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

**Protocol Amendment 1 Date**: 22Sept2017

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|---|---|
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| Protocol Number: | 1894-701-008 |
| Protocol Date: | 22 September 2017 |
| Protocol Version Number: | Amendment 1.0 |
| Product Name: | JUVÉDERM® VOLUMA® with Lidocaine Injectable Gel |
| Development Phase: | Pivotal |
| Sponsor: | Allergan Information Consulting (Shanghai) Co., Ltd.<br>Contact address: [redacted] |
| Manufacturer: | Allergan [redacted] |
| Safety reporting: | [redacted] |

## INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
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| Investigator: | |
| Study Location: | |

I agree to:

- Implement and conduct this study diligently and in strict compliance with this protocol, good clinical practices (GCP), and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Ethics Committee (EC), or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

| Principal Investigator Printed Name | Signature | Date |
|---|---|---|

## RETURN TO ALLERGAN

# Synopsis

**NUMBER AND TITLE OF STUDY:**

Protocol 1894-701-008: 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

**DEVELOPMENT PHASE:** Pivotal

**STUDY CENTERS:** Up to 9 Chinese sites

**NUMBER OF SUBJECTS:** At least 160 subjects will be randomized

**OBJECTIVES:** The objectives of this study are to evaluate the safety and effectiveness of JUVÉDERM® VOLUMA® with Lidocaine Injectable Gel (hereafter, VOLUMA with Lidocaine) for the improvement of volume and aesthetic appearance of the nose in a Chinese population.

**STUDY DESIGN:**

This is a prospective, multicenter, randomized, "no-treatment" control design study of the safety and effectiveness of VOLUMA with Lidocaine for the improvement of volume and aesthetic appearance of the nose in Chinese adults.

This trial consists of 2 periods: Control Period and Post-control Period. The Control Period is the period from the randomization visit until 24 weeks after the last treatment (primary endpoint) for the treatment group or randomization for control group. During the Control Period, subjects randomized to the treatment group will receive treatment and will be followed for safety and effectiveness evaluation. Subjects randomized to the control group will not receive treatment and will be followed for safety and effectiveness evaluation. The main purpose of Control Period is to compare the primary effectiveness parameter, the volume change of nose area based on 3-dimensional (3D) imaging data, between the treatment and control groups. The Post-control Period is the period after the primary endpoint visit until the end of the study, which is either 48 weeks after the last treatment for the treatment group or 24 weeks after the last treatment for the control group. The main purpose of the Post-control Period is to collect long-term safety and effectiveness data for treatment group subjects, and to collect safety and effectiveness data for control group subjects who received treatment.

**Screening Period**

All Subjects: Screening

At screening, after written informed consent has been obtained, the Principal Investigator or the assigned site staff will document demographic information (eg, sex, age); medical/surgical/cosmetic/dental procedure history; vital signs (ie, height, weight, blood pressure in the sitting position, pulse, respiratory rate, temperature), perform blood collection for routine hematology and chemistry tests, and urine collection for routine urinalysis and urine pregnancy testing (female subjects of childbearing potential only). All subjects must have the treatment goals aligned with the Treating Investigator (TI) during screening phase. Subject eligibility will be confirmed during screening phase prior to randomization.

**Control Period**

All Subjects: Randomization

Before randomization, female subjects of childbearing potential must have urine pregnancy testing repeated on the day of randomization, if the screening pregnancy test was not performed within 7 days before the randomization day. Subjects will be randomized at a 3:1 ratio either to have treatment with VOLUMA with Lidocaine at the outset of the study (treatment group) or to be followed for 24 weeks of observation followed by an optional delayed treatment (no-treatment control group). At the randomization visit, 3D digital images of the nose area must be captured for all eligible subjects which will be used as baseline data for subsequent calculation of the nose volume change and nose aesthetic improvement including dorsal height, dorsal width, nasofrontal angle, nasolabial angle, nasal root height, nasal length, and ala depth. These 3D images must be captured before randomization.

Treatment Group Subjects: Postrandomization, Treatment(s) and Follow-up

Vital signs (ie, blood pressure at sitting position, pulse, respiratory rate, and temperature) will be collected for all treatment group subjects at this visit, prior to treatment.

The treatment group subjects will undergo initial treatment on the same day as randomization. If initial

treatment does not occur on the randomization day for these subjects, it must occur within 4 weeks after signing the informed consent form (ICF).

The TI must re-confirm that the treatment goal has been aligned with the subject before performing treatment at the Initial Treatment visit. The trained TI will administer treatment to enhance the volume and aesthetic appearance of nose with VOLUMA with Lidocaine to subjects randomized to the treatment group. The allowed study injection sites are the nasal dorsum, columella and anterior nasal spine. Non-midline areas of the nose, nasal tip, and glabella area are not allowed for injection. VOLUMA with Lidocaine must be injected into upper-periostea ( supraperiosteal and/or supraperichondrial) layer following a specified injection technique to obtain optimal nose aesthetic improvement with minimal safety concern. Following treatment, the TI will document treatment characteristics, including injection volume, injection site, and injection plane. The TI will also use an 11-point scale to assess the ease of injection (ie, 0 = difficult, 10 = easy) and the product moldability (ie, 0 = stiff, 10 = moldable), separately. Subjects will assess the procedural pain on an 11-point scale (ie, 0 = no pain, 10 = worst pain imaginable) immediately after receiving treatment. The TI must observe the subject for any acute adverse events (AEs), such as vascular embolism, for at least 30 minutes after completing treatment.

The treatment group subjects may undergo a touch-up injection 8 (+1) weeks after initial treatment if both the subject and TI assess that the optimal aesthetic improvement goal of the nose was not achieved. Urine pregnancy testing must be confirmed as negative before treatment. If a touch-up treatment is performed, the TI will document treatment characteristics, assess the ease of injection, and the product moldability. Subjects will assess the procedural pain immediately after treatment. The TI must monitor the subject for any acute AEs, such as vascular embolism, for 30 minutes after treatment.

Injection site responses (ISR) must be recorded by subjects daily for 56-days in a diary starting from the day of treatment (initial treatment and touch-up treatment, if performed). If an ISR is ongoing at the end of the 56-day post-treatment subject diary after the last treatment (onging ISR from initial treatment will be recorded in the touch-up 56-day post-treatment subject diary, if performed), the TI (or designee) will follow the outcome of the ongoing ISR and will document the entire course of the ISR. Safety phone calls will occur 3 days after treatment (initial and touch-up, if performed).

For treatment group subjects, routine follow-up visits for safety and effectiveness will occur at Weeks 8, 16, and 24 after the last treatment. 3D imaging and the 5-point Global Aesthetic Improvement Scale (GAIS) assessed separately by the Evaluating Investigator (EI) and subjects, will be performed at all 3 visits. At Weeks 8, 16 and 24, several effectiveness evaluations will be conducted including: the subject assessment of satisfaction with the treatment outcome using the 5-point Nose Satisfaction Scale (NSS) and subject's willingness to recommend the treatment to a friend. Laboratory sample collection for routine hematology, chemistry, and urinalysis will be performed at Week 24 and vital signs (ie, blood pressure at sitting position, pulse, respiratory rate, temperature) will be collected at all on-site visits.

Control Group Subjects: Post-randomization, Treatment and Follow-up

Control group subjects will undergo routine follow-up visits for safety and effectiveness, including 3D imaging and EI assessment of the GAIS, at Weeks 8, 16, and 24.

**Post-control Period**

Treatment Group Subjects: Post-randomization, Treatment(s) and Follow-up

For treatment group subjects, routine follow-up visits for safety and effectiveness will occur at Weeks 36 and 48 after the last injection. 3D digital imaging will be performed and the GAIS will be assessed separately by the EI and subject. Several effectiveness evaluations will be conducted including: the subject assessment of satisfaction with the treatment outcome using the NSS and subject's willingness to recommend the treatment to a friend. Vital signs will be collected at all on-site visits. Laboratory sample collection for routine hematology, chemistry, and urinalysis will be performed at Week 24. Urine pregnancy test must be conducted at study exit or at the time of withdrawal if the subject withdraws from the study prior to the Week 48 visit. The scheduled procedures for Week 48 must be conducted at the on-site visit for any treatment group subject who withdraws from the study.

Control Group Subjects: Post-randomization, Treatment and Follow-up

After completing the Week 24 visit, control group subjects have the option to receive initial treatment (no later than 10 days after completing the Week 24 visit) and touch-up treatment (8 weeks after initial treatment) if both the subject and TI assess that optimal aesthetic improvement of the nose appearance has not been achieved. Treatment (initial and touch-up) will be administered as described for the treatment group subjects. The same

procedures performed after initial and touch-up treatment for the treatment group subjects will be performed after initial and touch-up treatment for the control group subjects.

The 3D images captured at Week 24 before optimal initial treatment will be used as baseline data for subsequent calculation of the nose volume change and nose aesthetic improvement after treatment compared with the 3D images captured at the touch-up treatment visit (if performed), Weeks 8, 16, and 24 after the last treatment. The GAIS assessed by the EI must be conducted at Weeks 8, 16, and 24 after randomization. GAIS assessed by EI and subjects must be obtained at Weeks 8, 16, and 24 after the last treatment. Several effectiveness evaluations will be conducted including: the subject assessment of satisfaction with the treatment outcome using the NSS and a question about subject willingness to recommend the treatment must be conducted at Weeks 8, 16, and 24 after the last treatment. Laboratory samples (for urinalysis, hematology & chemistry) will be collected at Week 24 after the last treatment. Urine pregnancy test must be conducted at Week 24 after the last treatment or at the time of withdrawal if the subject withdraws from the study prior to the Week-24 post-treatment visit.

For any control group subject who withdraws from the study before completing the "no-treatment" control period visit, the scheduled procedures for the Week 24 visit of the "no-treatment" period must be conducted at his/her last on-site visit. For any control group subjects who receive treatment and withdraw before completing week 24 post-treatment visit, all scheduled procedures for week 24 post-treatment visits must be conducted at his/her last on-site visit.

Evaluation of Assessments

Treatment and safety assessments will be performed by the TI. The initial treatment and touch-up treatment (if performed) for each subject must be performed by the same TI. The effectiveness assessments for each subject are strongly recommended to be performed by the same EI throughout the study. The EI will remain blinded to treatment assignment throughout the study. The blinded independent technician will be responsible for all 3D image analyses which will be used as effectiveness assessments. At specified time points, subjects will complete questionnaires and 56-day post-treatment subject diary(ies).

After signing the ICF and until exit from the study, any untoward signs or symptoms or other AEs as well as concomitant medications, procedures, and therapies of all subjects (treatment and control groups) will be carefully monitored by the TI and documented by either the TI or assigned site staff.

**DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION: C**hinese adults seeking nose enhancement

**INCLUSION:**

1. Male or female, Chinese, at least 18 years of age
2. Is not satisfied with his/her aesthetic appearance due to structural features of his/her nose and assessed as either "dissatisfied" or "very dissatisfied" by using the 5-point NSS
3. Requires a total volume of at least 0.5 mL but not exceeding 3.0 mL of VOLUMA with Lidocaine for initial and touch-up treatment combined, and treatment to the nasal dorsum is mandatory to achieve an aesthetic improvement in the subject's nose appearance, in the TI's opinion
4. Has a reasonable treatment goal for aesthetic improvement in nose, in the TI's opinion. Subject and TI have aligned the treatment goals.
5. Give written informed consent to authorize the use of health and research study information
6. Be able and willing to follow study instructions, comply with the medication and treatment restrictions described in this protocol, and complete all required study visits

**EXCLUSION:**

[redacted]

3. Has a small, shallow nose such that the volume of filler implant needed to create the desired dorsal height is in excess of the ability of the skin and soft tissue to expand and accommodate the implant

[redacted]

[redacted]

13. Has active autoimmune disease

[redacted]

17. Is on a concurrent regimen of lidocaine or structurally-related local anesthetics (eg, bupivacaine)

[redacted]

19. Is on an ongoing regimen of anti-coagulation therapy (eg, warfarin)
20. Within 10 days of undergoing study device injection, is on an ongoing regimen of medications (eg, aspirin or ibuprofen) or other substances (eg, high doses of Vitamin C or Vitamin E or herbal supplements with garlic, gingko biloba, or ginseng) known to increase coagulation time, or is currently menstruating (study treatment may be delayed as necessary to accommodate menstrual period cessation and/or anti-coagulation washout interval)
21. Has participated in any clinical trials within 4 weeks prior to signing the ICF or is planning to participate in another clinical trial during the course of this study
22. Females who are pregnant, nursing, or planning a pregnancy during the course of the study. Females of childbearing potential who have a positive pregnancy test result during screening. Females who intend to breastfeed during the study. Females of childbearing potential who are unwilling to use birth control measures during the full course of the study. Birth control measures include oral contraceptives (stable use for 2 or more cycles prior to screening), intrauterine devices, hormonal injections, hormonal implants, bilateral tube ligation, vasectomy, condom or diaphragm plus either contraceptive sponge, foam, or jelly

[redacted]

**TEST PRODUCT, DEVICE VOLUME, AND MODE OF ADMINISTRATION:**
VOLUMA with Lidocaine HA dermal filler will be injected into the nose using a 27 G x ½-inch needle. The appropriate injection volume will be determined by the TI but is not to exceed a maximum total of 3.0 mL for initial and touch-up treatments combined.

**DURATION OF STUDY:** Treatment Group: control period is up to 8 weeks treatment and 24 weeks follow-up; post-control period is 24 weeks. Control Group: control period is 24 weeks; post-control period is up to 8 weeks treatment and 24 weeks follow-up

**RESPONSE MEASURES:**

**Effectiveness:** The primary effectiveness measure is the volume change from baseline in the nose area calculated by digital analysis of each subject's 3D images. Secondary effectiveness measures include the EI's and subject's assessments of GAIS, and subject's assessments of NSS. Other effectiveness measures include dorsal height, width, nasofrontal angle, nasolabial angle, nasal root height, nasal length, and ala depth based on 3D data analysis, and subject responses regarding treatment recommendation to a friend.

**Safety:** Safety will be evaluated by subject assessment of procedural pain and ISRs, AEs observed by the investigator or solicited from or spontaneously reported by the subject, concomitant medications and concurrent procedures, vital signs, and laboratory results.

**STATISTICAL METHODS:**

**Analysis Populations:** Three populations will be used in the analyses: safety population, modified intent-to-treat (mITT) population and per-protocol (PP) population. The safety population includes all treated subjects and will be used in the analyses of safety data. The mITT population includes all subjects who are randomized to study treatment, receive at least one 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). The mITT population will be used for effectiveness analyses and summary of baseline characteristics. The PP population includes all mITT subjects who do not have any significant protocol deviations that affect the primary effectiveness endpoint. The PP population will be used for sensitivity analyses of the primary effectiveness variable.

**Sample Size Calculation:** A sample size of 90 treatment and 30 control subjects 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 subjects complete 1 year follow-up, accounting for subject attrition of 15% during the whole study duration, at least 120 subjects in the treatment group and 40 subjects in the control group will be randomized.

**Effectiveness:** The primary effectiveness analysis is the mean volume change from baseline in nose area as calculated by digital analysis of 3D images at Week 24 (primary timepoint). A 2-sided, 2-sample t-test (or Wilcoxon rank-sum test, as appropriate) at a 5% significance level will be used to test whether the mean volume change from baseline in nose area for the treatment group is significantly greater than that for the control group at Week 24.

Secondary effectiveness analyses are responder analyses of EIs' and subjects' assessment of aesthetic improvement of the nose using the 5-point GAIS and subjects' assessment of NSS at Week 24. A "responder" is defined as a subject who shows improvement in the overall aesthetic assessment (Improved or Much improved on GAIS) posttreatment. Since the GAIS assessments are only collected after treatment, there will be no data for the control group subjects during the no-treatment control period. Responder analyses will be done for each treatment group separately. Responder analysis of NSS will be similar to GAIS. A "responder" is defined as the subject with a score of ≥1 point (satisfied or very satisfied) at Week 24 on the NSS.

**Safety:** Procedural pain will be summarized using descriptive statistics. ISRs reported in subject diaries will be summarized by treatment (initial and touch-up), symptom, severity, and duration. Summaries will include the incidence rate for each ISR.

AEs will be summarized by system organ class and preferred term and will be tabulated by onset, duration, severity, action taken, relationship to treatment, and outcome. Treatment-related AEs, serious AEs, AEs leading to study discontinuations, and deaths will be listed or tabulated.

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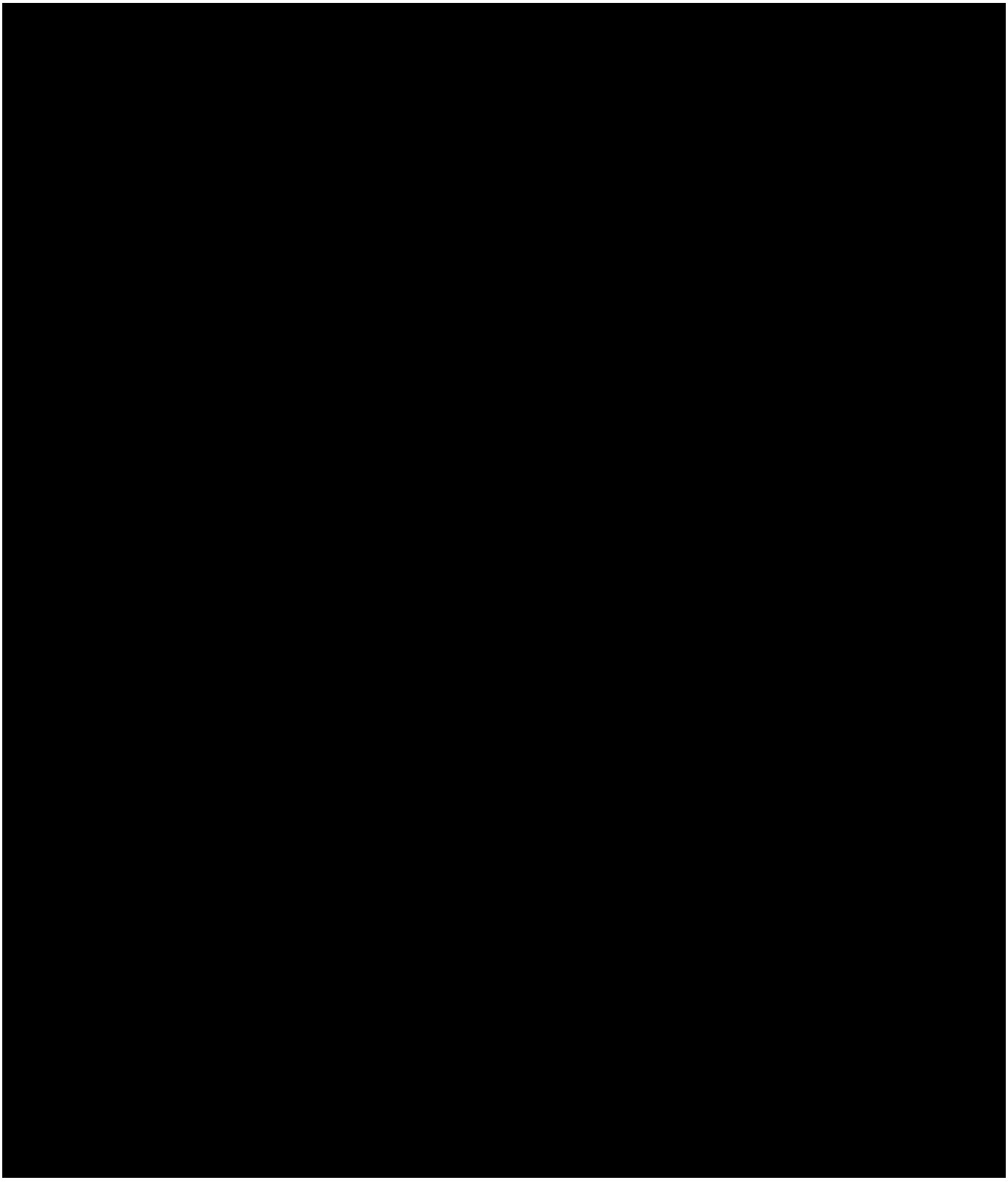
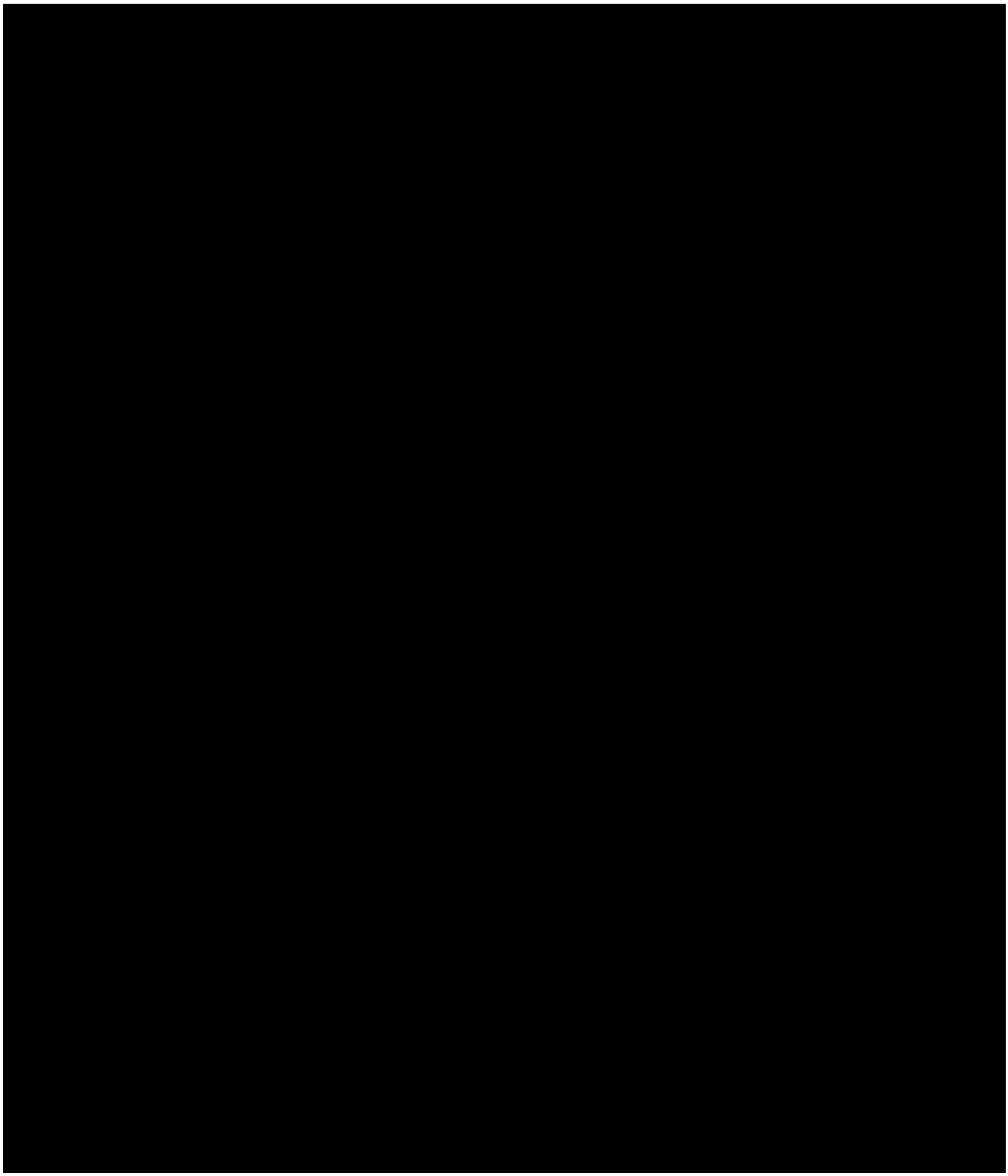
Approval Date: 22-Sep-2017

## List of Tables





# 1. Abbreviations and Terms

| Term/Abbreviation | Definition |
|---|---|
| 3D | 3-dimensional |
| ADE | Adverse device effect |
| AE | Adverse event |
| EC | Ethics Committee |
| eCRF | Electronic case report form |
| EI | Evaluating investigator |
| GAIS | Global Aesthetic Improvement Scale |
| HA | Hyaluronic acid |
| IC | Informed consent |
| ICF | Informed consent form |
| ISR | Injection site response |
| IWRS | Interactive web response system |
| mITT | Modified intent-to-treat |
| NSS | Nose Satisfaction Scale |
| PP | Per-protocol |
| SAE | Serious adverse event |
| SADE | Serious adverse device effect |
| TI | Treating investigator |
| USADE | Unanticipated serious adverse device effect |

# 2. Background, Risk and Benefit, and Clinical Rationale

## 2.1 Background

Surgical rhinoplasty is one of the most challenging procedures to perform in plastic surgery and has high rates of unfavorable outcomes (Bhangoo 2013, Christophel 2009, Surowitz 2013). In China, where the patient may present with a relatively flat nasal bridge, indistinct dorsal aesthetic line, under projected and broad nasal tip, wide alar base, and shortened columella, rhinoplasty is the second most common surgery performed by plastic surgeons, and augmentation rhinoplasty is the most common rhinoplasty procedure performed (Jang 2014, Kim 2012, Le 2002, Shirakabe 2003, Tanaka 2011). Materials frequently used to create the augmentation are autologous cartilage and alloplastic implants. Neither option is ideal as harvesting the autologous cartilage increases morbidity of the subject, and alloplastic implants in rhinoplasty are controversial as they are associated with a high rate of complications and revision rhinoplasty (Ferril 2013, Park 2013).

Dermal fillers offer an alternative approach to surgical augmentation rhinoplasty. Administered by injection, dermal fillers are less invasive, have much lower rates of infection and scarring, and have much shorter recovery times. A variety of filler products have been used for this indication including silicone, polytetrafluoroethylene, polymethylmethacrylate, calcium hydroxyapatite, polylactic acid, and hyaluronic acid (HA) (Bray 2010, Kim 2012, Redaelli 2008, Soloman 2012, Tanaka 2011, Xue 2012).

As the use of HA-based dermal fillers has increased in the past decade for a variety of facial aesthetic indications, such as lip augmentation, perioral enhancement, correction of nasolabial folds, and treatment of mid-face volume deficit, HA-based injectable gels have accrued an established record of safety and effectiveness (Callan 2013, Jones 2013, Raspaldo 2015). One such HA filler, JUVÉDERM® VOLUMA® with Lidocaine (hereafter, VOLUMA with Lidocaine) has ideal properties for providing structure, shape, and support to cartilaginous and soft tissues of the nose, and has been shown to be an effective, well-tolerated treatment option for facial volume enhancement in young Asian women (Bae 2013). Approved for restoring volume of the face in Europe, the United States, Australia, and some Asian countries, VOLUMA with Lidocaine has been established as safe and effective with results maintained for up to 18 to 24 months following 1 or 2 treatment sessions over the initial 4-week treatment period (Callan 2013, Jones 2013). However, the safety and effectiveness of using VOLUMA with Lidocaine to augment the nose have not been tested. One critical aspect of conducting such a study is first to establish safeguards against vascular compression or embolization. These risks can be minimized by using a

specified injection technique that restricts treatment to the midline dorsum, columella, and anterior spine while prohibiting injection into the glabellar area and the alar crease junction.

The purpose of the current study is to evaluate the safety and effectiveness of VOLUMA with Lidocaine for aesthetic improvement of the nose in a Chinese population.

## 2.2 Risk and Benefit

The injection procedure, anesthetic agents, or VOLUMA with Lidocaine may cause some of the risks and/or discomforts listed below. Unforeseeable risks or results are also a possibility. The risk of developing a serious complication is small. If a complication occurs, subjects will be advised to contact the Treating Investigator (TI) who will use his/her medical judgment to do whatever is necessary to treat the subject.As with any skin injection, risks can be posed by the injection procedure itself, the anesthetic agent, and injection of VOLUMA with Lidocaine. Risks related to the injection procedure include redness, itching, pain, tenderness, swelling, bruising, and lumps and bumps, which are common to dermal filler injection procedures, in general. The use of a small gauge needle to deliver VOLUMA with Lidocaine used in this study is intended to minimize tissue trauma. Risks associated with the anesthetic agent include allergic reactions that may manifest as an anaphylactic reaction, skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient loss of skin color. The inclusion of 0.3% lidocaine in the formulation is meant to reduce pain during the injection and this should be taken into account when administering concomitant additional anesthetics.

Treatment using VOLUMA with Lidocaine as an alternative to surgical augmentation rhinoplasty has many benefits. VOLUMA with Lidocaine is less invasive, has much lower rates of infection, has little or no risk of scarring, has no risk of surgery or general anesthesia, and has much shorter recovery times. From a medical aesthetic side, dermal filler could meet customers' high anticipation on the improvement of nose appearance by adjusting injection sites and injected product volume during treatment. Furthermore, as an HA-based filler, VOLUMA with Lidocaine is much safer than fat injections or particulate fillers. It is anticipated that the safety and effectiveness of treatment to the nose are similar to those identified in studies of JUVÉDERM products for similar indications.

## 2.3 Clinical Rationale

The benefits of using VOLUMA with Lidocaine to achieve aesthetic improvement of the nose in a Chinese population are expected to outweigh the risks of treatment with surgical augmentation rhinoplasty.

# 3. Study Objectives and Clinical Hypotheses

## 3.1 Study Objectives

The objectives of this study are to evaluate the safety and effectiveness of VOLUMA with Lidocaine for the improvement of volume and aesthetic appearance of the nose in the Chinese population.

## 3.2 Clinical Hypotheses

The mean volume change in nose area from baseline to Week 24 based on digital analysis of each subject's 3-dimensional (3D) images will be significantly greater in subjects treated with VOLUMA with Lidocaine than in untreated control subjects.

# 4. Study Design

## 4.1 Structure

This is a prospective, multicenter, randomized, no-treatment-controlled study. Up to 9 investigational sites will enroll and follow subjects who meet the study criteria.

This trial consists of 2 periods including a Control Period and a Post-control Period. The Control Period is the period from the randomization visit until the primary endpoint visit (24 weeks after the last treatment for the treatment group or randomization for the control group). The main purpose of the Control Period is to compare the primary effectiveness parameter, the volume change of nose area basing on 3D imaging data, between the treatment group and the control group. During the Control Period, subjects randomized to the treatment group will receive treatment and be followed for evaluation of safety and effectiveness. During this period, subjects randomized to the control group will not receive treatment but will be followed for safety and effectiveness evaluations.

The Post-control Period is the period after the primary endpoint visit until the end of the study visit (48 weeks after the last treatment for the treatment group or 24 weeks after the last treatment for the control group). The main purpose of Post-control Period is to collect long-term safety and effectiveness data for the treatment group subjects, and to collect safety and effectiveness data for control group subjects who received treatment. Safety and effectiveness data from the treated control group subjects will be analyzed separately.

## 4.2 Duration

The study will span a total approximately 96 weeks. Enrollment will take approximately 36 weeks. Each subject's participation will encompass: up to 4 weeks for screening for both treatment group and control group, up to 8 weeks treatment and 48 weeks follow-up (after the last treatment) for the treatment group, and 24 weeks no-treatment follow-up, up to 8 weeks treatment, and 24 weeks follow-up for the control group.

## 4.3 Treatment Groups and Treatment Regimen

### 4.3.1 Study Treatment

VOLUMA with Lidocaine.

### 4.3.2 Control Treatment

No treatment during the 24-week control period. Optional treatment with VOLUMA with Lidocaine during the Post-Control period.

### 4.3.3 Methods for Blinding

Neither the TI nor the subject will be blinded to treatment.

The Evaluating investigator (EI) will remain blinded to treatment assignment throughout the study. The blinded independent Canfield Scientific technician will be responsible for all 3D digital image analyses which will be used for the effectiveness evaluation.

### 4.3.4 Touch-up Treatment Criteria

Eight weeks after the initial treatment, the subject and the TI will discuss the results of the initial treatment and determine whether optimal aesthetic improvement of the nose has been achieved. If optimal aesthetic improvement has not been achieved, the TI may perform a touch-up treatment. Moreover, if the injected product volume is less than 0.5 mL during initial treatment, the TI must conduct a touch-up treatment to meet the minimal injected product volume defined by the protocol. Beside the intial treatment and optional touch-up treatment, no additional treatment will be administered during the trial period.

## 4.4 Permissible and Prohibited Medications/Treatments

### 4.4.1 Permissible Medications/Treatments

All medications and treatments are permitted with the exception of the restricted medications and treatments described in Section 4.4.2.

After the subject consents to the study, the use of any concomitant medication, prescription or over-the-counter, and other therapy procedures are to be recorded on the subject's electronic case report form (eCRF) at each visit along with the reason the medication/ therapy/procedure is taken/administered.

Medication/therapy/procedure considered necessary for the subject's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/therapy/ procedure is in question, please contact Allergan.

### 4.4.2 Prohibited Medications/Treatments

During the course of this study, the subject may not be enrolled in another investigational study. The subject may not undergo nasal surgery, including cartilage grafts; may not receive facial implants of any biomaterials or filler injections of any kind in the nose area (other than filler injections done as part of this study protocol); may not undergo surgery on the eye area; may not undergo orthodontics operations; may not undergo botulinum toxin injections anywhere in the face; and may not undergo desensitization therapy to HA, streptococcal protein, or lidocaine or other amide-based anesthetic.

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan is to be notified before the prohibited medication/treatment is administered.

### 4.4.3 Escape Medications

Administration of hyaluronidase must not be performed during this study.

### 4.4.4 Special Diet or Activities

Within the first 24 hours after treatment, subjects should avoid strenuous exercise, extensive sun or heat exposure, and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection site.

After treatment, the subject should avoid unnecessary external compression of the nose that could cause product displacement, indentation, or depression of the dorsal surface where product has been placed. The subject should not sleep face down and should avoid any pressure or trauma to the nasal area, including the use of goggles and sunglasses or reading glasses for 1 week. During this time, the subject is advised not to have a facial massage, enter a sauna or hot spring, receive excessive sun exposure, or go swimming. No phototherapy or laser treatment should be performed for 3 months after the last treatment is administered.

## 4.5 Treatment Allocation Ratio and Stratification

Subjects will be randomized at a 3:1 ratio either to receive VOLUMA with Lidocaine treatment at the outset of the study (treatment group) or to have treatment delayed by 24 weeks (control group).

# 5. Study Population

## 5.1 Number of Subjects

At least 160 subjects will be randomized at up to 9 investigational sites at 3:1 randomization ration in order to have 120 subjects assigned to the VOLUMA with Lidocaine treatment group and 40 subjects assigned to the no-treatment control group. Approximately 136 subjects, including 102 treated subjects will complete the 48-week visit after last treatment with an anticipated dropout rate of 15%.

## 5.2 Study Population Characteristics

Subjects will be recruited from a population of healthy Chinese adults who desire aesthetic improvement of the nose.

## 5.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, Chinese, at least 18 years of age
2. Is not satisfied with his/her aesthetic appearance due to structural features of his/her nose and assessed as either “dissatisfied” or “very dissatisfied” by using the 5-point NSS
3. Requires a total volume of at least 0.5 mL but not exceeding 3.0 mL of VOLUMA with Lidocaine for initial and touch-up treatment combined, and treatment to the nasal dorsum is mandatory to achieve an aesthetic improvement in the subject’s nose appearance, in the TI’s opinion

4. Has a reasonable treatment goal for aesthetic improvement in nose, in the TI's opinion. Subject and TI have aligned the treatment goals
5. Give written informed consent to authorize the use of health and research study information
6. Be able and willing to follow study instructions, comply with the medication and treatment restrictions described in this protocol, and complete all required study visits

## 5.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

[redacted]

3. Has a small, shallow nose such that the volume of filler implant needed to create the desired dorsal height is in excess of the ability of the skin and soft tissue to expand and accommodate the implant

[redacted]

13. Has active autoimmune disease

[redacted]

[redacted]

17. Is on a concurrent regimen of lidocaine or structurally-related local anesthetics (eg, bupivacaine)

[redacted]

19. Is on an ongoing regimen of anti-coagulation therapy (eg, warfarin)
20. Within 10 days of undergoing study device injection, is on an ongoing regimen of medications (eg, aspirin or ibuprofen) or other substances (eg, high doses of Vitamin C or Vitamin E or herbal supplements with garlic, gingko biloba, or ginseng) known to increase coagulation time, or is currently menstruating (study treatment may be delayed as necessary to accommodate menstrual period cessation and/or anti-coagulation washout interval)
21. Has participated in any clinical trials within 4 weeks prior to signing the informed consent form (ICF) or is planning to participate in another clinical trial during the course of this study
22. Females who are pregnant, nursing, or planning a pregnancy during the course of the study. Females of childbearing potential who have a positive pregnancy test result during screening. Females who intend to breastfeed during the study. Females of childbearing potential who are unwilling to use birth control measures during the full course of the study. Birth control measures include oral contraceptives (stable use for 2 or more cycles prior to screening), intrauterine devices, hormonal injections, hormonal implants, bilateral tube ligation, vasectomy, condom or diaphragm plus either contraceptive sponge, foam, or jelly

[redacted]

# 6. Procedures

## 6.2 Procedures to be Performed

The procedures to be performed at each visit are described below.

### 6.2.1 Screening Visit

A subject is considered enrolled when s/he has signed the informed consent in the presence of the investigator or appropriately qualified designee. A unique number assigned to each enrolled subject will serve as the subject identification number on all study documents.

For all consented subjects, the investigator or the assigned site staff will document demographic information (sex, age, race); medical/surgical/cosmetic/dental procedure history; vital signs (height, weight, blood pressure in sitting position, pulse, respiratory rate, temperature); perform blood collection for routine hematology and chemistry; and urine collection for routine urinalysis and urine pregnancy testing for female subjects of childbearing potential. All subjects must have treatment goals aligned with the TI during the screening phase. Subject eligibility will be confirmed prior to randomization. The procedures to be performed at the screening visit are specified in Table 1.

### 6.2.2 Control Period

#### 6.2.2.1 Randomization Visit – All Subjects

Before randomization, female subjects of childbearing potential (sexually active and not sterile, surgically sterilized, or postmenopausal for at least 1 year) must have a negative urine pregnancy test confirmed on the day of randomization, if the screening pregnancy test was not performed within 7 days of the day of randomization.

All eligible subjects will be randomized at a 3:1 ratio either to receive VOLUMA with Lidocaine treatment at the outset of the study (ie, treatment group) or to be followed in a 24-week "no-treatment" observation period followed by an optional delayed treatment (ie, control group).

Before randomization, 3D digital images of the nose area must be captured for all eligible subjects, which will be used as baseline data for subsequent calculation of the nose volume change and nose aesthetic improvement including dorsal height, dorsal width, nasofrontal angle, nasolabial angle, nasal root height, nasal length, and ala depth. These 3D images must be captured before receiving treatment (treatment group subjects). 3D photos need not be repeated before treatment if study treatment is not administered at the randomization visit. The procedures to be performed during the randomization visit are specified in Table 2.

#### 6.2.2.2 Post-randomization, Treatment(s) and Follow-up – Treatment Group

Vital signs (blood pressure in sitting position, pulse, respiratory rate, and temperature) will be collected for all treatment group subjects prior to treatment.

The treatment group subjects will undergo initial treatment on the same day as randomization. If initial treatment does not occur on the randomization day for these subjects, it must occur within 4 weeks after signing the ICF.

The TI must re-confirm that the treatment goal has been aligned with the subject before performing the initial treatment. The TI will administer treatment with VOLUMA with Lidocaine to enhance the volume and aesthetic appearance of the nose.

Following treatment, the TI will document treatment characteristics, including anesthesia usage, injection site, and injection plane, injection volume, injection ease and product modability. The TI will use an 11-point scale to assess the ease of injection (0 = difficult, 10 = easy) and the product moldability (0 = stiff, 10 = moldable). Subjects will assess the

procedural pain on an 11-point scale (0 = no pain, 10 = worst pain imaginable) immediately after receiving treatment. The TI must observe the subject for the occurrence of any acute adverse events (AEs), such as vascular embolism, for at least 30 minutes after completing treatment. The TI will document treatment characteristics, and the subject will assess the procedural pain immediately after receiving treatment. The TI must monitor the subject for the occurrence of any acute AEs, such as vascular embolism, for at least 30 minutes after completing treatment.

Injection site responses (ISR) must be recorded daily by the subject using the 56-day post-treatment subject diary starting from the day of treatment (initial and touch-up, if performed) (see example diary in Section 14). If an ISR is ongoing at the end of the 56-day post-treatment subject diary after the last treatment, the TI (or designee) will continue to follow the ongoing ISR to resolution via recommended weekly evaluation and will document the entire course of the ISR on the Ongoing ISR form (ISR type, severity [mild, moderate, or severe] ISR start date and ISR end date. Safety phone calls will occur 3 days after treatment (initial and touch-up, if performed).

During the visit scheduled 8 weeks after initial treatment, before conducting any scheduled actions, the TI must confirm whether the subject needs touch-up treatment after evaluating the initial treatment outcome and getting the subject's agreement. If a touch-up treatment is agreed on, then the Touch-up Treatment Visit and all scheduled procedures will be conducted, if the decision is not to conduct touch-up treatment, then the Week 8 Visit and all scheduled procedures will be conducted. Urine pregnancy testing must be conducted and confirmed as negative before performing touch-up treatment.

For treatment group subjects, routine follow-up visits for safety and effectiveness will occur at Weeks 8, 16, and 24 (primary timepoint) after the last treatment. 3D digital images will be collected, and the 5-point Global Aesthetic Improvement Scale (GAIS) will be assessed separately by the EI (judged live) and the subject (using a mirror) by comparing with pre-treatment (baseline) photos. In addition, the subject (using a mirror) will assess satisfaction with the treatment outcome using the 5-point Nose Satisfaction Scale (NSS) and the subject's willingness to recommend the treatment to a friend. Vital signs will be collected at all visits, and laboratory sample collection for routine hematology, chemistry and urinalysis will be performed at Week 24. The procedures to be performed during the control period are specified in Table 2.

#### 6.2.2.3 Post-randomization, Treatment(s) and Follow-up – Control Group

The control group subjects will undergo 3D imaging and EI assessment of the GAIS at Weeks 8, 16, and 24. The procedures to be performed during the control period are specified in Table 3.

### 6.2.3 Post-control Period

#### 6.2.3.1 Treatment Group Subjects

For treatment group subjects, routine follow-up visits for safety and effectiveness will occur at Weeks 36 and 48 after the last treatment (initial or touch-up). 3D digital images as well as the GAIS, assessed separately by the EI and the subject, will be performed in addition to the subject assessment of satisfaction with the treatment outcome using the NSS and the subject's willingness to recommend the treatment to a friend. Vital signs will be collected at all visits.

Any treatment group subject who withdraws from the study prior to the Week 48 visit must undergo the procedures scheduled for Week 48 at his/her last on-site visit. A urine pregnancy test must be conducted at study exit or at the time of withdrawal if the subject withdraws from the study prior to the Week 48 visit. The procedures to be performed during the post-control period are specified in Table 2.

#### 6.2.3.2 Control Group Subjects

After completing the Week 24 visit (primary timepoint), all control group subjects have the option to receive initial treatment (no later than 10 days after completing the Week 24 visit) and touch-up treatment (8 weeks after initial treatment). If a subject decides not to receive the optional treatment(s), s/he will be considered as completing the study. If a subject decides to receive the optional treatment(s), the TI must re-confirm that the treatment goal has been aligned with the subject before performing the initial treatment. Prior to treatment (initial and touch-up, if administered), female subjects of childbearing potential must have a confirmed negative urine pregnancy test.

All treatment procedures and safety procedures conducted for the treatment group subjects must be followed. The procedures to be performed during the post-control period are specified in Table 3.

For any control group subjects who withdraw from the study before completing the "no-treatment" control period visit, the scheduled procedures for the Week 24 visit of "no-treatment" period must be conducted at his/her last on-site visit. For any control group subjects who receive treatment and withdraw before completing the Week 24 post-treatment visit, all scheduled procedures for the Week 24 post-treatment visit must be conducted at his/her last on-site visit.

## 6.3 Instructions for the Subjects

At the screening visit, the TI (or designee) will discuss routine alternative treatments that may be available with any subject who is interested in participating in the study. The available alternative treatments include plastic surgery, autologous fat injection, etc; s/he will counsel the subject regarding his/her treatment goals and the potential benefit and limitations of study treatment. After counseling, if the subject's expectations are not realistic, the TI (or designee) will not proceed with obtaining the subject's signature on the ICF and will discontinue the subject from the study.

During each study visit, subjects will be required to remove all jewelry, make-up, and lipstick, to avoid interference with the digital photographs.

Starting from the treatment day, the subject must record any ISRs on the 56-day post-treatment subject diary by following the instructions provided on the diary and by the TI.

For 10 days before and 3 days after study treatment administration, subjects should avoid using a regimen of anti-coagulation, antiplatelet, or thrombolytic medications; nonsteroidal anti-inflammatory drugs; supplements of Vitamin C or E, garlic, gingko biloba, or ginseng; or other supplements known to increase coagulation time. These precautions are recommended to reduce the risk of posttreatment bleeding or bruising.

For at least 24 hours after treatment, subjects should avoid strenuous exercise, consumption of alcoholic beverages, and extended exposure to sun or heat to reduce the risk of posttreatment redness, swelling, and/or itching.

After treatment, the subject should avoid unnecessary external compression of the nose that could cause product displacement, indentation, or depression of the dorsal surface where product has been placed. The subject should not sleep face down and should avoid any pressure or trauma to the nasal area, including the use of goggles and sunglasses or reading glasses for 1 week. During this time, the subject is advised not to have a facial massage, enter a sauna or hot spring, receive excessive sun exposure, or go swimming. No phototherapy,

laser treatment, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures should be performed in nose and nose adjacent area during the study period.

Subjects will also be instructed to contact the TI or his/her research staff to report any unexpected symptoms or to ask questions about the study.

## 6.4 Unscheduled Visits

An unscheduled visit may occur for safety purposes (eg, if the subject needs to obtain information regarding AEs or ISRs). An unscheduled visit may also occur to repeat facial digital images if those obtained at the scheduled visit are poor quality images. Applicable procedures will be performed and recorded on the eCRF.

## 6.5 Early Discontinuation of Subjects

Each subject reserves the right to withdraw from the study at any time without jeopardy to his/her future medical care. All follow-up procedures scheduled to be performed at the final site visit should be performed at the subject's last site visit. Subjects may also be administratively withdrawn if they do not return for follow-up visits. For any subject who withdraws from the study, the date and reason for withdrawal will be recorded on the eCRF. If a treatment-related AE is ongoing at the time of withdrawal, the TI will attempt to follow the subject until the AE has been resolved or follow-up is no longer possible. The TI shall ask for the subject's permission to follow his/her status/condition outside the study.

Randomized subjects who withdraw before treatment will not be replaced by another subject. The subject number and associated randomization number of the withdrawn subject should not be reassigned to a different subject.

If a subject fails to return for 1 or more scheduled study visits, the TI (or designee) will attempt to contact the subject to determine and document the reason the subject has failed to return and to encourage compliance with the study visit schedule.

At regular intervals, the TI (or designee) will record on the eCRF the reasons for which any subjects are discontinued from the study, including subjects who signed the ICF but do not proceed to randomization.

## 6.6 Withdrawal Criteria

The subject may withdraw at will at any time for any reason.

If a subject has a positive urine pregnancy test prior to initial treatment, the subject will not be eligible for treatment and will be withdrawn from the study. If a subject has a positive urine pregnancy test after treatment, she will continue all scheduled visit and non-treatment procedures. The pregnancy will be followed as described in Section 10.3. If a subject receives hyaluronidase or dermal fillers in the nose area during the trial, s/he will be withdrawn from the study.

# 7. Response Measures and Summary of Data Collection Methods

## 7.1 Effectiveness Measures

### 7.1.1 Primary Effectiveness Measure

The primary effectiveness measure is the volume change from baseline in the nose area as calculated by digital analysis of each subject's 3D images.

### 7.1.2 Secondary Effectiveness Measures

Secondary effectiveness measures include the EI's and subject's assessments of aesthetic improvement of the nose using the 5-point GAIS (Table 4), and subject's assessment of treatment outcome using the 5-point NSS (Table 5).

**Table 4 5-Point Global Aesthetic Improvement Scale**

| Score | Grade | Description |
|---|---|---|
| 2 | Much improved | Marked improvement in appearance |
| 1 | Improved | Improvement in appearance, but a touch-up or retreatment is indicated |
| 0 | No change | The appearance is essentially the same as the original condition |
| -1 | Worse | The appearance is worse than the original condition |
| -2 | Much worse | The appearance is much worse than the original condition |

**Table 5 5-Point Nose Satisfaction Scale**

| Score | Grade |
|---|---|
| +2 | Very satisfied |
| +1 | Satisfied |
| 0 | Neutral (neither satisfied or dissatisfied) |
| -1 | Dissatisfied |
| -2 | Very dissatisfied |

[redacted]

## 7.2 Safety Measures

Safety measures will include:

- subject assessment of procedural pain (pain during injection) on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable)
- AEs, including AEs of special interest, from TI observation and inquiry at scheduled follow-up visits. AEs will be monitored continuously throughout the study and documented on as AE eCRF.
- monitoring of concomitant medications and concurrent procedures
- routine hematology and blood chemistry testing and urinalysis
- vital sign measurements, including blood pressure (systolic and diastolic, while subject is seated), temperature, pulse, and respiratory rate
- symptom, severity (mild, moderate, or severe) and duration of ISRs, which will be recorded in the 56-day post-treatment subject diary

The 56-day post-treatment subject diary will list the following ISRs that have been reported previously with HA dermal filler injections:

- redness
- pain after injection
- tenderness to touch
- firmness
- swelling
- lumps/bumps
- bruising
- itching
- discoloration

The 56-day post-treatment subject diary will list the following severities for ISRs to be recorded:

| | |
|---|---|
| Mild | Symptoms causing little, if any, discomfort leading to little, if any, effect on daily activities. |
| Moderate | Symptoms causing some discomfort leading to some effect on daily activities. |
| Severe | Symptoms causing great discomfort leading to compromised performance of daily activities. |

The TI (or designee) will review the 56-day post-treatment subject diary and discuss any unusual signs/symptoms with the subject. If an ISR of initial treatment is ongoing at the touch-up treatment, it will be recorded and followed in the touch-up 56-day post-treatment subject diary. If an ISR is ongoing at the end of the safety diary after the last treatment, the TI (or designee) will continue to follow the ongoing ISR to resolution via the recommended weekly evaluation and will document the entire course of the ISR on the Ongoing ISR form (ISR type, severity [mild, moderate, or severe], ISR start date, and ISR end date) in the eCRF.

## 7.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics to be collected include sex, age, race, medical/surgical/cosmetic/dental procedure history, and prior medications.

## 7.4 Treatment Characteristics

Treatment characteristics will be evaluated by collecting information on anesthesia usage (ice, lidocaine cream, local anesthesia, nerve block), injection site (midline dorsum, columella, and anterior spine), injection plane (supraperiosteally and supraperichondrially), injection volume, injection ease (11-point scale where 0 = difficult and 10 = easy), and product moldability (11-point scale where 0 = stiff and 10 = moldable).

## 7.5 Summary of Methods of Data Collection

Electronic data capture will be used to collect study-specific information, such as subject and investigator assessments. Completed eCRFs will be reviewed by the TI or EI as applicable (or designee), and the designated monitor will verify the data. Investigators will provide access to hospital files, medical records, and other source documents containing subject clinical/medical information. Source document verification will be performed.

Treatment and safety assessments will be performed by the TI. The initial treatment and touch-up treatment (if performed) for each subject must be performed by the same TI. The effectiveness assessments for each subject are strongly recommended to be performed by the same EI throughout the study. The blinded independent technician will be responsible for all 3D digital image analyses which will be used as effectiveness assessments. At specified timepoints, subjects will complete questionnaires and 56-day post-treatment subject diary(ies).

After signing the ICF and until exit from the study, any untoward signs or symptoms or other AEs as well as concomitant medications, procedures and therapies of all subjects (treatment and control groups) will be carefully monitored by the TI and documented by either the TI or assigned site staff.

Subjects will complete the paper ISR diaries, and responses will be entered into the clinical database.

Canfield Scientific will be responsible for analyzing 3D digital imaging data by independent, blinded technicians. Sites will save photographs onto supplied electronic media and send the storage device to Canfield Scientific. Alternatively, files containing the facial digital photographs may be directly uploaded to Canfield Scientific from the Canfield Scientific equipment.



# 8. Statistical Procedures

Allergan developed the statistical design of this trial. A separate statistical analysis plan will be prepared to provide specifications for all analyses. The plan will be finalized and approved prior to clinical database lock.

Descriptive statistics will be presented for key outcome measures. Categorical variables will be summarized with frequency and relative frequency. Continuous variables will be summarized by number of subjects, mean, median, standard deviation, minimum, and maximum. Where appropriate, 2-sided 95% CIs for population mean, or population proportion, will be provided as part of the descriptive summary.

Every attempt will be made to collect complete data and limit the occurrence of missing data. Imputation of missing data will be performed for the primary effectiveness analysis as a sensitivity analysis.

## 8.1 Analysis Populations

The following analysis populations will be used in the analyses for this study:

- modified intent-to-treat (mITT) population: 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)
- per-protocol (PP) population: all mITT subjects who do not have any significant protocol deviations affecting the primary effectiveness endpoint
- safety population: subjects who receive at least 1 study treatment

Unless specified otherwise, effectiveness analyses and baseline characteristics will be conducted using the mITT population. The PP population will be used to perform sensitivity analyses for the primary effectiveness variable. All safety analyses will be conducted using the safety population. Control subjects' data after treatment will also be summarized.

## 8.2 Collection/Derivation of Primary and Secondary Effectiveness Assessments

### 8.2.1 Primary Effectiveness Variable

The primary effectiveness variable is the mean change in volume in subject's nose area from baseline as calculated by digital analysis of each subject's 3D images, where baseline is the pretreatment image at the randomization visit for the treatment group and the control group.

The primary effectiveness endpoint is the comparison of the mean change in nose area volume from baseline to the Week 24 visit for the treatment group versus that for the control group prior to treatment.

### 8.2.2 Secondary Effectiveness Variables

Secondary effectiveness variables include:

- The responder rate for the treatment group based on the GAIS assessment by the EI, which is defined as the percentage of subjects who note improvement (Improved or Much Improved) on the GAIS
- The responder rate for the treatment group based on the GAIS assessment by the subject, which is defined as the percentage of subjects who note improvement (Improved or Much Improved) on the GAIS

- The responder rate for the treatment group based on the NSS assessment by the subject, which is defined as the percentage of subjects who note satisfaction (Satisfied or Very Satisfied) on the NSS

## 8.3 Hypothesis and Methods of Analysis

### 8.3.1 Primary Effectiveness Analyses

The primary effectiveness endpoint is the comparison of mean change in volume in nose area based on 3D imaging between the treatment group and the control group (prior to treatment) at Week 24. The following hypothesis will be tested:

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

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

A 2-sided 2-group t-test (or Wilcoxon rank-sum test as appropriate) will be performed at the 5% level to test whether the mean volume change from baseline in the nose area for the treatment group is significantly greater than that for the control group at Week 24.

### 8.3.2 Secondary Effectiveness Analyses

Secondary effectiveness analyses will include:

- The observed responder rate with 95% exact CI at Week 24 for the treatment group based on the GAIS assessment by the EI
- The observed responder rate with 95% exact CI at Week 24 for the treatment group based on the GAIS assessment by the subject
- The observed responder rate with 95% exact CI at Week 24 for the treatment group based on the NSS assessment by the subject

A “responder” is defined as a subject who shows improvement in the overall aesthetic assessment (Improved or Much improved on GAIS) posttreatment. Since the GAIS assessments are only collected after treatment, there will be no data for the no-treatment control period for the control subjects. Responder analyses will be done for each treatment group separately. Responder analysis of the NSS will be similar to the GAIS. A “responder” is defined as a subject with a score of ≥1 point (Satisfied or Very satisfied) at Week 24 on the NSS.

[redacted]

### 8.3.4 Safety Analyses

ISRs will be summarized by treatment (initial and touch-up), incidence, severity, and duration. Incidence of AEs will be tabulated by primary system organ class (SOC) and by preferred term, and will be tabulated by onset, duration, severity, action taken, relationship to treatment, and outcome. Treatment-related AEs, SAEs, AEs leading to study discontinuations, and deaths will be listed or tabulated. Procedural pain, vital signs and laboratory results will be summarized by frequency distributions or descriptive statistics.

### 8.3.5 Demographic and Baseline Characteristics Analyses

Subject demographics and vital signs data collected at the screening visit will be summarized descriptively by treatment group. Past medical/surgical/cosmetic/dental procedure history will be listed. Prior medications will be listed.

### 8.3.6 Treatment Characteristics Analyses

Treatment administration characteristics including anesthesia usage, injection site, planes of injection, volume injected (summarized by injection sites and overall), injection ease, and product moldability will be summarized descriptively for initial and touch-up treatment as well as treatment group subjects and control group subjects who received treatment.

## 8.4 Subgroup Analyses

The effectiveness and safety analyses will be performed by investigational site. Details will be provided in the statistical analysis plan.

## 8.5 Sample Size Calculation

A sample size of 90 treatment and 30 control subjects 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 subjects complete 1 year follow-up, accounting for subject attrition of 15% during the whole study duration through Week 48, at least 120 subjects in the treatment group and 40 subjects in the control group will be randomized.

## 8.6 Interim Analyses

No interim analysis is planned for this study. All data collected though the study completion will be analyzed in the final study report.

# 9. Materials

## 9.1 Study Treatment

### 9.1.1 Product Description

VOLUMA with Lidocaine is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized injectable gel implant (dermal filler) that is currently available in the United States, Europe, Canada, Australia, Russia, Israel, Taiwan, Thailand, and Brazil for the approved indication of mid-face volume deficit. VOLUMA with Lidocaine contains HA derived from fermentation of *Streptococcus equi*. The HA derived from this process is purified, crosslinked using 1,4-butanediol diglycidyl ether to form a 3-dimensional gel matrix, and repurified.

[redacted]

### 9.1.2 Instructions for Use and Administration

The TIs and EIs must be experienced in the use and administration of HA implants and be practicing in the field of aesthetic medicine, dermatology, or plastic/cosmetic/reconstructive

surgery. Before the study begins, the TIs will receive training in administration of VOLUMA with Lidocaine according to the technique specified for this study. During this training session, study procedures, visit schedule, and effectiveness and safety assessments will be discussed.

The Investigational Manual for VOLUMA with Lidocaine will be provided.

### 9.1.3 Treatment Regimen Adjustments

Up to 2 treatment sessions (initial and touch-up) approximately 8 weeks apart are allowed. The TI will determine the appropriate volume of VOLUMA with Lidocaine to inject at the initial and touch-up treatments based on his/her clinical experience and the randomization assignment, but the minimal volume must exceed 0.5 mL and maximum volume is not to exceed 3.0 mL for initial and touch-up treatments combined.

## 9.2 Other Study Supplies

Allergan will provide urine pregnancy test kits, digital imaging equipment, shipping materials for shipment of laboratory samples to the central laboratory, study device kits, and additional 27G x ½ inch needles. The investigational site is responsible for routine supplies related to device administration and follow-up visits (eg, antiseptics, drapes, gloves, gauze, anesthesia, ice packs, blood pressure cuff, and internet connection for interactive web response system [IWRS] and eCRF completion).

# 10. Study Administration Procedures

The clinical study shall not begin until the required approvals from the appropriate regulatory authorities and ECs have been obtained.

## 10.1 Subject Entry Procedures

### 10.1.1 Overview of Entry Procedures

Prospective subjects as defined by the criteria in Sections 5.3 and 5.4 (inclusion/exclusion criteria) will be considered for entry into this study. A subject is considered to have entered the study upon signing the ICF, which will occur prior to any screening procedures. Screening procedures include:

- collection of demographic information
- collection of medical/surgical/cosmetic/dental procedure history
- collection of concurrent medications and procedures

- a urine pregnancy test for female subjects of childbearing potential
- capture of 3D digital images of the face
- evaluation of inclusion/exclusion criteria

Subjects choosing not to participate in photos per checkbox selection on the ICF will be excluded from the study. Allergan shall have full ownership rights to any photographs derived from the study.

### 10.1.2 Informed Consent and Subject Privacy

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject. The subject must also give written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

The investigator or his/her authorized designee conducts the informed consent (IC) discussion and will document in the subject's medical records the acquisition of IC and the subject's agreement or refusal to notify his/her primary care physician about the study. The IC shall include all aspects of the study that are relevant to the subject's decision to participate throughout the study. The IC process is to avoid any coercion or undue influence on, or inducement of, the subject to participate. The subject is to personally sign and date the ICF. The investigator will retain the original copy of the signed form, and the subject will receive a copy. Upon signing the ICF, the subject is considered to be enrolled in the study and receives a subject number that will be used on all documentation for the subject throughout the study. Subject numbers will be assigned in ascending order, and numbers will not be omitted or reused. The subject number is coupled with the site identification number for unique identification of each subject. The investigator is to ensure important new information is provided to new or existing subjects throughout the study.

### 10.1.3 Method for Assignment to Treatment Groups

At the time of randomization (ie, at or within 4 weeks after screening/signing of the ICF), eligible subjects will be randomly assigned to 1 of 2 treatment groups (treatment and no-treatment control) in a 3:1 ratio to receive VOLUMA with Lidocaine treatment immediately or to delay treatment by 24 weeks until the end of the control period. Subjects will be assigned to a treatment group based on a central randomization schedule. An automated IWRS will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan. Study treatments will be labeled with kit numbers. This number will be recorded on the appropriate eCRF. The IWRS will provide the

site with the specific kit number(s) for each randomized subject at the time of randomization and at each subsequent treatment visit. Sites will administer treatment according to the IWRS instructions provided by the system.

## 10.2 Compliance with Protocol

The Principal Investigator and designee are responsible for compliance with the protocol at the investigational site. A representative of Allergan will make frequent contact with the investigator and his/her research staff, and will conduct regular monitoring visits at the site to review subject and device accountability records for compliance with the protocol. Any protocol deviations will be discussed with the investigator upon identification. The use of the data collected for the subject will be discussed to determine if the data are to be included in the analysis. All protocol deviations will be reported to the EC according to the EC's reporting requirements.

## 10.3 Pregnancy

If a female becomes pregnant during the study, the TI (or designee) will notify Allergan immediately after the pregnancy is confirmed. The TI (or designee) shall (1) instruct the subject to notify her physician of the presence of the investigational device and (2) follow the pregnancy to term. Best practices are to be followed in order to ensure the welfare of the subject and the fetus. The Medical Safety Physician (or designee) will contact the TI (or designee) to obtain information about the pregnancy outcome. The subject will continue to be followed as part of the mITT population, and the pregnancy will be documented as a protocol deviation.

Pregnancy by itself will not be considered an AE or serious adverse event (SAE). Hospitalization for a normal delivery or elective abortion of a normal fetus does not constitute a SAE. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an AE or SAE, and these are to be reported as described in Sections 11.3 and 11.4.

## 10.4 Study Termination

If conditions arise during the study that indicate that the study or an investigational site needs to be terminated, Allergan and the investigator, monitor, EC, and/or regulatory agencies will discuss the situation and take appropriate action after consultation. Conditions that may warrant termination of the study or site include, but are not limited to:

- the discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- the decision on the part of Allergan to suspend or discontinue testing, evaluation, or development of the study device
- failure of the investigator to comply with pertinent national or state regulations, EC-imposed conditions, or protocol requirements
- investigator submission of knowingly false information to Allergan, a study monitor, the EC, or any regulatory agency

Per ISO 14155, if a study is prematurely terminated or suspended due to safety issues, Allergan shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The EC is also to be informed promptly and provided the reason(s) for the termination or suspension by Allergan or by the investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, Allergan shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of subjects enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled subjects, if applicable.



# 11. Adverse Events

Throughout the course of the study, all AEs will be monitored and reported (Common Terminology Criteria for Adverse Events, Version 4.0) on an AE eCRF, including seriousness, severity, action taken, and relationship to study treatment. If AEs occur, the first concern will be the safety of the study participants.

Although the risk of developing a serious complication is small, the TI and the research staff will monitor each subject closely, and, if a complication occurs, they will use their medical judgment to do whatever is necessary to treat the problem. Additional information is available in the Investigational Manual.

Typical or expected adverse events or risks include bruising, swelling, redness, tenderness, and/or itching at the treatment site. Additional information about the possible side effects is available in the Investigational Manual for VOLUMA with Lidocaine.

## 11.1 Definitions

### 11.1.1 Adverse Event

An AE is defined in accordance with ISO 14155 as "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device." This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational medical devices.

Disease signs and symptoms that existed prior to the study treatment are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

AEs will be monitored throughout the study beginning with signing the ICF. At each post-baseline visit, the investigator will begin querying for AEs by asking each subject a general, non-directed question such as "Have you had any changes to your condition since your last visit?" Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate eCRF.

### 11.1.2 Serious Adverse Event

A SAE is defined in accordance with ISO 14155 as an AE that:

a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
    1. A life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

See Section 11.4 for procedures for reporting an SAE/serious adverse device effect (SADE).

### 11.1.3 Adverse Device Effect

An adverse device effect (ADE) is defined in accordance with ISO 14155 as "an adverse event related to the use of an investigational medical device." This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.

See Section 11.3 for procedures for reporting an ADE.

### 11.1.4 Serious Adverse Device Effect

A SADE is defined in accordance with ISO 14155 as "an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event."

See Section 11.4 for procedures for reporting a SADE.

### 11.1.5 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is defined in accordance with ISO 14155 as "any serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report." The investigator is to consult the Investigational Manual for anticipated risks or anticipated AEs.

### 11.1.6 Device Deficiency

A device deficiency is defined in accordance with ISO 14155 as "inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance." Device deficiencies include malfunctions, use errors, and inadequate labeling.

If a device deficiency occurs, the investigator will notify Allergan using the fax number or email on the front page of the protocol. Device deficiencies shall be documented throughout the study and appropriately managed by Allergan. Allergan shall review all device deficiencies and determine and document in writing whether they could have led to a SADE. These shall be reported to the regulatory authorities and ECs as required by national regulations.

### 11.1.7 Severity

Severity is a clinical determination of the intensity of an AE. The severity assessment for a clinical AE is to be completed using the following definitions as guidelines:

| | |
|---|---|
| Mild | Awareness of sign or symptom, but easily tolerated |
| Moderate | Discomfort enough to cause interference with usual activity |
| Severe | Incapacitating with inability to work or do usual activity |

### 11.1.8 Relationship to Treatment

Relationship to treatment refers to a determination of the relationship (if any) between an AE and the device or treatment procedure. An AE could be considered treatment-related when, in the judgment of the TI, it is reasonable to believe that the event may have been caused by the device or is associated with the procedure, such as an event that can be attributed to other products, surgical techniques, or medications required specifically for the procedure.

Relationship to treatment must be determined by the TI and cannot be delegated to other study staff.

## 11.2 Timelines for Reporting

The investigator is to adhere to the following schedule in reporting different types of AEs.

| Adverse Event Type | Reporting to Allergan | Start of Collection | End of Collection |
|---|---|---|---|
| AEs, ADEs | Record on AE eCRF upon awareness for review by the Clinical Monitor | Signing ICF | Last subject visit |
| SAEs, SADEs | Record on SAE Form and fax to Allergan within 24 hours of awareness | Signing ICF | Last subject visit |

AE = adverse event; ADE = adverse device effect; ICF = informed consent form; SAE = serious adverse event; SADE = serious adverse device effect

## 11.3 Procedures for Reporting an AE or ADE

All AEs or ADEs occurring during the study period (beginning with signing the ICF) are to be recorded on the appropriate eCRF. For any treatment-related AE that is ongoing at the exit, the Investigator will attempt to follow the subject until the AE has been resolved or follow-up is no longer possible.

AEs that start after the study follow-up period has ended will be considered outside the scope of the study but will be captured by Product Surveillance.

## 11.4 Procedures for Reporting an SAE or SADE

All SAEs and SADEs occurring during the study period (beginning with signing the ICF) are to be immediately reported to an Allergan representative at the e-mail address listed on the cover page and recorded on the appropriate eCRFs. All subjects with an SAE/SADE must be followed up and the outcomes reported. The TI is to supply Allergan and the EC with any additional requested information (eg, hospital discharge summary, autopsy reports and terminal medical reports). Allergan will evaluate all SADEs and determine and document in writing whether they meet the definition of USADE. These shall be reported to all participating investigators, the regulatory authorities, and ECs as required by national regulations.

In the event of an SAE/SADE, the investigator must:

1. Notify Allergan immediately by email using the SAE/SADE reporting forms. For the SAE/SADE email address, see the front page of the protocol.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3. Promptly inform the governing EC of the event, if it is treatment-related. For other SAEs, notify the governing EC as required by the EC, local regulations, and the governing health authorities.

## 11.5 Procedures for Unblinding Study Treatments

EIs may be become unblinded after the final database lock upon notification by Allergan or an Allergan representative.

# 12. Administrative Issues

## 12.1 Protection of Human Subjects

### 12.1.1 Compliance with Informed Consent Regulations

Written IC is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative.

### 12.1.2 Compliance with EC Regulations

This study is to be conducted in accordance with applicable EC regulations. The Principal Investigator must obtain approval from a properly constituted EC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible EC has been disqualified or if proceedings leading to disqualification have begun.

### 12.1.3 Compliance with Good Clinical Practice

This protocol is to be conducted in compliance with GCP guidelines, and with ethical principles for clinical research.

### 12.1.4 Compliance with Electronic Records and Signature Regulations

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

## 12.2 Changes to the Protocol

The Principal Investigator is not to implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the EC of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (eg, change of telephone numbers). Allergan may amend the protocol during the course of the study. The amended protocol shall be distributed to the investigators and ECs.

## 12.3 Subject Confidentiality and Privacy

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study device may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to Allergan and the governing health authorities, if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

## 12.4 Documentation

### 12.4.1 Source Documents

Source documents may include a subject's medical records, hospital charts, laboratory notes, device accountability records, subject questionnaires and diaries, photographic negatives or digital images, radiographs, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as laboratory tests.

### 12.4.2 Case Report Form Completion

The Principal Investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents. The eCRF should be completed in a timely manner after the visits are performed. The queries generated on eCRF should be answered by the investigator in a timely manner.

### 12.4.3 Investigator Reports

In accordance with the applicable regulatory requirements, the investigator is to submit written summaries of study status to the EC annually (or more frequently if requested by the EC). Upon completion of the study and where required by the applicable regulatory requirements, the investigator is to inform the institution of the completion of the study.

### 12.4.4 Retention of Documentation

All study related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs are to be maintained on file.

The site will retain the study-specific essential documents for at least 10 years after study completion. Allegan will retain the essential documents until the product is no longer marketed in China.

Allergan requires notification in writing if an investigator wishes to store study documents off-site or to relinquish the study data records so that mutually agreed-upon arrangements can be made for transfer of the data records to a suitably qualified, responsible person. Notification is to go to Allergan Medical, Attn: Clinical Research Dept., Suite 1804-05 SK Tower, 6A Jianguomenwai Avenue, Chaoyang District, Beijing, China, 100022.

## 12.5 Labeling, Packaging, Storage, and Return of Study Devices

### 12.5.1 Labeling/Packaging

VOLUMA with Lidocaine will be provided sterile in syringes. An investigational caution label, such as the following will appear on the individual blister package and the outer box:

FOR CLINICAL TRIAL USE ONLY

PROTOCOL 1894-701-008

[redacted]

### 12.5.2 Storage of Study Devices

The study device must be stored in a secure area accessible to delegated study personnel only and administered only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in this protocol.

VOLUMA with Lidocaine must be stored at [redacted] with a continuous temperature monitoring device (provided by Allergan, if necessary). Use of the temperature monitoring device is required to ensure that the study product is being maintained within the acceptable storage-range conditions. If the storage temperature varies from the programmed limits, the monitoring device alarm will trigger indicating an excursion that may impact the stability of the study product. Sites must report any alarmed temperature excursion to Allergan, and avoid administering the impacted study product, by isolating the product, until receiving further instructions from Allergan. Do not freeze or expose to extreme heat. Do not use if the package is open or damaged or if the product is not clear.

### 12.5.3 Study Device Accountability

The TI (or designee) must keep an accurate accounting of the number of study devices received from Allergan, dispensed to subjects, and returned to Allergan (or designee) during and at the completion of the study. A detailed inventory must be completed for the study devices including subject initials, device serial/lot number, date of implantation, and date of explantation if applicable. The study product must be administered to study subjects by a TI only.

### 12.5.4 Return of Study Devices

Upon completion of the treatment period, the quantities of all used and unused study devices will be reconciled. The blister/outer packaging of used syringes will be retained for verification against the eCRF by Allergan's study monitor. The used syringes will be destroyed appropriately at the site by following the site's routine internal practices and China local regulations. Unused syringes of VOLUMA with Lidocaine will be returned to an Allergan-contracted local depot in China for destruction according to Allergan instructions.

Devices that are damaged during shipment or at the site or that malfunction during use (eg, faulty syringe or plunger) must be accounted for, and the nature of the malfunction will be recorded on the appropriate form. The TI (or designee) will promptly notify Allergan's Medical Safety Physician or Clinical Research Department of any device malfunction. Any faulty syringe will be sent to an Allergan-contracted local depot in China for destruction.

## 12.6 Monitoring by Allergan

Appropriately trained representatives of Allergan will monitor the conduct of the trial at each investigational site, including visits to the site to review, verify, and retrieve copies of study-related documents. It is the responsibility of the Principal Investigator (or designee) to be present or available for consultation and to assure that Allergan has access to all study-related records during scheduled monitoring visits.

Allergan will review device accountability records and completed eCRFs to ensure completeness and consistency with the source records and compliance with the protocol requirements.

## 12.7 Testing of Biological Specimens

At screening and at month 6 posttreatment, blood samples will be collected and prepared for routine hematology and chemistry testing by a central laboratory located in China.

Routine hematology tests including:

- levels of hemoglobin and hematocrit, concentration of red blood cells, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, red blood cell morphology, and the concentration of white blood cells, neutrophils (%, absolute), lymphocytes (%, absolute), monocytes (%, absolute), eosinophils (%, absolute), basophils (%, absolute), and platelets

Chemistry tests including:

- hepatic function tests: total bilirubin, direct bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, total protein, and albumin
- renal function tests: urea nitrogen, creatinine, uric acid, calcium, and phosphorous
- others: lactate dehydrogenase, glucose, triglycerides, cholesterol, and creatinine kinase

At screening and at month 6 posttreatment, urine samples will be collected for routine macro and micro panel of tests conducted by the central laboratory in China to assess color and clarity, specific gravity, pH, and concentration of protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocyte esterase, and for microscopic analysis.

At screening, on treatment days prior to injection, and at study exit, a trained research staff member at each investigational site will perform pregnancy testing on urine samples from women of childbearing potential. The urine pregnancy test employed will test for the presence of human chorionic gonadotropin and should have a sensitivity of at least 50 mIU/mL.

All blood and urine samples (ie, not including samples for urine pregnancy testing) will be stored at the central laboratory for the duration of the study. The central laboratory will be responsible for sample destruction when the study sites have been closed. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.



## 12.8 Publications

This study will be registered and results posted on www.clinicaltrials.gov. Allergan, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study Investigators and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

## 12.9 Coordinating Investigator

A Coordinating Investigator will be designated prior to enrollment of subjects.

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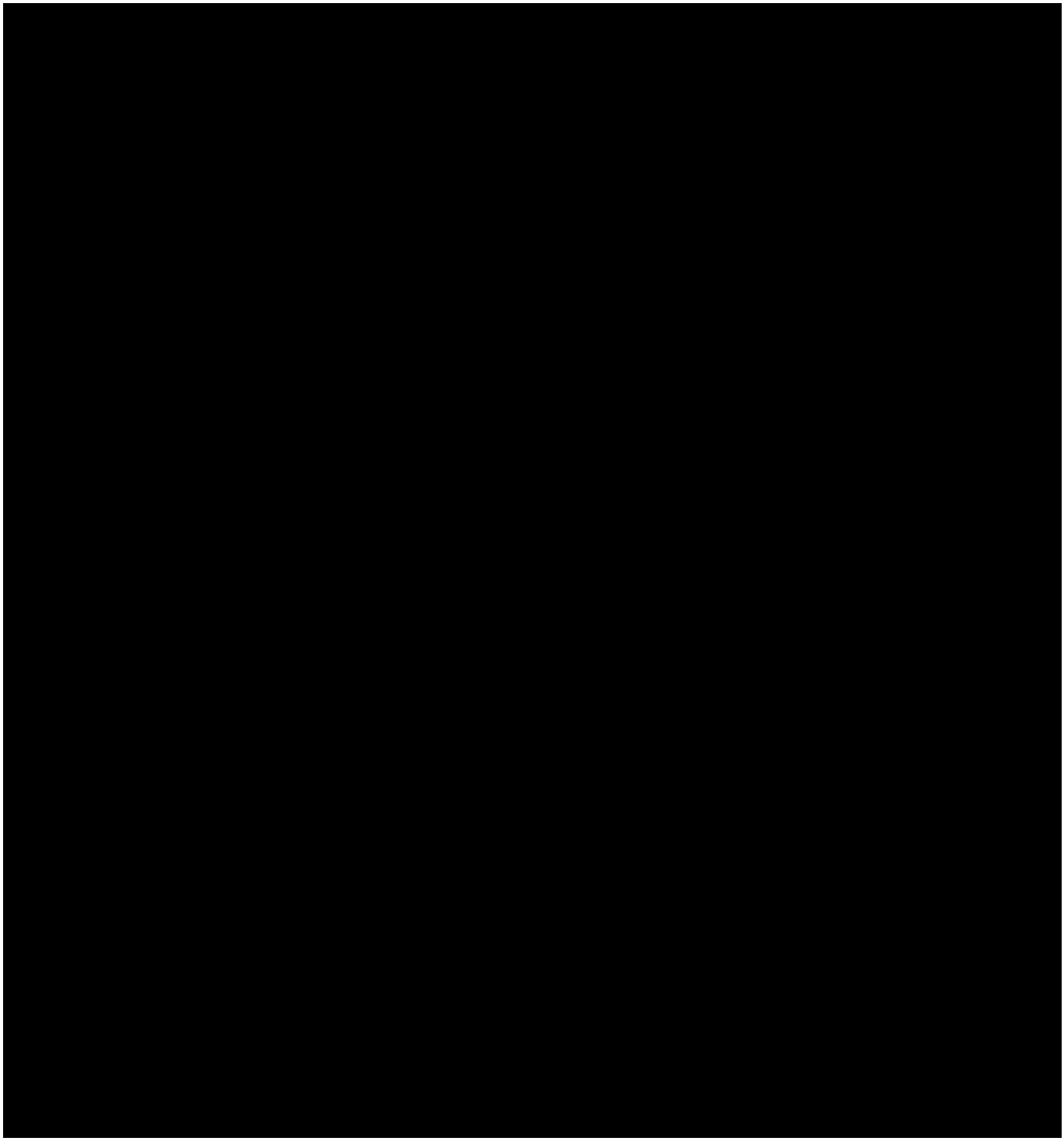

# 15. Protocol Amendment Summary

| Version Date/ Amend. No. | Changes to Protocol |
|---|---|
| 22 Sep 2017/1 | • Header – added "Amendment 1"<br>• Title page – revised protocol date, updated protocol version number to Amendment 1<br>• Investigator Signature page - revised protocol date, updated protocol version number to Amendment 1<br>• Synopsis – NUMBER OF SUBJECTS – replaced "An estimated"with "At least"<br>• Synopsis – Control Period – 1) clarified anatomical characteristics measurements; added "nasal root height, nasal length and ala depth", and deleted "nasofacial angle"; 2) the interval between initial and touch-up injection was modified from 4 weeks to 8 weeks; 3) 28-day post-treatment subject diary updated to 56-day post-treatment subject diary; 4) routine follow-up visits for safety and effectiveness revised from Weeks 4 and 12 to Weeks 8 and 16<br>• Synopsis – Post-control Period – 1) the interval between initial and touch-up injection was modified from 4 weeks to 8 weeks; 3) 28-day post-treatment subject diary updated to 56-day post-treatment subject diary; 4) timing of effectiveness evaluations revised from Weeks 4 and 12 to Weeks 8 and 16<br>• [redacted]<br>• Synopsis - DURATION OF STUDY – control and post- control periods increased from 4 to 8 weeks<br>• [redacted]<br>• Synopsis – Sample Size Calculation – added "In order to have over 100 treatment group subjects complete 1 year follow-up", clarified subject attrition of 15% "during the whole study duration"<br>• [redacted]<br>• Section 4.2 – total study duration increased from 93 to 96 weeks, treatment increased from 4 to 8 weeks, clarified that the 48-week follow-up was "after last treatment"<br>• Section 4.3.4 – Revised timing of touch-up from 4 to 8 weeks after initial treatment<br>• Section 5.1 - Replaced "An estimated"with "At least" |

| Version Date/ Amend. No. | Changes to Protocol |
|---|---|
| | • [redacted]<br>• Section 6.2.2.1 - clarified anatomical characteristics measurements; added "nasal root height, nasal length, and ala depth", and deleted "nasofacial angle"<br>• Section 6.2.2.2 - 28-day post-treatment subject diary updated to 56-day post-treatment subject diary, routine follow-up visits for safety and effectiveness updated from Weeks 4 and 12 to Weeks 8 and 16<br>• Section 6.2.2.3 – timing of control group assessments updated from Weeks 4 and 12 to Weeks 8 and 16<br>• Section 6.2.3.2 – timing of touch-up treatment updated from 4 to 8 weeks<br>• Section 6.3 - 28-day post-treatment subject diary updated to 56-day post-treatment subject diary<br>• [redacted]<br>• Section 7.2 - 28-day post-treatment subject diary updated to 56-day post-treatment subject diary throughout<br>• Section 7.5 - 28-day post-treatment subject diary updated to 56-day post-treatment subject diary<br>• Section 8.5 - added "In order to have over 100 treatment group subjects complete 1 year follow-up", clarified subject attrition of 15% "during the whole study duration"<br>• Section 9.1.3 –timing of treatment sessions updated from 4 to 8 weeks apart<br>• Section 14 – 28-day post-treatment subject diary updated to 56-day post-treatment subject diary<br>• Section 15 – added protocol amendment summary |