NCT03430986

Study ID: 1894-701-008

Title: A Randomized, Multicenter, "No-Treatment" Control Study to Evaluate the Safety and Effectiveness of JUVÉDERM® VOLUMA® with Lidocaine Injectable Gel for the Improvement of Volume and Aesthetic Appearance of the Nose in Chinese Adults

Statistical Analysis Plan Amendment 1 Date: 3Feb2020

Title Page

Protocol Title: A Randomized, Multicenter, "No-Treatment" Control Study to Evaluate the Safety and Effectiveness of JUVÉDERM® VOLUMA® with Lidocaine Injectable Gel for the Improvement of Volume and Aesthetic Appearance of the Nose in Chinese Adults

Protocol Number: 1894-701-008

Compound Number: JUVÉDERM® VOLUMA® with Lidocaine Injectable Gel

Sponsor Name: Allergan

Legal Registered Address: 2525 Dupont Drive,
Irvine, CA 92612

Regulatory Agency Identifier Number(s)

NCT03728309

Approval Date: February 3, 2020

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SAP Version History

This SAP for study 1894-701-008 is based on the protocol Amendment 1 (dated 22-Sep-2017).

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1	August 13, 2019	Not Applicable	Original version
2		Baseline definition for efficacy analysis in control group	Including participants with baseline 3D photos taken after randomization due to Canfield setting-up error
		Add a rule of analysis for participants who have two measurements at one visit in Section 6.4.1	Dealing with data issues: some participants have more than one photo taken at one visit
		Add explanation of analysis population definition change	Providing justification of the changes
		Wording change: “subject” to “participant”	Following internal new guidance
		Change VITP to VOLUMA; VOTP to VOLUMA Post-Control in Table 5.1	Being consistent with wording in shell

1. Introduction

This SAP provides a more technical and detailed elaboration of the statistical analyses of the effectiveness and safety data as outlined and specified in study 1894-701-008 protocol Amendment 1 (approved version dated 22-Sep-2017). Specifications of tables, figures, and data listings are contained in a separate document.

1.1. Objectives and Endpoints

Objective Clinical Category	Statistical Category	Estimand/Variable
Primary Objective: to evaluate the safety and effectiveness of VOLUMA with Lidocaine injectable gel for the improvement of volume and aesthetic appearance of the nose in a Chinese population.		
Effectiveness[1]	Primary	• Variable: change from baseline in the nose volume calculated by digital analysis of each participant's 3D images at Week 24 • Population: mITT • IES: o Missing at random will be assumed in an MMRM model, therefore no imputation will be conducted • PLS: change from baseline between treatment and control groups o MMRM
	Secondary	• Variable: GAIS responder by EI and participant, NSS responder by participant at Week 24 • Population: mITT • IES: o Participants with missing data at Week 24 will not be imputed • PLS: responder rates between treatment and control groups o Fisher's exact test
Safety	Primary	• Variable: o TEAEs o ISRs • Population: Safety Population • Analysis: Categorical descriptive

IES = Intercurrent event(s) strategy; PLS = Population-level summary.
[1] All estimand attributes explicitly identified for primary/secondary and select key estimands only.

1.2. Study Design

Study 1894-701-008 is a prospective, multicenter, randomized, "no treatment" control design study to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA® with Lidocaine injectable gel (hereafter, VOLUMA with Lidocaine) to improve the volume and aesthetic appearance of the nose in Chinese adults.
The following treatment groups are defined for this study:

- Study Treatment: JUVÉDERM® VOLUMA® with Lidocaine Injectable Gel
- Control Treatment: No-treatment

This trial consists of 2 periods: Control Period and Post-Control Period.

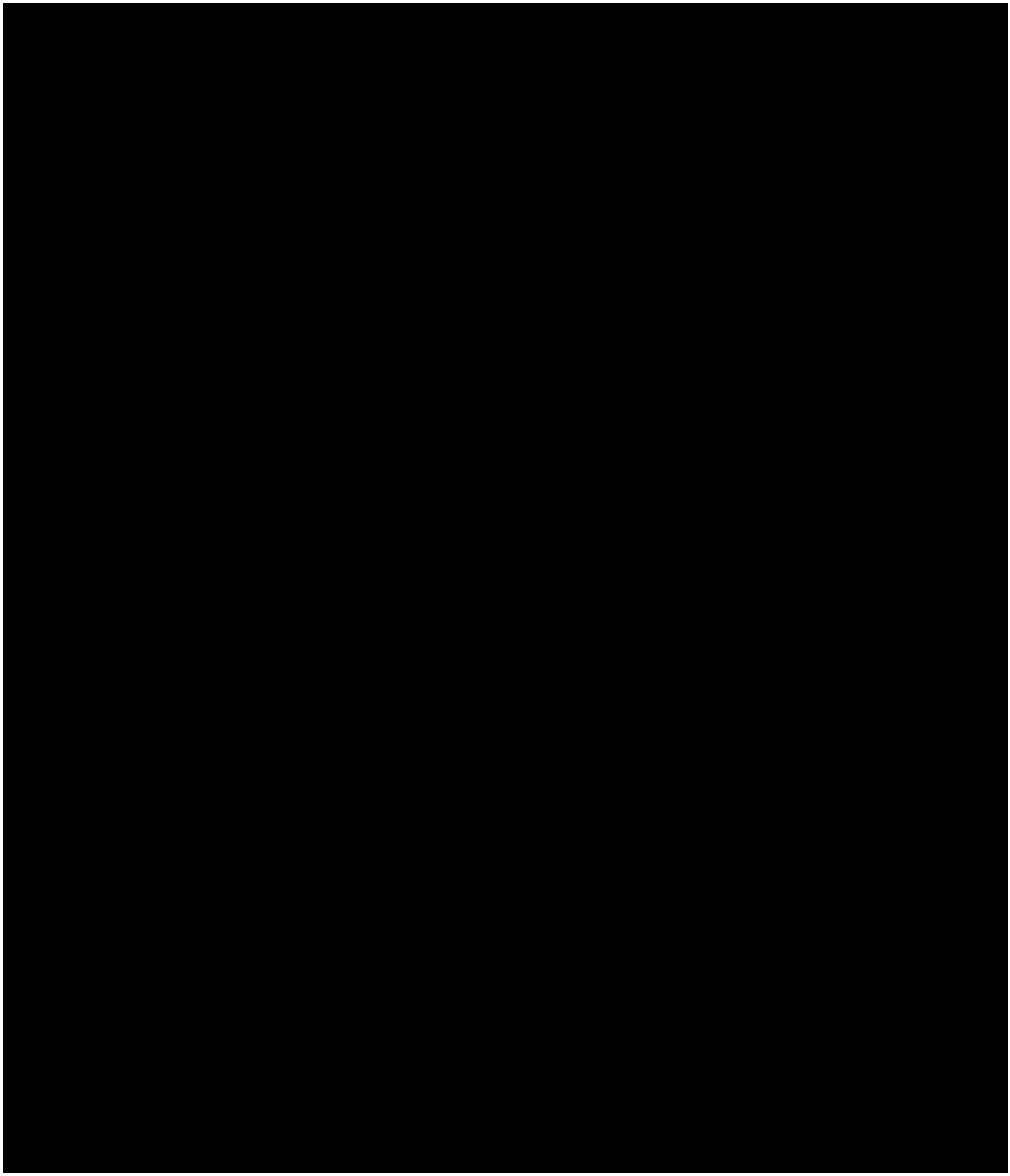
Participants will be randomized in a 3:1 ratio either to have treatment with VOLUMA with Lidocaine at the outset of the study (treatment group) or a 24-week control period followed by optional delayed treatment (control group).

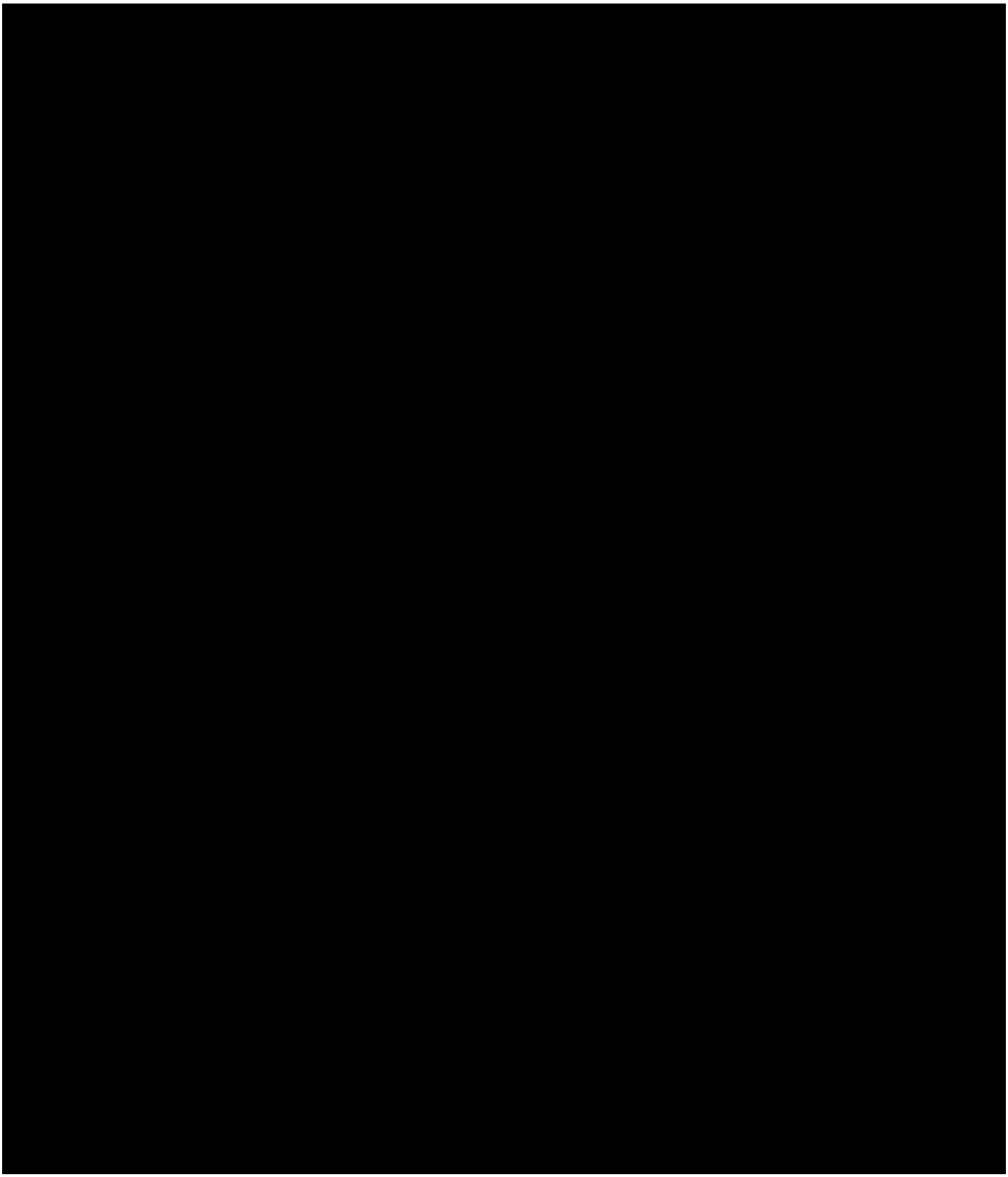
At least 160 participants will be randomized at up to 9 investigational sites.

No interim analyses are planned for this study.

The Schedule of Visits and Procedures during the study are presented in Table 1–1, Table 1–2, and Table 1–3.

[redacted]





2. Statistical Hypotheses

The null hypothesis is that there is no difference between the treatment group and the control group in mean change from baseline in volume in nose area based on 3D imaging. The alternative hypothesis is that there is a difference in mean change from baseline in volume in nose area based on 3D imaging between that treatment group and control group.

$$Ho: \mu T = \mu C \text{ versus } Ha: \mu T \neq \mu C$$

where μT and μC denote the mean change in volume from baseline for the treatment group and control group, respectively, at Week 24.

The hypotheses will be tested using an MMRM model with change from baseline in nose volume as the response variable, with treatment, timepoint (visit of Weeks 8, 16, and 24), treatment-by-timepoint interaction as fixed effect. Participant will be included in the model as a random effect.

3. Sample Size Determination

A sample size of 90 treatment and 30 control participants will provide 99.6% power to detect a difference of 0.9 mL in the mean volume change from baseline between the treatment and control group, assuming a mean change from baseline of 1.1 mL with standard deviation of 0.9 mL, and mean change from baseline of 0.2 mL with standard deviation of 0.9 mL, for the treatment and control groups, respectively. This calculation is based on a 2-sample, 2-sided t-test at 5% significance level. The assumptions of means and standard deviations are estimated from Allergan studies VOLXC-AP-ND-001 and VOLUMA-004. In order to have over 100 treatment group participants complete 1-year follow-up, accounting for participant attrition of 15% during the whole study duration through Week 48, at least 120 participants in the treatment group and 40 participants in the control group will be randomized.

4. Populations for Analysis

The analysis populations will consist of participants as defined in Table 4–1:

Table 4–1 Analysis Populations

Population	Definition	Study Treatment
mITT Population	All participants who are randomized and have at least 1 assessment of change from baseline in nose volume	As randomized
PP Population	All mITT participants who have baseline and Week 24 assessments of change from baseline in nose volume and do not have any significant protocol deviations affecting the primary effectiveness endpoint	As randomized
Safety Population	All randomized participants who receive VOLUMA treatment in the Control Period or who do not receive VOLUMA treatment in the Control Period and with at least 1 follow-up assessment	As treated
VOLUMA Initial Treated Population (VITP)	Participants randomized and received VOLUMA treatment in the Control Period with up to 48 weeks follow-up	As treated
VOLUMA Optionally Treated Population (VOTP)	Participants randomized to control group and received optional VOLUMA treatment in Post-Control Period. These participants will have up to 24 weeks follow-up after optional VOLUMA treatment (or touch-up treatment).	As treated

5. Statistical Analyses

5.1. General Considerations

- The primary analysis will be performed after the database is locked and randomization schedule is released.
- Participants will receive treatment at the outset of the study (treatment group) or have treatment delayed until Week 24 (control group). The delayed treatment for control group is optional and referred to as "Optional Treatment".
- Control Period (CP), Treated Period (TP) are defined in Table 5-1 .

Table 5-1 CP and TP definition

Randomization Group	Period	Treatment Group Label	Start Date	End Date
Treatment	CP	VOLUMA	Initial treatment date	The date of effective assessment for Week 24. • If multiple assessments fall into Week 24 window, the date of the assessment included in the Week 24 analysis will be used as end date. • For participants who exit before Week 24, the end date is study exit date. • For participants with intermittent missing assessment at Week 24, the target day for Week 24 (Day 169) will be the end day.
	TP	VOLUMA	Initial treatment date	Study exit date
Control	CP	Control	Randomization date	For participants who do not receive optional treatment • If multiple assessments fall into Week 24 window, the date of the assessment included in the Week 24 analysis will be used as end date. • For participants who exit before Week 24, the end date is study exit date. • For participants with intermittent missing assessment at Week 24, the target day for Week 24 (Day 169) will be the end day. For participants who receive optional treatment: The day before optional treatment
	TP	VOLUMA Post-Control	Optional initial treatment date	Study exit date

- For CP, effectiveness analyses and baseline characteristics will be performed on the mITT population using the "as-randomized" assignment. One of the sensitivity analyses for the primary endpoint will be based on PP population. Safety analyses for CP will be conducted using the Safety Population based on "as-treated" assignment.
- For TP, effectiveness and safety summaries will be performed on the VITP and VOTP using "as-treated" assignment.
- For applicable effectiveness endpoints, baseline is defined as the last non-missing value prior to the start of study treatment for treatment group or no later than randomization date for control group.
- Descriptive statistics for continuous variables include the sample size (n), mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum.
- Summary statistics for categorical variables include the sample size (N1), frequency count, and percentage.
- Partial dates will be treated as missing in computations but listed in the data listings as they appear on the eCRFs unless otherwise specified. No imputation of missing values will be performed, unless otherwise specified.
- The level of significance used for all statistical tests will be 0.05, 2-sided, unless stated otherwise.
- The change from baseline values will be computed as the value for the post baseline visit minus the baseline value, unless otherwise indicated.
- All statistical analysis will be performed using SAS version 9.3 or higher.
- MedDRA will be used to code adverse events and medical history.
- WHO Drug Dictionary will be used to code medications.

5.2. Participant Dispositions

The number of participants in each of the 5 study populations (mITT, PP, Safety, VITP and VOTP) will be summarized (by treatment group as appropriate).

The number of participants screened will be summarized. Screen-failure participants (ie, participants who are screened but are not randomized) and the associated reasons for failure as recorded in the eCRF will be listed for the all screened participants.

Summary of study disposition will be provided by treatment group for the following:

- Number of participants randomized
- Number of participants treated as randomized
- Number of participants treated not as randomized

For mITT Population during Control Period

- Number of participants completed Control Period
- Number of participants discontinued during Control Period
- Reasons for discontinuation during Control Period

For VITP during Post-Control Period

- Number of participants continued after Control Period
- Number of participants completed Post-Control Period
- Number of participants discontinued during Post-Control Period
- Reasons for discontinuation during Post-Control Period

For VOTP during Post-Control Period

- Number of participants continued after Control Period
- Number of participants completed Post-Control Period
- Number of participants discontinued during Post-Control Period
- Reasons for discontinuation during Post-Control Period

For mITT Population during the study

- Number of participants completed the study
- Number of participants discontinued from the study
- Reasons for discontinuation from the study

5.3. Primary Effectiveness Endpoint Analysis

5.3.1. Definition of Endpoint

The primary effectiveness endpoint is the change from baseline in mean change in the nose volume based on 3D imaging at Week 24, which is calculated by digital analysis of each participant's 3D images. The change from baseline in nose volume is also referred to as nose volume change.

5.3.2. Main Analytical Approach

The hypotheses described in Section 2 will be tested based on the mITT population using MMRM model. The model will include nose volume change as the response variable, and treatment, timepoint (visit of Weeks 8, 16, and 24), treatment-by-timepoint interaction as fixed effect. Participant will be included in the model as a random effect. Restricted maximum likelihood method will be used. The within-participant correlation will be modeled using the unstructured covariance matrix. If the model does not converge, then the Toeplitz covariance structure will be used. If the model with the Toeplitz covariance structure does not converge, then other methods will be further explored and used. The Kenward-Roger approximation (Kenward 1997) will be used to estimate denominator degrees of freedom. In this MMRM model, missing at random will be assumed, therefore no imputation will be conducted.

Each treatment effect and treatment comparisons will be estimated by the LS Means and their differences in LS Means, along with their SE and 95% CIs, and the p-value corresponding to the between-treatment group difference.

The sample SAS code is given as follows

```
proc mixed data = effectiveness_dataset METHOD=REML;
  class trt visit subjid;
  model chg = trt visit trt*visit / s ddfm= kr;
  Repeated visit / type = UN subject = subjid;
  lsmestimate trt*visit;
  run;
```

5.3.3. Sensitivity Analyses

In addition, sensitivity analysis of the primary effectiveness endpoint will be done using MMRM based on PP population. The analysis model is the same for the primary analysis. Listing of the participants with effectiveness data excluded PP analysis will be provided for mITT population.

Additional sensitive analyses include using t-test and Wilcoxon rank test for group comparison using observed data based on mITT population.

Summary of sensitivity analyses are presented in Table 5–2.

Table 5–2 Sensitivity Analyses of Primary endpoint

Endpoint	Description	Timing	Methodology
Nose volume change based on 3D digital imaging (sensitivity analyses)	Superiority of the treatment group over control group (PP population)	Weeks 8, 16, and 24	MMRM
	Superiority of the treatment group over control group using observed data (mITT population)	Week 24	2-sample t-test
	Superiority of the treatment group over control group using observed data (mITT population) This analysis will be done when normality is not established	Week 24	Wilcoxon test

5.3.4. Supplementary Analyses

Descriptive statistics will be summarized for VITP and VOTP, which includes all visits after study injection (i.e., Weeks 8, 16, 24, 36, and 48 for the former and Weeks 8, 16, and 24 for latter).

5.4. Secondary Effectiveness Endpoints Analysis

5.4.1. Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are the proportion of GAIS responders by EI at Week 24, the proportion of GAIS responders by participant at Week 24, and the proportion of NSS responders by participant at Week 24.

A GAIS responder is defined as a participant with "Improved [1]" or "Much improved [2]" marked on the 5-point GAIS (Much Improved [2], Improved [1], No Change [0], Worse [-1], Much Worse [-2]) as assessed by EI or participant at Week 24.

An NSS responder is a participant with "Satisfied [1]" or "Very Satisfied [2]" marked on the 5-point NSS (Very satisfied [2], Satisfied [1], Neutral [0], Dissatisfied [-1], Very dissatisfied [-2]) at Week 24.

5.4.2. Main Analytical Approach

The secondary effectiveness endpoints will be analyzed using Fisher's exact test based on mITT population as observed.

The exact binomial 95% CI will be provided for the proportion of responders within each treatment group. For comparison of treatment group versus control group at Week 24, the responder rate difference, 95% exact unconditional CI for risk difference, and p-value from 2-sided Fisher's exact test will be presented.

Secondary effectiveness analyses are summarized in Table 5–3.

Table 5–3 Secondary Effectiveness Analyses

Endpoint	Description	Timing	Methodology
Responder status based on GAIS by EI	Number (%) of responders by treatment group	Week 24	Fisher's exact test
Responder status based on GAIS by participant	Number (%) of responders for treatment group	Week 24	Fisher's exact test
Responder status based on NSS by participant	Number (%) of responders for treatment group	Week 24	Fisher's exact test

[redacted]

[redacted]

5.6. Safety Analyses

5.6.1. Extent of Exposure

Treatment exposure-related variables will be summarized for the VITP and VOTP, respectively. The summary will be performed for initial treatment, touch-up treatment, and by treatment area as described in Table 5–5.

Table 5–5 Exposure to Study Treatment

Endpoint	Description	Timing	Methodology
Volume injected • Total • Nasal dorsum • Columella • Anterior nasal spine	Summary by treatment group, treatment (initial or touch-up), and treatment area	Initial, Touch-up	Continuous descriptives
Treatment sites • Total • Nasal dorsum • Columella • Anterior nasal spine	Summary by treatment group, treatment (initial or touch-up)	Initial, Touch-up	Categorical descriptives

5.6.2. Administration of Study Treatment

Variables related to administration of treatment will be summarized for the VITP and VOTP, respectively. The summary will be performed for initial treatment, touch-up treatment, and by treatment area as described in Table 5–6.

Table 5–6 Administration of Study Treatment

Endpoint	Description	Timing	Methodology
Pre-treatment Anesthesia type • Ice • Lidocaine cream • Nerve block • Other	Summary by treatment group, treatment (initial or touch-up)	Initial, Touch-up	Categorical descriptives
Pre-treatment anesthesia duration (minutes) • Anesthesia duration is computed as injection time minus start of anesthesia administration time. Summarize by treatment group, treatment, and anesthesia type.	Summary by treatment group, treatment (initial or touch-up)	Initial, Touch-up	Continuous descriptives
Treatment administration • Planes of injection • Device/Needle problem or malfunction	Summary by treatment group, treatment (initial or touch-up), and treatment area	Initial, Touch-up	Categorical descriptives
Treatment Characteristics • Injection ease • Product moldability	Summary by treatment group, treatment (initial or touch-up), and treatment area	Initial, Touch-up	Categorical descriptives

5.6.3. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the initial treatment for treatment group and after randomization for control group.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

TEAEs will be summarized by treatment group for CP using the Safety population.

TEAEs will also be summarized for TP using VITP and VOTP, respectively.

The number and percentage of participants with TEAEs as well as the events in the following AE categories will be summarized for the above populations as described in Table 5-7.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Listings of all TEAEs, TESAEs, TEAEs leading to discontinuation, and death will be presented.

Table 5-7 TEAE Summaries

Endpoint	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • TEAEs • Treatment-related TEAEs • Treatment-related TEAEs at injection site • Treatment-related TEAEs not at injection site • TESAEs • Treatment-related TESAEs • Treatment-related TESAEs at injection site • Treatment-related TESAEs not at injection site • Discontinued due to TEAE • Deaths	CP, TP	Categorical descriptives, event descriptives
TEAEs	• Overall summary and by SOC and PT • Overall summary and by SOC, PT, and maximum severity	CP, TP	Categorical descriptives, event descriptives
Treatment-related TEAEs	• Overall summary and by SOC and PT • Overall summary and by SOC, PT, and maximum severity • Overall summary by maximum severity, time to onset, duration, action taken and outcome	CP, TP	Categorical descriptives, event descriptives
TESAEs	Overall summary and by SOC and PT	CP, TP	Categorical descriptives, event descriptives
AEs leading to discontinuation	Overall summary and by SOC and PT	CP, TP	Categorical descriptives, event descriptives

5.6.4. Injection Site Response

ISRs recorded in participant diaries after each treatment (initial and touch-up) will be summarized for the VITP and VOTP, respectively. The summaries of below endpoints will be performed for initial treatment, touch-up treatment by pre-defined symptoms as described in Table 5-8.

Table 5-8 ISR Analyses

Endpoint	Description	Timing	Methodology
ISR severity	Maximum reported severity. For combined initial and touch-up, use the maximum severity of the 2 treatments.	Initial, Touch-up	Categorical descriptives
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 56-day diary period. Duration is derived as date of last ISR minus date of first ISR plus one.	Initial, Touch-up	Categorical descriptives
Ongoing ISR	ISR ongoing at end of the 56-day diary period, including ISR, severity, start date, end date.	Initial, Touch-up	Listing

ISR day will be derived as ISR date – most recent treatment date + 1.

5.6.5. Procedural Pain

Participant assessment of procedural pain (pain during injection) on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable) after each treatment (initial and touch-up) will be summarized for the VITP and VOTP, respectively. The summary will be performed for initial treatment, touch-up treatment as described in Table 5-9.

Table 5-9 Procedural Pain Analyses

Endpoint	Description	Timing	Methodology
Procedural pain	Summary of pain scores as continuous scale	Initial, Touch-up	Continuous descriptive

[redacted]

[redacted]

5.6.8. Pregnancy Test Analyses

Urine pregnancy test is taken at screening, prior to every treatment (initial and touch-up), and study exit. Participants with a positive result for the Safety Population throughout the study period will be presented as a listing.

[redacted]

5.8. Interim Analyses

No interim analysis is planned for this study.

6. Supporting Documentation

6.1. Appendix 1: List of Abbreviations

3D	3-dimensional
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BOCF	baseline value carry forward
CI	confidence interval
CP	control period
eCRF	electronic case report form
EI	Evaluating Investigator
GAIS	Global Aesthetic Improvement Scale
IES	Intercurrent event(s) strategy
ISR	injection site response
LS	least square
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
NSS	Nose Satisfaction Scale
PCP	Post-Control period
PLS	Population-level summary
PP	per-protocol
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TP	treated period
Tx	treatment
VITP	voluma initial treated population
VOTP	voluma optionally treated population
WHO	World Health Organization

6.2. Appendix 2: Changes to Protocol-Planned Analyses

In this SAP, the primary analysis will be done by an MMRM. The original primary analysis in Protocol 1894-701-008 Amendment 1 was based on observed data. The original analysis based on observed data will be included as one of the sensitivity analyses.

The definition of mITT is changed from "Subjects who are randomized to study treatment, receive at least 1 study device treatment and complete at least 1 effectiveness assessment (Treatment Group); and subjects who are randomized to no treatment and complete at least 1 effectiveness assessment (Control Group)" in protocol to "All participants who are randomized and have at least 1 assessment of change from baseline in nose volume" in SAP. The changes make it clear that participants need to have at least one primary effectiveness variable (purpose of effectiveness assessment). Participant who are randomized to treatment but don't receive study device treatment will be withdrawn from the study and have no any follow-up visits. So device treatment requirement was not necessary and excluded from definition in SAP for simplicity.

The definition of PP is changed from "All mITT subjects who do not have any significant protocol deviations affecting the primary effectiveness endpoint" in protocol to "All mITT participants who have baseline and Week 24 assessments of change from baseline in nose volume and do not have any significant protocol deviations affecting the primary effectiveness endpoint" in SAP. This change adds one requirement for the availability of primary endpoint in line with key criteria of PP definition in ICH E9.

6.3. Appendix 3: Supporting Study Information

6.3.1. Demographics

Demographic parameters (age [years]; sex; race [Asian]; ethnicity [Chinese]) will be summarized descriptively by treatment group for the mITT populations. Age (years) were calculated relative to informed consent date.

6.3.2. Baseline and Disease Characteristics

Baseline characteristics including weight, height, and body mass index will be summarized descriptively by treatment group for the mITT population.

6.3.3. Protocol Deviations

Significant protocol deviations will be identified. Unique participants reporting significant protocol deviations will be summarized in total and by treatment group for all randomized participants as described in Table 6-1.

Listing of significant protocol deviations will be provided.

Table 6-1 Protocol Deviation Summary

Endpoint	Description	Timing	Methodology
Significant protocol deviations	Number (%) of participants with significant protocol deviation will be summarized (All randomized)	During study period	Categorical descriptives

6.3.4. Medical History

Abnormalities in participants' medical, surgical, cosmetic and dental history, encompassing abnormalities, surgeries, and procedures reported as occurring before the Screening Visit, will be coded using MedDRA, version 21.0 or newer. Listing will be provided for the mITT population.

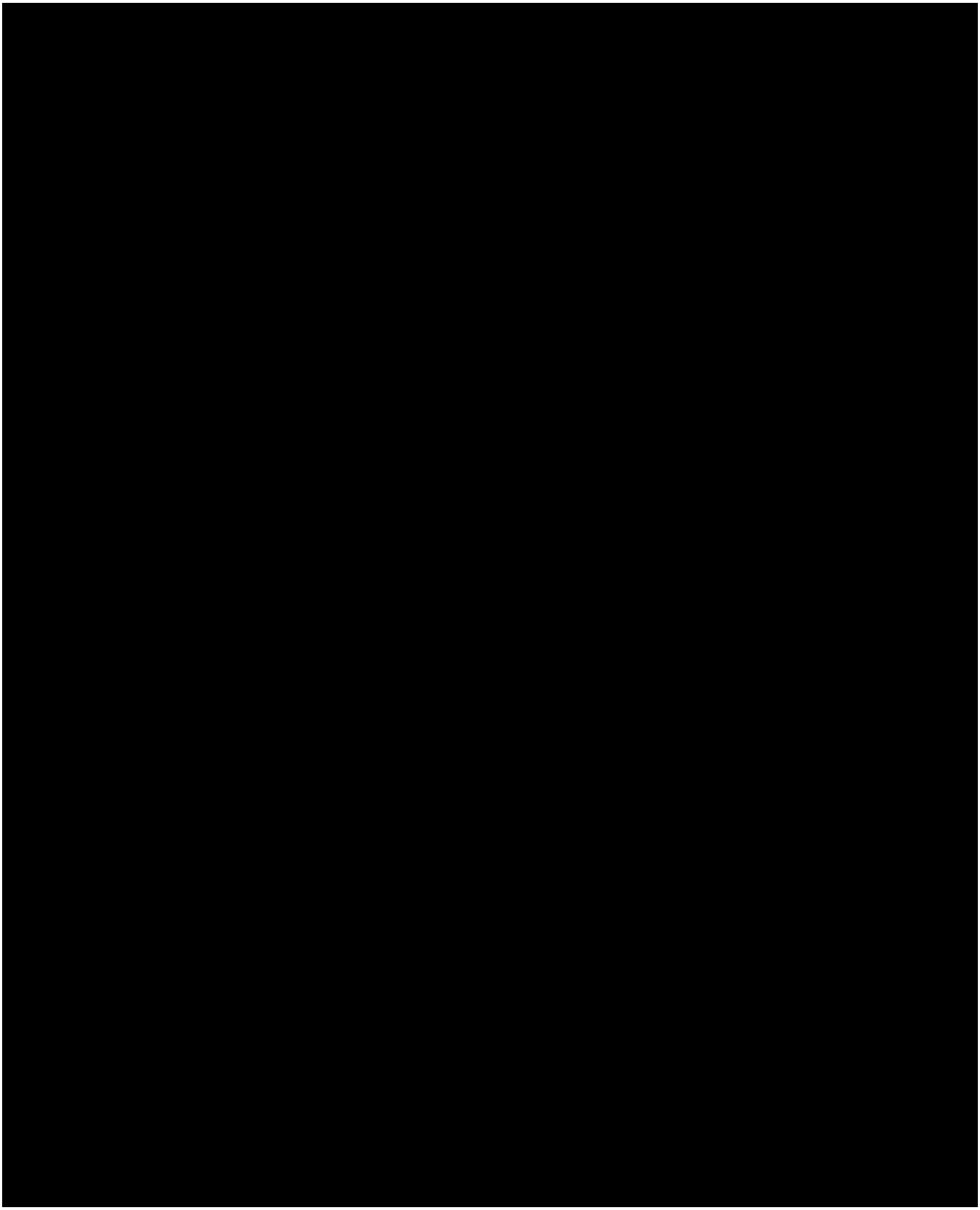
6.3.5. Prior/Concomitant Medications

Medications will be coded using the WHO Drug Dictionary, version March 2017 or newer. Unique participants who reported medications (Anatomical Therapeutic Chemical [ATC] 4 class and PT) will be summarized. Prior medication will be summarized by treatment group and total for screening period based on mITT Population. Concomitant medication will be summarized by treatment group for CP using the mITT Population, for TP using VITP VOTP as described in Table 6-2.

Table 6-2 Prior and Concomitant Medications

Endpoint	Description	Timing	Methodology
Prior medications	Medications taken before the study treatment by treatment group and in total (mITT)	Screening	Categorical descriptives
Concomitant medications	Medications taken during the corresponding period	CP, TP	Categorical descriptives

[redacted]



6.4. Data Handling Convention

6.4.1. Analysis Window

6.4.1.1. Effectiveness

Most recent treatment refers to initial treatment if touch-up is not performed, otherwise touch-up treatment. The reference day is defined for each group and each study period. The analysis visit windows for effectiveness endpoints are defined in Table 6-1 for the treatment group and in Table 6-2 and Table 6-3 for the control group. If more than 1 measurement exist in one visit, the measurement that close to the target date of the visit will be used for summary analysis. If both measurements have the same time interval to the target date, the later one will be used for summary analysis. But all measurements will be listed in data listings

If analysis date ≥ reference date, then
Analysis day = analysis date – reference date + 1

If analysis date < reference date, then
Analysis day = analysis date – reference date

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

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Most Recent Treatment	Day 1	Day 1
Week 8	Day 57	Days [2, 85]
Week 16	Day 113	Days [86, 141]
Week 24	Day 169	Days [142, 211]
Week 36	Day 253	Days [212, 295]
Week 48	Day 337	Day 296 to study exit day

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

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Randomization Day	Day 1	Day 1
Week 8	Day 57	Days [2, 85]
Week 16	Day 113	Days [86, 141]
Week 24	Day 169	Day 142 to study exit day if the participant does not receive optional treatment, or to the day of treatment if the participant receives optional treatment

Table 6-5 Effectiveness Analysis Visit Definitions for Control Group during Treated Period

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Most Recent Treatment	Day 1	Day 1
Week 8 Post-optional treatment	Day 57	Days [2, 85]
Week 16 Post-optional treatment	Day 113	Days [86, 141]
Week 24 Post-optional treatment	Day 169	Day 142 to study exit day

6.4.1.2. Safety

No analysis visit windows are defined.

6.4.2. Missing Date Imputation

Missing date will be only imputed for TEAEs. Dates may be imputed with year, month, and day values under certain scenarios in Table 6-6.

Table 6-6 Imputation Scenarios

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

[a] Not allowed per database design.

6.4.2.1. Missing/Incomplete AE Start Date

For scenario 2, i.e. if day is missing but month and year are available, then the imputed day will be the first day of the month or the initial injection date (randomization date for control group) if they have the same month and year, whichever is later (because TEAE onset is not expected prior to administration of study treatment);

For scenario 4, i.e. if day and month are missing but year is available, then the imputed day and month will be 01 Jan or the initial injection date (randomization date for control group) if they have the same year, whichever is later;

For scenario 8, i.e. if day, month and year are all missing, impute start date as the earliest possible date on or after initial injection date for treatment group. And impute start date as the earliest possible date on or after randomization date for control group.

6.4.2.2. Missing/Incomplete AE End Date

For scenario 2, i.e. if day is missing but 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.

For scenario 4, i.e. 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

For scenario 8, i.e. if day, month and year are all missing, then the imputed date will be the latest possible date on or before study exit date.

7. References

Kenward, M.G., Roger, J.H. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-997.

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