatment The assessments before the optional treatment on that day will be accounted for Month 3 visit.

Table 6-4 Effectiveness Analysis Visit Definitions for Control Group during Treatment Period

Analysis Visit	Target Day of the Visit	Analysis Visit Window
Baseline	N/A	Randomization visit
Initial treatment[a]	N/A	N/A
Touch-up treatment[b]	Day 30 After Initial Treatment	Day 30 after initial treatment visit
Last treatment[c]	Day 1	Day 1
Month 1	Day 31	Days [2, 61]

Month 3	Day 91	Days [62, 136]
Month 6	Day 181	>=Day 137

[a] Initial treatment is at Month 3 visit.

[b] Not all subjects will receive touch-up treatment.

[c] Initial treatment if touch-up is not performed, otherwise touch-up treatment.

If there are multiple visits occurring within a single visit window with relevant data, the visit closest to the target day listed above will be used in the analysis of the corresponding visit windows regardless of scheduled or unscheduled visit. If two visits are equal distant to the target day and are the same type of visit, then the later visit will be used.

6.2.2 Safety

No analysis visit windows are required for TEAEs and ISRs.

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 treatment date if they have the same month and year, whichever is later

6.3.2 Missing/Incomplete AE End Date

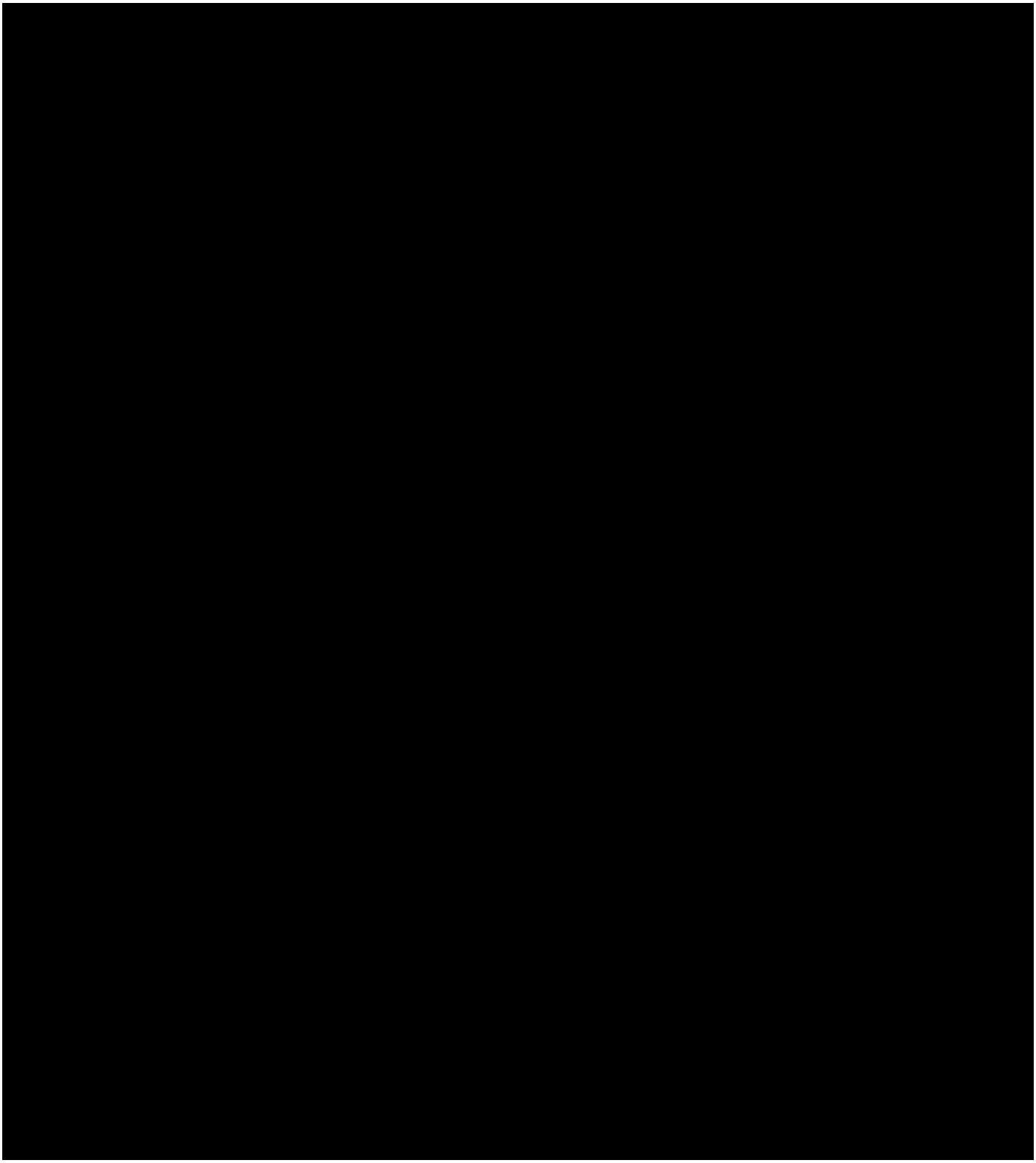
Imputation of dates with missing day and/or month is only applied to TEAEs. If adequate information is available, no imputation is needed. TEAE end dates with missing day or month will be imputed as following:

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

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

6.4 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.



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Statistical Analysis Plan VOLBELLA-005 China

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]