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Study ID: VOLBELLA-005

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

Protocol Amendment 2 Date: 29-July-2015

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

Protocol Number: VOLBELLA-005 Amendment 2


Protocol Date: 29 July 2015

Product Name: JUVÉDERM® VOLBELLA® with Lidocaine injectable
gel

Development Phase: Pivotal

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Approval Date: 29-Jul-2015

INVESTIGATOR SIGNATURE PAGE

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

Protocol Number: VOLBELLA-005 Amendment 2

Protocol Date: 29 July 2015

Product Name: JUVÉDERM® VOLBELLA® with Lidocaine injectable gel

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 Independent Ethics Committee (IEC) 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.

_____ Investigator Printed Name	_____ Signature	_____ Date
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Synopsis

NUMBER AND TITLE OF STUDY: VOLBELLA-005: A randomized, multicenter, no-treatment-controlled study of the safety and effectiveness of JUVÉDERM® VOLBELLA® with Lidocaine for lip enhancement in Chinese adults
DEVELOPMENT PHASE: pivotal
STUDY CENTERS: up to 9 Chinese sites
NUMBER OF SUBJECTS: Up to 176 eligible subjects will be randomized (approximately 132 subjects will be assigned to the JUVÉDERM® VOLBELLA® with Lidocaine [hereafter referred to as VOLBELLA with Lidocaine] group and approximately 44 subjects will be assigned to the no-treatment control group).
OBJECTIVES: The objective of this study is to evaluate the safety and effectiveness of VOLBELLA with Lidocaine for lip enhancement in a Chinese population.
STUDY DESIGN: <p>This is a prospective, multicenter, randomized, no-treatment-controlled study to evaluate the safety and effectiveness of VOLBELLA with Lidocaine for lip enhancement in a Chinese population.</p> <p>Subjects will be randomized at a 3:1 ratio either to have treatment with VOLBELLA with Lidocaine at the outset of the study (VOLBELLA with Lidocaine group, also referred to as the treatment group) or to have treatment delayed by 3 months (no-treatment control group). Treatment and safety assessments of a subject throughout the study will be performed by the same Treating Investigator (maximum 2 Treating Investigators per site), and effectiveness assessments will be performed by the same Evaluating Investigator. The Evaluating Investigator will remain blinded to treatment assignments throughout the duration of the study. Subjects randomized to the treatment group should undergo treatment on the same day as randomization. If initial treatment does not occur on the randomization day for subjects in the treatment group, it must occur within 30 days after screening. Subjects randomized to the no-treatment control group will attend study visits at months 1 and 3 of the no-treatment control period at which they will undergo effectiveness measures also performed at randomization. These measures include the Evaluating Investigator's assessment of the subject's lip fullness using the 5-point Lip Fullness Scale (LFS; 5 points: Minimal, Mild, Moderate, Marked, and Very Marked) and facial 3-dimensional (3D) imaging. [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED] In addition, vital signs will be collected. After the completion of the control period, subjects randomized to the no-treatment control group will receive optional treatment for lip enhancement and follow the same schedule of visits and procedures in the treatment period as described below and in Table 1 for subjects randomized to the treatment group.</p> <p>On the initial treatment day, the trained Treating Investigator will inject VOLBELLA with Lidocaine into the lips, as needed for lip enhancement. Allowable treatment areas are the vermilion body, vermilion border (including the Cupid's bow), and philtral columns. Prior to initial treatment, the Evaluating Investigator and the subject will rate the subject's lip fullness by using the LFS, and the Evaluating Investigator will rate the subject's philtral column definition by using a 5-point scale (Not Defined, Barely Defined, Somewhat Defined, Well-defined, and Very Well-defined). On day 30 after initial treatment, the Evaluating Investigator will again rate the subject's lip fullness and philtral column definition. Subjects may undergo an optional touch-up treatment at the day 30 visit after initial treatment, if the Treating Investigator assesses that optimal correction was not achieved. At each treatment visit, the subject will rate procedural pain on an 11-point scale immediately after receiving the injections, and the Treating Investigator will assess the ease of injection and the product moldability. Subjects will complete a safety diary for 30 days after each treatment and will complete a safety follow-up telephone call at 3 days after each treatment. Before treatment on each treatment day, the subject will undergo facial 3D imaging, which will also be performed 30 days after treatment.</p> <p>Routine follow-up visits for safety and effectiveness will occur at 1, 3, and 6 months after the last treatment for both groups. At these visits, facial 3D imaging will be performed, [REDACTED]</p>

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[REDACTED]

Long-term safety data will be collected by telephone call at 9 months after the last treatment for the control group and at 9 and 12 months after the last treatment for the treatment group. Throughout the study, the Treating Investigator (or designee) will monitor the subjects for safety.

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION: Chinese adults seeking lip enhancement

INCLUSION:

1. male or female, 18 years of age or older
2. has an overall baseline score of Minimal, Mild, or Moderate on the 5-point LFS, as assessed by the Evaluating Investigator, and desires to achieve at least a 1-point improvement in overall LFS score after treatment

[REDACTED]

4. has the ability to follow study instructions and is likely to complete all required visits

[REDACTED]

EXCLUSION:

1. has lip tattoos, piercings, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10. is on an ongoing regimen of anti-coagulation therapy (eg, warfarin)

[REDACTED]

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[REDACTED]

14. has current cutaneous inflammatory or infectious processes (eg, acne or herpes), an abscess, an unhealed wound, or a cancerous or precancerous lesion in the mouth area (study treatment may be delayed so that subjects with a history of recurrent oral herpes can take prophylactic antiviral/herpes medication for 2 days)

[REDACTED]

TEST PRODUCT, DEVICE VOLUME, AND MODE OF ADMINISTRATION:
VOLBELLA with Lidocaine hyaluronic acid dermal filler will be injected into the lips and, if needed, the philtral columns using a 30 G x 1/2-inch needle. The appropriate injection volume will be determined by the Treating Investigator but is not to exceed a maximum total of 4.0 mL for initial and touch-up treatments combined.

DURATION OF STUDY: treatment period: 1 to 30 days; follow-up period: up to 12 months

RESPONSE MEASURES:
Effectiveness: The primary effectiveness measure is the Evaluating Investigator's assessment of overall lip fullness using the 5-point LFS. The secondary effectiveness measures are the subject's assessment of overall lip fullness using the 5-point LFS, the volume of the overall lips measured from 3D images, and the lip surface area change measured from 3D images. [REDACTED]

Safety: Safety will be evaluated by subject assessment of procedural pain; by the severity and duration of injection site responses (ISRs), which will be reported in the subject safety diary for 30 days after each treatment; and by any reported adverse events at all follow-up visits throughout the study.

STATISTICAL METHODS:
Sample Size Calculation: A sample size of 111 randomized subjects treated with VOLBELLA with Lidocaine and 37 randomized untreated control subjects will provide > 96% power to detect the superiority of

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VOLBELLA with Lidocaine over no treatment for responder rate at month 3. Responder rate is the percentage of subjects who show at least a 1-point improvement compared with baseline on the 5-point LFS based on the Evaluating Investigator's assessment of overall lip fullness. A 2-sided Fisher's Exact test with 5% significance level will be used to calculate the power, assuming responder rates of 79.0% for the VOLBELLA with Lidocaine group and up to 44.1% for the no-treatment control group at month 3. The assumed responder rates are based on the results of a US study of JUVÉDERM® Ultra XC for the lips (Study JULIDO-002). The power calculation was performed using an Inequality Test for 2 Independent Proportion [Difference] in PASS software (Version 2008). The planned sample size is considered to be adequate for evaluation of long-term (ie, 12-month) safety.

Approximately 15% of subjects may drop out after receiving treatment or not provide data at month 3. To accommodate this, 176 subjects will be randomized, with at least 132 subjects assigned to the VOLBELLA with Lidocaine group and approximately 44 subjects assigned to the no-treatment control group.

Effectiveness: The primary effectiveness variable is lip response based on the Evaluating Investigator's assessment of overall lip fullness using the 5-point LFS. A subject showing ≥ 1 -point improvement (increase in fullness) compared with baseline will be considered to be a lip responder. The primary evaluation timepoint is month 3 after last treatment for subjects in the VOLBELLA with Lidocaine group and month 3 after randomization for subjects in the no-treatment control group.

The primary effectiveness analysis will test for superiority of VOLBELLA with Lidocaine over no treatment in the difference in overall lip fullness responder rate. Two-sided Fisher's exact test with 5% significance level will be used to compare treatment effects between VOLBELLA with Lidocaine group and the no-treatment control group. If the 2-sided p-value is less than 0.05 and the responder rate is greater for the VOLBELLA with Lidocaine group than for the no-treatment control group, then VOLBELLA with Lidocaine will be considered superior to no-treatment.

Secondary effectiveness analyses will include 1) responder rate and the corresponding 2-sided 95% exact CI based on the subject's assessment of overall lip fullness at month 3 for the treatment group, 2) change from baseline to month 3 in volume of the overall lips, and 3) the percentage change from baseline to month 3 in lip surface area using t-test or Wilcoxon rank-sum test, as appropriate.

All effectiveness analyses will be performed on the modified intent-to-treat (mITT) population, defined as all subjects who are randomized to study treatment (treatment group), receive at least 1 study device treatment, and have baseline and at least 1 posttreatment assessment of the primary variable, and subjects who are randomized to the no-treatment control group and have baseline and at least 1 follow-up assessment of the primary variable. Additional sensitivity analyses for the primary effectiveness variable will be performed on the per-protocol (PP) population, defined as all mITT subjects who do not have any significant protocol deviations that affect the primary effectiveness endpoint. All analyses will be performed without data imputation.

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

Adverse events will be summarized by System Organ Class and Preferred Term and will be tabulated by duration, severity, causality, action taken, relationship to treatment, and outcome. The summary will include incidence rate as well as total number of events.

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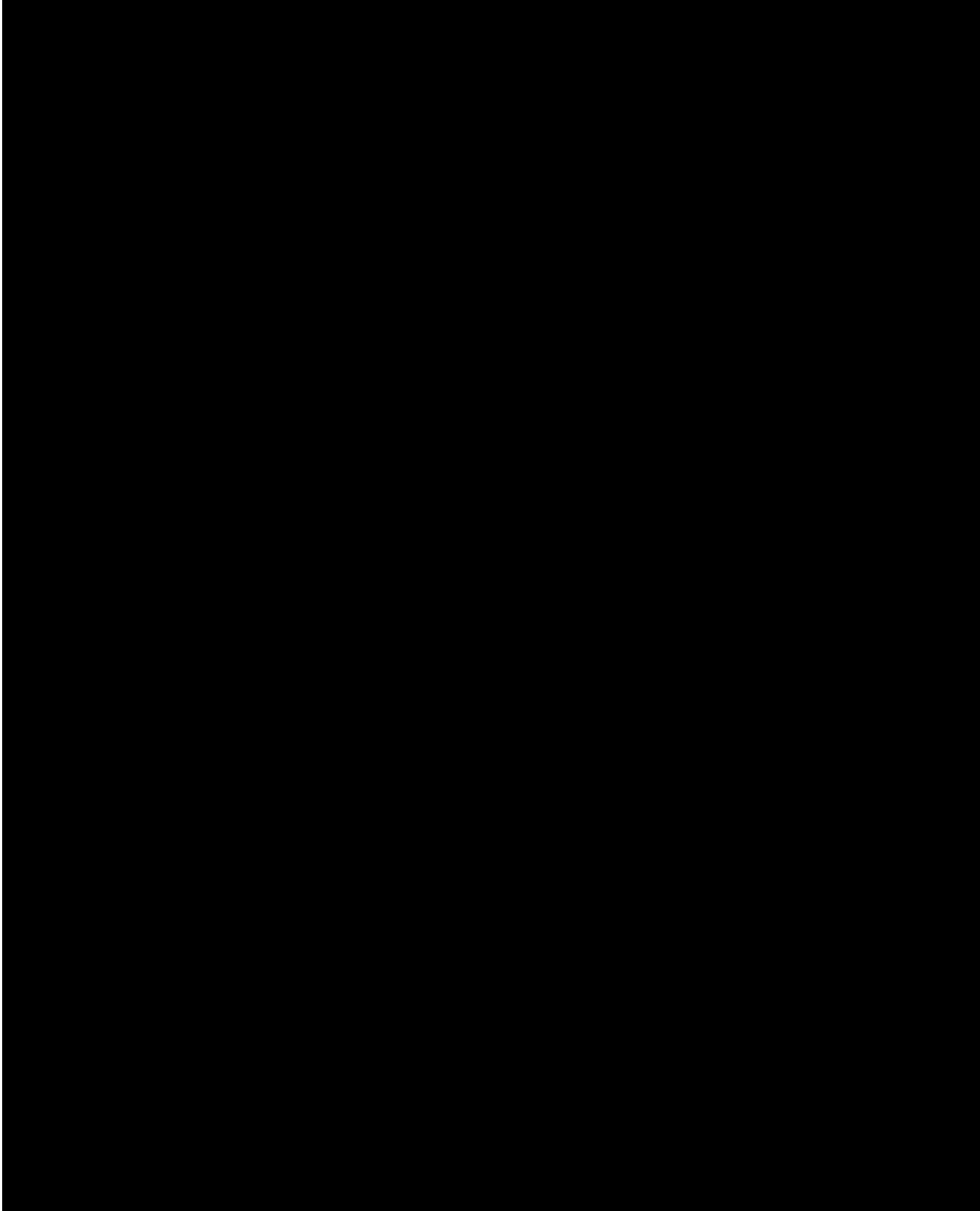
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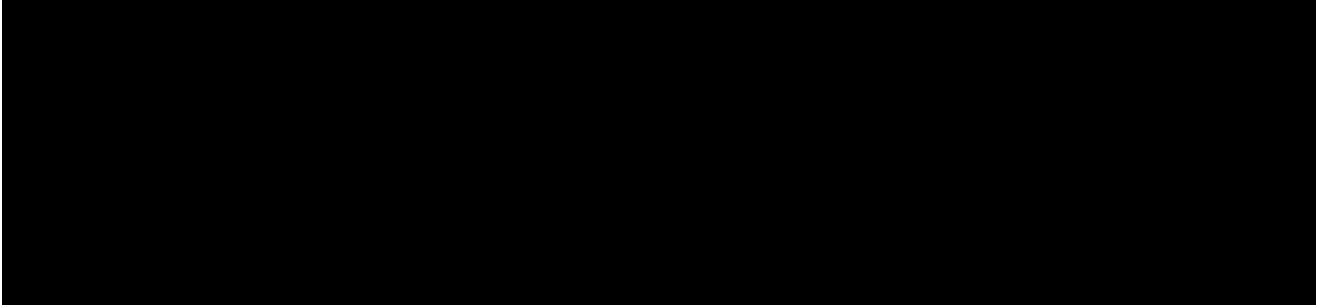
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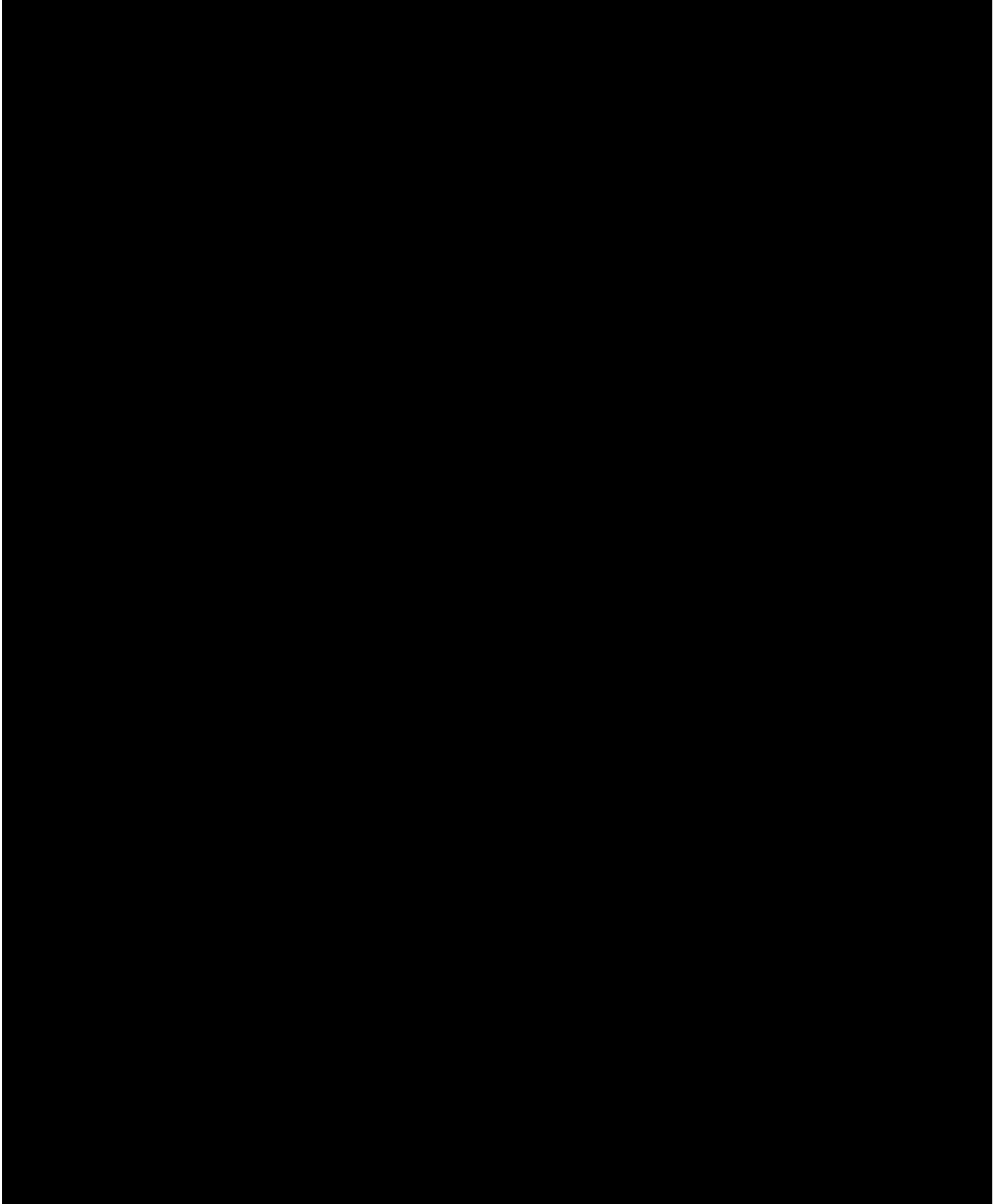




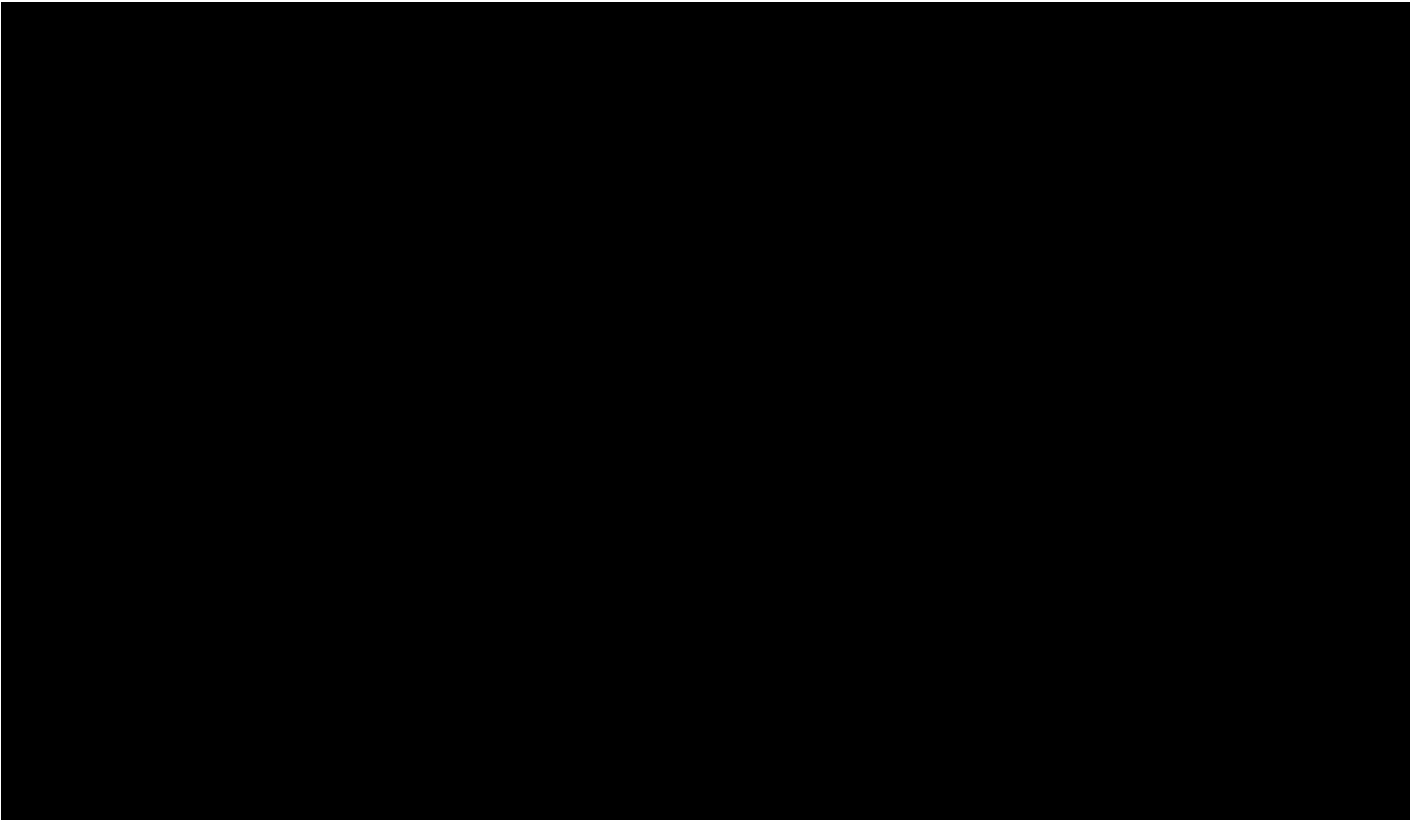
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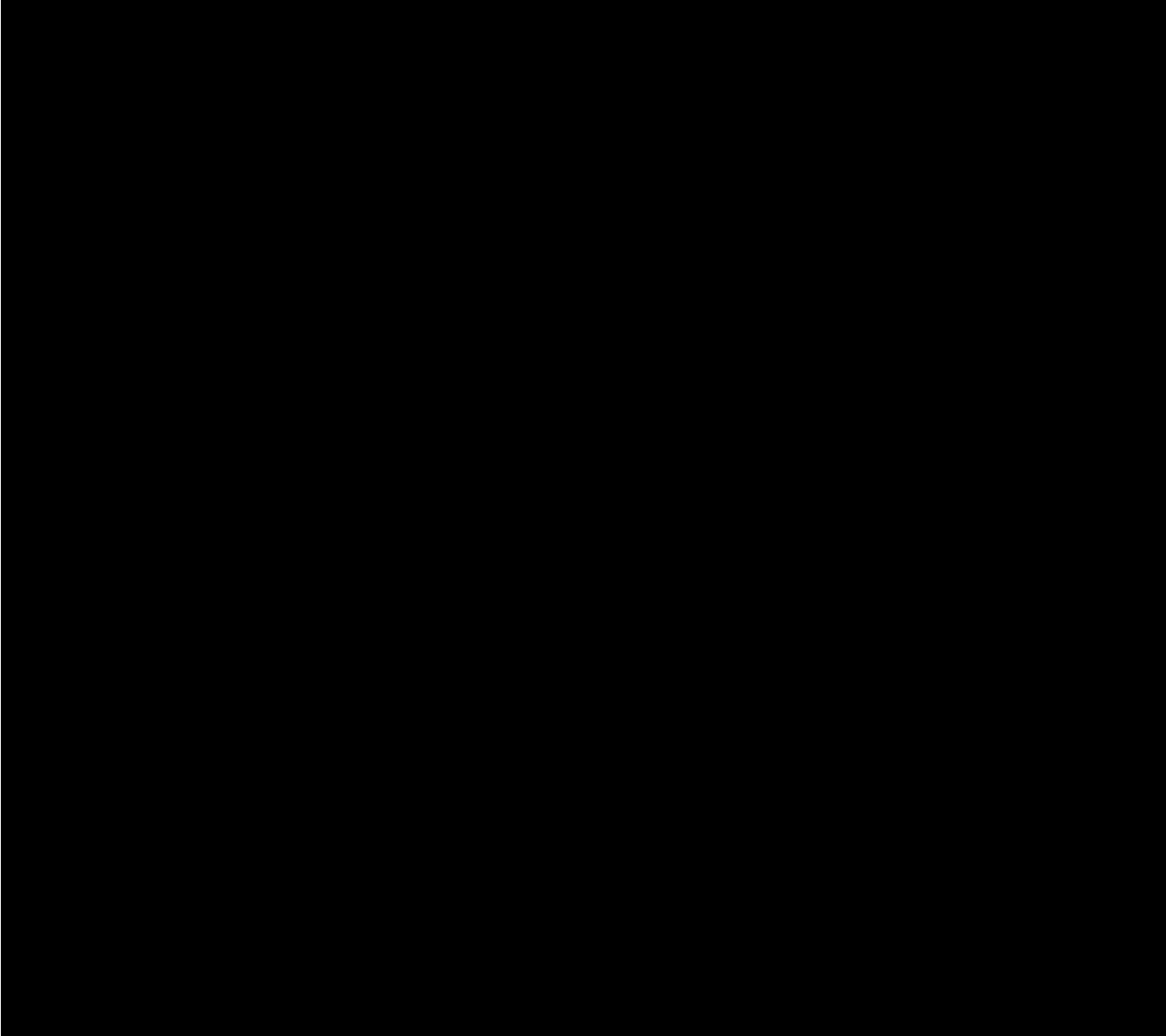
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1. Abbreviations and Terms

Term/Abbreviation	Definition
3D	3-dimensional
BDDE	1,4-butanediol diglycidyl ether
CFDA	Chinese Food and Drug Administration
CI	confidence interval
eCRF	electronic case report form
EKG	electrocardiogram
FDA	Food and Drug Administration
████	██
HA	hyaluronic acid
ICF	informed consent form
ICH	International Conference on Harmonisation
IDFU	investigational directions for use
IEC	Independent Ethics Committee
ISO	International Organization for Standardization
ITT	intent-to-treat
ISR	injection site response
IVRS	interactive voice response system
IWRS	interactive web response system
LFS	Lip Fullness Scale
mITT	modified intent-to-treat
PP	per-protocol
QS	quantity sufficient to make
US	United States

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2. Background, Risk and Benefit, and Clinical Rationale

2.1 Background

Lip augmentation to restore fullness and definition loss due to hypoplasia or aging has become a common use for hyaluronic acid (HA) dermal fillers ([Eccleston and Murphy, 2012](#); [Philipp-Dormston et al, 2014](#)). Treatment with temporary HA fillers can provide volume to the lips and perioral area, restoring fullness and the natural contour of the region to which it is applied.

JUVÉDERM® VOLBELLA® with Lidocaine (hereafter referred to as VOLBELLA with Lidocaine), CE-marked in 2011 and included in the JUVÉDERM range of products, is a malleable gel that meets the physical constraints that would be experienced with injection and volume expansion of the lips. VOLBELLA with Lidocaine is formulated using a combination of high and low molecular weight HA, which reduces the concentration of crosslinking reagent needed while increasing overall crosslinking efficiency. The final formulation includes a small quantity of noncross-linked HA to decrease extrusion force during injection, and lidocaine (0.3% w/w) to increase patient comfort. In a postmarketing study, JUVÉDERM VOLBELLA without Lidocaine (received European marking of conformity [CE mark] in 2007) was demonstrated to be safe and effective in providing smooth and natural improvement in lip fullness ([Eccleston and Murphy, 2012](#)). VOLBELLA with Lidocaine represents an improvement with the addition of 0.3% (w/w) lidocaine hydrochloride to reduce procedural pain.

In Europe and other countries, numerous fillers have been used in the lips and perioral area. In the US, Restylane® and Restylane-L® (with lidocaine) are the only dermal fillers currently approved for lip augmentation. In China, no dermal fillers are approved for lip augmentation. As described below, investigations assessing the safety and effectiveness of HA-based dermal fillers for volume restoration of the lips have demonstrated treatment success and high patient satisfaction.

- In a multicenter European postmarket study of the safety and effectiveness of JUVÉDERM VOLBELLA without Lidocaine, 60 subjects desiring lip enhancement were treated. The filler was injected into the upper and lower lips, perioral lines, and oral commissures. Three months after treatment, 93.2% of subjects displayed ≥ 1 point improvement on the 4-point Lip Fullness Scale (LFS). After treatment, 84.0% of subjects displayed ≥ 1 -point improvement on the 4-point Perioral Lines Severity Scale

and 70.0% displayed ≥ 1 -point improvement on the 4-point Oral Commissures Severity Scale. At the end of the study (12 months), 94.1% of subjects were satisfied with the overall effects of the treatment ([Eccleston and Murphy, 2012](#)).

- In the pivotal study evaluating the safety and effectiveness of Restylane for soft tissue augmentation of the lips, 92.6% of 134 treated subjects displayed ≥ 1 -point improvement 8 weeks after treatment on the 5-point Medicis LFS compared with baseline assessment, and 90.1% of subjects displayed ≥ 1 -point improvement 12 weeks after treatment (Restylane Directions for Use, 2011).
- In a multicenter, feasibility study of lip enhancement conducted in the United States (US), 50 subjects were injected with JUVÉDERM Ultra in the upper and lower lips, perioral lines, and oral commissures. At 12 weeks after treatment, 71% of subjects improved by ≥ 1 point on the 4-point LFS, 51% of subjects improved by ≥ 1 point on the Perioral Lines Severity Scale, and 64% of subjects improved by ≥ 1 point on the Oral Commissures Severity Scale (all of which were evaluated by a blinded Evaluating Investigator). Overall subject satisfaction at 12 weeks was 82% ([Fagien et al, 2013](#)).
- In a large, non-randomized study, 1,446 subjects were treated with Restylane for lip augmentation and visible facial rhytides (2,242 treated areas). Subject satisfaction was 77.8% at 3 months, declining to 36.4% at 9 months. The filling effect lasted longer in areas that were not subjected to animation (eg, glabellar lines), which was reflected in subject satisfaction trends ([Bosniak et al, 2004](#)).
- Sixty-six subjects were treated with Restylane for lip augmentation in specific lip zones to allow for targeted volume enhancement in which the gel could easily be injected with a 30 G needle. Mean satisfaction on a scale of 0 to 5 (5 being most satisfied) was 4.5. Mean persistence until lips returned to preoperative appearance was 4.9 months. No adverse events were observed ([Jacono, 2008](#)).
- In an open-label pilot study assessing the effectiveness of Restylane for restoring lip fullness, lip volume changes were measured in 21 subjects at several timepoints through 12 weeks after treatment. At 12 weeks after treatment, 79% of subjects had ≥ 1 -point improvement on a 5-point lip fullness scale, as rated by an independent evaluator ([Solish and Swift, 2011](#)).

- A postmarketing surveillance study assessed treatment comfort and aesthetic effect in 57 patients treated with JUVÉDERM Ultra Smile. The most common site for injection was the vermilion border, and 95% of injectors found the gel easy to inject. Furthermore, 99% of injectors rated an improved aesthetic compared to baseline. Patient satisfaction with the product was 96% (Lanigan, 2011).

As with any dermal filler injection, pain during administration is a possible side effect and may compromise the physician's ability to inject precisely (Segall and Ellis, 2007). Physicians typically use pain-relieving agents concomitant with injection, such as a nerve block, topical anesthetic, or a local anesthetic. The inclusion of lidocaine in HA dermal fillers is intended to reduce the patient's pain during the procedure and reduce or eliminate the need for additional pain-relieving agents. Ninety-three percent of subjects, randomized to treatment with JUVÉDERM Ultra or Ultra Plus in 1 nasolabial fold and JUVÉDERM Ultra or Ultra Plus including 0.3% lidocaine in the other nasolabial fold, rated the lidocaine formulations less or slightly less painful than the JUVÉDERM Ultra or Ultra Plus (Weinkle et al, 2009). As reviewed by Smith and Cockerham (2011), additional studies have demonstrated significantly less pain associated with dermal fillers containing lidocaine, allowing for a quick treatment, reduced recovery time, and high patient satisfaction. Furthermore, lidocaine in HA fillers has been shown not to affect the rheology, duration of effect, or frequency of adverse events (Andre, 2008; Gold, 2009; Raspaldo et al, 2010; Rivkin, 2009).

2.2 Risk and Benefit

A risk analysis linked to the manufacturing, biocompatibility, and use of VOLBELLA with Lidocaine was conducted according to International Organization for Standardization (ISO) 14971:2007 and is detailed in the risk management file. An overview of these risks and additional risks related to the injection procedure is contained within the Investigational Plan Risk Analysis. Each device contains 15 mg HA of nonanimal origin cross-linked with a minimal amount of 1,4-butanediol diglycidyl ether (BDDE), 3 mg lidocaine hydrochloride, and 1 mL QS phosphate buffer pH 7.2 supplied in a syringe composed of cyclic olefin copolymer. Assessment of overall risks that could have a high severity of consequences revealed that preventative actions guaranteed residual risks graded "very low," "low," or "moderate," with no risk graded as "unacceptable."

However, as with any skin or lip injection, risks exist with the injection procedure itself, the anesthetic agent, and the type of injection (in this case an HA facial injection). Risks related to the injection procedure and/or the device include redness, pain, tenderness, swelling,

itching, firmness, lumps and bumps, and delayed adverse reactions. These risks are common to all dermal filler injection procedures. 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 use of a small-gauge needle to deliver the experimental device used in this clinical study is intended to minimize tissue trauma. The inclusion of 0.3% lidocaine in VOLBELLA with Lidocaine is meant to reduce pain during the injection and during the hours following injection as well as to provide consistency in anesthetic dosing. It is advisable to take the potential risks into account. Furthermore, the literature analysis and medical device reporting from US Food and Drug Administration (FDA) approved dermal filler products reveal that pre-existing pathological conditions of patients along with the contraindications and precautions for use as written in the investigational directions for use (IDFU) should be carefully reviewed.

The benefit of using HA dermal fillers for lip enhancement has been demonstrated by the published literature showing the safety and effectiveness of treatment and by studies of JUVÉDERM products for equivalent indications. Characteristics of VOLBELLA with Lidocaine potentially increase the benefit of use of HA dermal fillers for lip enhancement.

2.3 Clinical Rationale

Although various materials have been investigated as potential candidate soft-tissue fillers, none have produced as consistent and optimal lip enhancement as HA dermal fillers. HA can enhance lip volume ([Sarnoff et al, 2012](#)). The safety and effectiveness of VOLBELLA (without lidocaine) for lip enhancement has been demonstrated in European subjects ([Eccleston and Murphy, 2012](#)). However, European and Chinese ideals of beautiful lips differ; consequently, the use of dermal fillers and their safety and effectiveness for lip enhancement may differ.

Risks associated with VOLBELLA with Lidocaine have been mitigated by the product's formulation, and potential complications that may arise have been described in the literature and IDFU. Therefore, VOLBELLA with Lidocaine is expected to be safe and effective. Study VOLBELLA-005 is intended to provide safety and effectiveness data on VOLBELLA with Lidocaine for lip enhancement to support a Chinese Food and Drug Administration (CFDA) pre-market application.

3. Study Objectives and Clinical Hypotheses

3.1 Study Objectives

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

3.2 Clinical Hypotheses

The percentage of subjects with a clinically significant change in lip fullness from baseline to month 3 will be significantly greater in subjects treated with VOLBELLA 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.

4.2 Duration

The study will span a total of approximately 22 months including an estimated 8 months for recruitment, up to 30 days between screening and randomization, up to 1 month for treatment, and up to 12 months for follow-up. Participation for subjects randomized to the treatment group will encompass up to 1 month for treatment and 12 months of follow-up. Participation for subjects randomized to the no-treatment control group will encompass a 3-month no-treatment period, up to 1 month for optional treatment, and 9 months of follow-up.

4.3 Treatment Groups and Treatment Regimen

4.3.1 Study Treatment

VOLBELLA with Lidocaine injectable gel

4.3.2 Control Treatments

A no-treatment control group is included.

4.3.3 Methods for Blinding

The Evaluating Investigator will remain blinded to treatment assignments throughout the duration of the study. The Evaluating Investigator will not be present during the injection procedures.

The Treating Investigator will not discuss the randomized treatment assignments with or in the presence of the Evaluating Investigator.

The Treating Investigators, study coordinators, and subjects will not be blinded to treatment, but they will secure the randomization and other records (eg, records of study treatments and prior study assessments) from potential discovery by the Evaluating Investigator.

The device accountability log will include the kit numbers. The Evaluating Investigator will not have access to the device accountability log.

4.3.4 Retreatment Criteria

One month (30 days) after the initial treatment, the subject and Treating Investigator will discuss the results of the initial treatment and determine whether optimal correction has been achieved. If optimal correction has not been achieved, the Treating Investigator may perform a touch-up treatment. Moreover, if the Evaluating Investigator has determined that the subject's LFS score has not improved by at least 1 point, the subject should receive a touch-up injection.

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.

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the subject's electronic case report form (eCRF) at each visit along with the reason the medication is taken.

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

4.4.2 Prohibited Medications/Treatments

Concurrent enrollment in another clinical investigation for a medicinal product or device is prohibited. Subjects must not be on an ongoing regimen of anti-coagulant medications (eg, warfarin). Subjects must not be on an ongoing regimen of medications or other substances known to increase coagulation time (eg, aspirin; ibuprofen; high doses of Vitamin C or Vitamin E; herbal supplements with garlic, ginkgo biloba, or ginseng) within 10 days prior to and 3 days after study device injection.

Subjects must not use lip plumping product or begin any new regimen of over-the-counter or prescription, oral or topical, antiwrinkle products for the lips or around the mouth. Subjects must not undergo facial tissue augmentation with dermal fillers or fat injections, semi-permanent fillers or permanent facial implants, botulinum toxin injections, mesotherapy, or cosmetic facial procedures (eg, face-lift, laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) below the inferior orbital rim at any time during the study.

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 should not be performed during the 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.

4.5 Treatment Allocation Ratio and Stratification

Subjects will be randomized at a 3:1 ratio either to have treatment with VOLBELLA with Lidocaine at the outset of the study (treatment group) or to have treatment delayed by 3 months (no-treatment control group). Randomization will be stratified by baseline LFS score (ie, LFS score rated as Minimal, Mild, or Moderate at the randomization visit by the Evaluating Investigator).

5. Study Population

5.1 Number of Subjects

An estimated 176 subjects will be randomized in a 3:1 ratio resulting in 132 subjects assigned to the VOLBELLA with Lidocaine group and 44 subjects assigned to the no-treatment control group. Approximately 148 subjects including 111 treated subjects and 37 untreated control subjects will complete the 3-month visit (primary endpoint) with an anticipated dropout rate of 15% by month 3. An estimated 133 subjects will complete the 12-month visit (end of study) based on an anticipated dropout rate of 10% after month 3.

5.2 Study Population Characteristics

Subjects will be recruited from a population of healthy Chinese adults who desire lip enhancement.

5.3 Inclusion Criteria

The following are requirements for entry into the study:

1. male or female, 18 years of age or older
2. has an overall baseline score of Minimal, Mild, or Moderate on the 5-point LFS, as assessed by the Evaluating Investigator, and desires to achieve at least a 1-point improvement in overall LFS score after treatment

[REDACTED]

4. has the ability to follow study instructions and is likely to complete all required visits

[REDACTED]

5.4 Exclusion Criteria

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

[REDACTED]

[REDACTED]

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10. is on an ongoing regimen of anti-coagulation therapy (eg, warfarin)

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- 14. has current cutaneous inflammatory or infectious processes (eg, acne or herpes), an abscess, an unhealed wound, or a cancerous or precancerous lesion in the mouth area (study treatment may be delayed so that subjects with a history of recurrent oral herpes can take prophylactic antiviral/herpes medication for 2 days)

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6. Procedures

6.1 Washout or Run-In Intervals

6.1.1 Washout Intervals

Washout Period	Medication or Procedure
10 days before treatment	<ul style="list-style-type: none">• medications known to increase coagulation time (eg, aspirin or ibuprofen)• other pharmaceutical, vitamin, or herbal preparations with clinically significant anticoagulation effects (eg, high doses of Vitamin C or Vitamin E, herbal supplements with garlic, ginkgo biloba, or ginseng) <p>NOTE: This 10-day washout period for anticoagulants must continue for 3 days after treatment is administered.</p>
10 days before enrollment	<ul style="list-style-type: none">• lip plumping products
30 days before enrollment	<ul style="list-style-type: none">• any investigational product

6.1.2 Run-in Intervals

Run-In Period	Medication or Procedure
2 days before treatment	<ul style="list-style-type: none">• prophylactic herpes treatment for subjects with a history of recurrent oral herpes lesions
30 days before enrollment	<ul style="list-style-type: none">• over-the-counter or prescription, oral or topical, anti-wrinkle products for the lips or around the mouth for subjects who will use such products during the study

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6.3 Instructions for the Subjects

At the screening visit, the Treating Investigator (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; he/she 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 Treating Investigator (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, and male subjects will not be allowed to have facial hair in the perioral area to avoid interference with the digital photographs.

For 10 days before and 3 days after study treatment administration, subjects should avoid taking anti-coagulation, antiplatelet, or thrombolytic medications; nonsteroidal anti-inflammatory drugs; supplements of Vitamin C or E, garlic, ginkgo 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.

Subjects will also be instructed to contact the Treating Investigator 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 adverse events 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.

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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 an adverse event is ongoing at the time of withdrawal, the Treating Investigator will attempt to follow the subject until the adverse event has been resolved or follow-up is no longer possible. The Treating Investigator 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 Treating Investigator (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 Treating Investigator (or designee) will record on the eCRF and will report to Allergan and the Independent Ethics Committee (IEC) 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.

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 Evaluating Investigator's assessment of overall lip fullness using the LFS described in Table 4.

Table 4 5-Point Lip Fullness Scale

Score	Grade	Description
4	Very Marked	Very significant red lip show, lower lip pout, and upper lip pout
3	Marked	Significant red lip show and lower lip pout
2	Moderate	Moderate red lip show with slight lower lip pout
1	Mild	Some red lip show; no lower lip pout
0	Minimal	Flat or nearly flat contour, minimal red lip show

7.1.2 Secondary Effectiveness Measures

The secondary effectiveness measures are the subject’s assessment of overall lip fullness using the 5-point LFS, the volume of the overall lips measured from 3D images, and the lip surface area measured from 3D images.

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[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)
- severity and duration of ISRs, which will be obtained by a subject safety diary

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- adverse events reported to and recorded by the investigators

Vital sign measurements, including blood pressure (systolic and diastolic, while subject is seated), temperature, pulse, and respiratory rate, will be performed at screening, treatment visit, Month 1, Month 3 and Month 6 visits. Urine pregnancy tests for women of childbearing potential (sexually active and not sterile, surgically sterilized, or postmenopausal for at least 1 year) will be performed at screening, treatment visit, and the month 6 posttreatment follow-up visit. Routine hematology and blood chemistry testing and urinalysis will be performed at screening and at the months 1 and 6 posttreatment follow-up visit.

7.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics to be collected include sex, age, height, weight, Fitzpatrick skin phototype and sun exposure, smoking history, medical/surgical/cosmetic/dental procedure history, and prior medications.

7.4 Treatment Characteristics

Treatment characteristics will be evaluated by collecting information on anesthesia usage, treatment area, injection ease, and volume injected.

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 Treating or Evaluating Investigator 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.

Subjects will either complete the ISR diaries electronically, or they will complete them on paper, and responses will be entered into the clinical database. Sites will save photographs onto supplied electronic media and send the storage device to [REDACTED]. Alternatively, files containing the facial digital photographs may be directly uploaded to [REDACTED].

8. Statistical Procedures

One database lock is planned after all subjects exit the study. A statistical analysis plan will be prepared to provide specifications for all analyses. The plan will be finalized and approved prior to clinical database lock.

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 (treatment group) and receive at least 1 study device treatment and have baseline and at least 1 posttreatment assessment of the primary variable, and subjects who are randomized to the no-treatment control group and have baseline and at least 1 follow-up assessment of the primary variable
- 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 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.

8.2 Collection/Derivation of Primary and Secondary Effectiveness Assessments

8.2.1 Primary Effectiveness Variable

The primary effectiveness variable is lip response based on the Evaluating Investigator's assessment of overall lip fullness using the 5-point LFS. A subject showing ≥ 1 -point improvement (increase in fullness) in LFS score compared with baseline will be considered to be a lip responder. The primary evaluation timepoint is month 3 after last treatment for subjects in the VOLBELLA with Lidocaine group and month 3 after randomization for subjects in the no-treatment control group.

8.2.2 Secondary Effectiveness Variables

The 3 secondary effectiveness variables are:

- subject's lip response based on the subject's assessments of overall lip fullness using the 5-point LFS
 - A subject showing ≥ 1 -point improvement (increase in fullness) in 5-point LFS score compared with baseline will be considered to be a lip responder. The evaluation timepoint is month 3 after last treatment for subjects in the VOLBELLA with Lidocaine group.
- percentage change from baseline to month 3 in overall lip volume
 - The evaluation timepoint is month 3 after last treatment for subjects in the VOLBELLA with Lidocaine group and month 3 after randomization for subjects in the no-treatment control group.
- change from baseline to month 3 in lip surface area
 - The percentage change from baseline in lip surface area will be calculated as the difference (ie, month 3 lip surface area minus the baseline lip surface area) divided by baseline value. Month 3 refers to 3 months after last treatment for subjects in the VOLBELLA with Lidocaine group and 3 months after randomization for subjects in the no-treatment control group.

8.3 Hypothesis and Methods of Analysis

In general, descriptive statistics will be presented. Categorical variables will be summarized with frequency and percentage. Continuous variables will be summarized by number of subjects, mean, median, standard deviation, minimum, and maximum. Where appropriate, 2-sided 95% confidence intervals (CIs) for mean or proportion will be provided as part of the descriptive summary.

Unless otherwise noted, during posttreatment follow-up visits (for both the VOLBELLA with Lidocaine group and the no-treatment control group), baseline refers to the last evaluation prior to initial treatment; during the no-treatment period (for the no-treatment control group), baseline refers to the last evaluation prior to the month 1 visit.

No imputation for missing data will be performed. However, sensitivity analyses for the primary endpoint will be performed using applicable missing imputations to assess the potential effect of missing data.

8.3.1 Primary Effectiveness Analyses

The primary effectiveness analysis will test for superiority of VOLBELLA with Lidocaine over no treatment in the difference in overall lip fullness responder rate based on the Evaluating Investigator's assessment at month 3. Month 3 refers to 3 months after the last treatment for subjects in the VOLBELLA with Lidocaine group and 3 months after randomization for subjects in the no-treatment control group.

The null hypothesis is that the responder rate for VOLBELLA with Lidocaine group is equal to the responder rate for the no-treatment control group. The alternative hypothesis is that the responder rates are not equal for the VOLBELLA with Lidocaine and the no-treatment control groups. These hypotheses are stated as:

$$H_0: P_v - P_c = 0$$

$$H_a: P_v - P_c > 0 \text{ or } P_v - P_c < 0$$

where P_v and P_c denote the responder rates for the VOLBELLA with Lidocaine group at month 3 after last treatment and no-treatment control group at month 3 after randomization, respectively. Two-sided Fisher's exact test with 5% significance level will be used to compare treatment effects between VOLBELLA with Lidocaine and the no-treatment control group. If the 2-sided p-value is less than 0.05 and the responder rate is greater for VOLBELLA with Lidocaine than for the no-treatment control group, then VOLBELLA with Lidocaine will be considered superior to the no-treatment control group. The primary effectiveness analysis will be performed on the mITT population.

8.3.2 Secondary Effectiveness Analyses

The following analyses will be performed for each of the secondary effectiveness endpoints:

- For overall lip fullness based on the subject's assessments using the 5-point LFS, responder rate and 95% exact CI will be presented only for the treatment group at month 3.

- The overall lip volume change from baseline to month 3 will be summarized using descriptive statistics. Treatment effect will be analyzed using t-test or Wilcoxon rank-sum test as appropriate.
- The lip surface area percentage change from baseline to month 3 will be summarized descriptively. Treatment effect for this endpoint will be analyzed using t-test or Wilcoxon rank-sum test, as appropriate.

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8.3.4 Safety Analyses

Procedural pain will be summarized using descriptive statistics. ISRs reported by subjects will be summarized by symptom, maximum reported severity, and maximum reported duration for initial and touch-up treatments, separately. Summaries will include the incidence rate for each ISR.

Adverse events will be summarized by System Organ Class and Preferred Term and will be tabulated by duration, severity, causality, action taken, relationship to treatment, and outcome. The summary will include incidence rate as well as total number of events.

Adverse events that may occur before treatment (ie, the initial treatment for subjects randomized to the treatment group and the optional treatment at month 3 for subjects randomized to the no-treatment control group) will be listed but not summarized.

8.4 Subgroup Analyses

The primary effectiveness endpoint will be summarized by baseline lip LFS score, volume injected, and investigational site. Details will be provided in the statistical analysis plan.

8.5 Sample Size Calculation

A sample size of 111 randomized subjects treated with VOLBELLA with Lidocaine and 37 randomized untreated control subjects will provide > 96% power to detect the superiority of VOLBELLA with Lidocaine over no treatment for responder rate at month 3. Responder rate is the percentage of subjects who show at least a 1-point improvement compared with baseline on the 5-point LFS based on the Evaluating Investigator's assessment of overall lip fullness. A 2-sided Fisher's Exact test with 5% significance level will be used to calculate the power, assuming responder rates of 79.0% for the VOLBELLA with Lidocaine group and up to 44.1% for the no-treatment control group at month 3 (based on interim data from Study [JULIDO-002](#)). The power calculation was performed using an Inequality Test for 2 Independent Proportion [Difference] procedure in PASS software (Version 2008). The planned sample size is considered to be adequate for evaluation of long-term (ie, 12-month) safety.

Allowing for attrition of 15% up to month 3 due to early discontinuations, missed visits, or out-of-analysis-window visits, 176 subjects will be randomized, with at least 132 subjects assigned to the VOLBELLA with Lidocaine group and approximately 44 subjects assigned to the no-treatment control group.

8.6 Interim Analyses

No interim analysis is planned.

9. Materials

9.1 Study Treatment

[REDACTED]



9.1.2 Instructions for Use and Administration

For investigational use in this clinical study, VOLBELLA with Lidocaine HA dermal filler will be injected into the lips mucosa and superficial or mid dermis using a 30 G x ½-inch needle and aseptic injection technique.

The Treating Investigator should inject the treatment slowly using gentle, even pressure on the syringe into the vermilion body, vermilion border (including the Cupid's bow), and philtral columns in accordance with the randomization scheme and the IDFU. The IDFU will be provided to the Treating Investigator.

Treating Investigators must be experienced in the use and administration of HA implants and be practicing in the field of aesthetic medicine, plastic/cosmetic/reconstructive surgery, or dermatology.

9.1.3 Treatment Regimen Adjustment

Up to 2 treatment sessions 30 days apart are allowed. The Treating Investigator will determine the appropriate volume of VOLBELLA with Lidocaine to inject at the initial and touch-up treatments based on his/her clinical experience and the randomization assignment, but the maximum volume is not to exceed 4.0 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, explant kits, and other supplies specific to this study (eg, 30 G 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, internet connection for eCRF completion and IWRS, and telephone connection for IVRS).

10. Study Administration Procedures

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

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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 informed consent, which will occur prior to any screening procedures. Screening procedures include:

- Evaluating Investigator assessment of the subject's overall lip fullness using the 5-point LFS
- evaluation of inclusion/exclusion criteria
- collection of demographic information
- collection of height; weight; and vital signs, including blood pressure (systolic and diastolic, while subject is seated), temperature, pulse, and respiratory rate
- evaluation of Fitzpatrick skin phototype and sun exposure
- collection of smoking history
- collection of medical/surgical history
- collection of cosmetic/dental procedures history
- conduct EKG test
- collection of blood for routine hematology and chemistry
- collection of urine from all enrolled subjects for urinalysis
- urine pregnancy test for women of childbearing potential (sexually active and not sterile, surgically sterilized, or postmenopausal for at least 1 year)
- collection of adverse events and concurrent medications and procedures

Subjects choosing not to participate in photos through 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 sign the ICF prior to any study-related procedures or change in treatment.

The Principal Investigator or his/her authorized designee conducts the informed consent discussion and will document in the subject's medical records the acquisition of informed

consent and the subject's agreement or refusal to notify his/her primary care physician about the study. The informed consent shall include all aspects of the study that are relevant to the subject's decision to participate throughout the study. The informed consent 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 informed consent. The Principal 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 Principal 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 30 days 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 VOLBELLA with Lidocaine treatment immediately or to delay treatment by 3 months until the end of the no-treatment control period. Subjects will be assigned to a treatment group based on a central randomization schedule. An automated IVRS/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 IVRS/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 dispense treatment according to the IVRS/IWRS instructions provided by the system.

10.2 Compliance with Protocol

The Principal Investigator is 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 is to be included in

the analysis. All protocol deviations will be reported to the IEC according to the IEC's reporting requirements.

10.3 Pregnancy

No VOLBELLA studies have been conducted in pregnant women. Therefore, females who are of childbearing potential must have a negative result on a pregnancy test prior to receiving injection of products. As stipulated in the exclusion criteria, all females of childbearing potential must be willing to use contraception and not become pregnant during the full course of the study to avoid potential risks to the pregnancy.

If a female becomes pregnant during the study, the Treating Investigator (or designee) will notify Allergan immediately by completing the Pregnancy Surveillance Form after the pregnancy is confirmed and faxing or e-mailing it to the appropriate number on the front page of this protocol. The Treating Investigator (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. Once the pregnancy has reached term, the second page of the Pregnancy Surveillance Form concerning outcome is to be completed. The Medical Safety Physician will contact the Treating Investigator (or designee) to obtain information about the pregnancy outcome. The subject will continue to be followed as part of the mITT population, but the pregnancy will be documented as a protocol deviation. The subject will not be evaluated as part of the PP population for timepoints after the pregnancy is confirmed.

Pregnancy by itself will not be considered an adverse event or serious adverse event. Hospitalization for a normal delivery or elective abortion of a normal fetus does not constitute a serious adverse event. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an adverse event or serious adverse event, 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 Principal Investigator, monitor, IEC, 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, IEC-imposed conditions, or protocol requirements
- investigator submission of knowingly false information to Allergan, a study monitor, the IEC, 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 IEC 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 adverse events will be monitored and reported on an adverse event eCRF, including seriousness, severity, action taken and relationship to study treatment. If adverse events occur, the first concern will be the safety of the study participants.

Although the risk of developing a serious complication is small, the Treating Investigator 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 IDFU.

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 IDFU for VOLBELLA with Lidocaine.

11.1 Definitions

11.1.1 Adverse Event

An adverse event 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 adverse events 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.

Adverse events will be monitored throughout the study beginning with signing of the ICF. At each postscreening visit, the Treating Investigator (or designee) will begin querying for adverse events by asking each subject a general, nondirected question such as “Have you had any changes to your condition since your last visit?” Previous adverse events and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable adverse events and clinically significant abnormal laboratory findings will be documented on the appropriate eCRF.

11.1.2 Serious Adverse Event

A serious adverse event is defined in accordance with ISO 14155 as an adverse event that:

1. led to death
2. led to serious deterioration in the health of the subject, that either resulted in:
 - a. a life-threatening illness or injury, or
 - b. a permanent impairment of a body structure or a body function, or
 - c. in-patient or prolonged hospitalization, or
 - d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

3. 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 a serious adverse event.

See Section 11.4 for procedures for reporting a serious adverse event/serious adverse device effect.

11.1.3 Adverse Device Effect

An adverse device effect 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 adverse device effect.

11.1.4 Serious Adverse Device Effect

A serious adverse device effect 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 serious adverse device effect.

11.1.5 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect 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 Principal Investigator is to consult the IDFU for anticipated risks or anticipated adverse events.

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 Treating Investigator (or designee) 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 serious adverse device effect. These shall be reported to the regulatory authorities and IECs as required by national regulations.

11.1.7 Severity

Severity is a clinical determination of the intensity of an adverse event. The severity assessment for a clinical adverse event 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 adverse event and the device or treatment procedure. An adverse event could be considered treatment-related when, in the judgment of the Treating Investigator, 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 Treating Investigator and cannot be delegated to other study staff.

11.2 Timelines for Reporting

The Treating Investigator (and designees) is to adhere to the following schedule in reporting different types of adverse events.

Adverse Event Type	Reporting to Allergan	Start of Collection	End of Collection
Adverse events, adverse device effects	Record on adverse event eCRF upon awareness for review by the clinical monitor	Signing of ICF	Last subject visit
Serious adverse events, serious adverse device effects	Record on Serious Adverse Event Form and fax or e-mail to Allergan within 24 hours of awareness	Signing of ICF	Last subject visit

ICF = informed consent form

11.3 Procedures for Reporting an Adverse Event or Adverse Device Effect

All adverse events or adverse device effects occurring during the study period (beginning with signing of the ICF) are to be recorded on the appropriate eCRF. Any adverse event that is ongoing at the exit visit must be followed up as appropriate.

11.4 Procedures for Reporting an Serious Adverse Events or Serious Adverse Device Effects

All serious adverse events and serious adverse device effects occurring during the study period (beginning with signing of the ICF) are to be immediately reported to an Allergan representative at the fax number/e-mail address listed on the cover page and recorded on the appropriate eCRFs. All subjects with an serious adverse event/serious adverse device effect must be followed up and the outcomes reported. The Treating Investigator (or designee) is to supply Allergan and the IEC with any additional requested information (eg, hospital discharge summary, autopsy reports, and terminal medical reports). Allergan shall evaluate all serious adverse device effects and determine and document in writing whether they meet the definition for “unexpected.” These shall be reported to all participating Treating Investigators, the regulatory authorities, and IECs as required by national regulations.

In the event of a serious adverse event/serious adverse device effect, the Treating Investigator (or designee) must:

1. Notify Allergan immediately by fax or by e-mail using the serious adverse event/serious adverse device effect reporting forms. For the serious adverse event/serious adverse device effect fax number and e-mail 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. Provide Allergan with a complete, written case history which includes a statement as to whether the event was or was not related to the use of the investigational device.
4. Promptly inform the governing IEC of the event, if it is device-related. For other serious adverse events, notify the governing IEC as required by the IEC, local regulations, and the governing health authorities.

11.5 Procedures for Unblinding Study Treatments

Evaluating Investigators may 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 informed consent is to be obtained from each subject prior to enrollment into the study according to ethical principles contained in the World Medical Association Declaration of Helsinki, International Conference on Harmonisation (ICH) guidelines, applicable state and local laws and regulations, and IEC requirements.

12.1.2 Compliance with Independent Ethics Committee Regulations

This study is to be conducted in accordance with applicable regulations of the IEC. The Principal Investigator must obtain approval from a properly constituted IEC prior to initiating

the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IEC correspondence with the Principal Investigator are to be provided to Allergan.

12.1.3 Compliance with Good Clinical Practice

This protocol is to be conducted in compliance with guidelines of good clinical practices, 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

No investigator is to implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IEC 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. Allergan may amend the protocol during the course of the study. The amended protocol shall be distributed to all Principal, Treating, and Evaluating Investigators and IECs upon approval by regulatory authorities.

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 or 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, photographic negatives or digital images, video recordings, radiographs, clinic charts, the Treating Investigator's subject study files, as well as the results of diagnostic tests such as X-rays, EKG data, laboratory tests, and magnetic resonance imaging. Other source records include the subject safety diaries, LFS scores and GAIS scores from the Evaluating Investigator and the subject, and philtral column definition scores from the Evaluating Investigator. The Serious Adverse Event Form and Pregnancy Surveillance Form are also considered source documents. The investigators' copies of the eCRFs serve as part of the investigators' record of a subject's study-related data.

The following information is to be entered into the subject's medical record:

- subject's name
- subject's contact information
- date that the subject entered the study and subject number
- study title and/or the protocol number and study Sponsor
- a statement that informed consent was obtained, including the date; and a statement that country and local subject privacy required documentation for this study has been obtained, including the date
- medical, surgical, dental, cosmetic, and smoking history
- subject's demographics, physical measurements, Fitzpatrick skin phototype, sun exposure estimate, and vital signs
- details of the injection procedure including anesthesia use, injection procedure, volume injected, treatment areas, kit numbers, needle gauge, procedure characteristics, and product characteristics
- dates of all subject visits and telephone calls
- all current medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications are to be recorded.)
- all concomitant procedures and therapies
- occurrence and status of any adverse events
- the date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation

- EKG data
- results of laboratory tests performed by the site (urine pregnancy tests) or central laboratory (blood chemistry, hematology, and urinalysis)

12.4.2 Case Report Form Completion

Each investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. An investigator who has signed the protocol signature page or his/her authorized designee is to personally sign the eCRFs (as indicated on the eCRF) to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on an eCRF shall be dated, initialed, and explained, if necessary, and shall not obscure the original entry (ie, an audit trail shall be maintained); this applies to both written and electronic changes and corrections.

12.4.3 Investigator Reports

In accordance with ICH E6 4.10 and 4.13 and IEC requirements, the Principal Investigator is to submit written summaries of study status to the IEC annually (or more frequently if requested by the IEC) and promptly provide written reports to Allergan, the IEC, and, where required by applicable regulatory requirements, the institution regarding any changes significantly affecting the conduct of the study and/or increasing the risk to subjects. Upon completion of the study and where required by the applicable regulatory requirements, the Principal Investigator is to inform the institution of the completion of the study. The investigator/institution is to provide Allergan with all required reports, the IEC with a summary of the study outcome, and the regulatory authorities with any reports they require of the investigator/institution.

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.

Allergan-specific essential documents are to be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents are to be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by Allergan.

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.

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

12.5.1 Labeling/Packaging

VOLBELLA with Lidocaine will be provided sterile in syringes composed of cyclic olefin copolymer. An investigational caution label, such as the following, will appear on the individual syringe package and the outer box:

FOR CLINICAL TRIAL USE ONLY

PROTOCOL VOLBELLA-005

Each kit of VOLBELLA with Lidocaine contains 5 blisters, each containing 1 syringe prefilled to 1.0 mL and 2 single-use sterile needles, 30 G x ½-inch, specifically intended for injecting VOLBELLA with Lidocaine.

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.

VOLBELLA with Lidocaine must be stored at [REDACTED] OR under refrigeration with a continuous temperature monitoring device (provided by Allergan). The temperature monitoring device has been pre-programmed by Allergan with temperature storage-range limits required to ensure study product stability during the study. Use of the 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 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 Treating Investigator (or designee) must keep an accurate accounting of the number of study devices received from Allergan, dispensed to subjects, and returned to Allergan 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, and date of implantation. The study product must be dispensed to study subjects by an appropriately qualified person and is to be used in accordance with the protocol under the direct supervision of a Treating Investigator.

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 VOLBELLA 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 Treating Investigator 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, audit, and retrieve copies of study-related documents. It is the responsibility of the Principal Investigator to be present or available for consultation and to assure that the monitor has access to all study-related records during scheduled monitoring visits.

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

Allergan representatives will meet with the Treating Investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

12.7 Testing of Biological Specimens

At screening and at months 1 and 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 months 1 and 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 month 6 posttreatment, a trained research staff member at each investigational site will perform pregnancy testing on urine samples from women of child-bearing 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. All samples will be returned to Allergan or Allergan designee for 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 signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

13. References

13.1 Study Report References

Data from the following study are on file at Allergan.

Study Number	Study Title
JULIDO-002	A multicenter, single-blind, randomized, controlled study of the safety and effectiveness of JUVÉDERM® Ultra XC Injectable Gel for lip augmentation

13.2 Literature References

Andre P. New trends in face rejuvenation by hyaluronic acid injections. *J Cosmet Dermatol.* 2008; 7:251-258.

Bosniak S, Cantisano-Zilkha M, Glavas IP. Nonanimal stabilized hyaluronic acid for lip augmentation and facial rhytid ablation. *Arch Facial Plast Surg.* 2004; 6:379-383.

Eccleston D, Murphy DK. Juvéderm® Volbella™ in the perioral area: a 12-month prospective, multicenter, open-label study. *Clin Cosmet Investig Dermatol.* 2012; 5:167-172.

Fagien S, Maas C, Murphy DK, Thomas JA, Beddingfield FC. 3rd; Juvéderm Lips Study Group. Juvéderm® Ultra for lip enhancement: An open-label, multicenter study. *Aesthet Surg J.* 2013;33(3):414-420.

Gold M. The science and art of hyaluronic acid dermal filler use in esthetic applications. *J Cosmet Dermatol.* 2009; 8(4):301-307.

Jacono A. A new classification of lip zones to customize injectable lip augmentation. *Arch Facial Plast Surg.* 2008; 10(1):25-29.

Lanigan S. An observational study of a 24 mg/mL hyaluronic acid with pre-incorporated lidocaine for lip definition and enhancement. *J Cosmet Dermatol.* 2011;10:11-14.

Philipp-Dormston WG, Hilton S, Nathan M. A prospective, open-label, multicenter, observational, postmarket study of the use of a 15 mg/mL hyaluronic acid dermal filler in the lips. *J Cosmet Dermatol.* 2014;13(2):125-134.

Raspaldo H, De Boule K, Levy P. Longevity of effects of hyaluronic acid plus lidocaine facial filler. *J Cosmet Dermatol* 2010;9:11-15.

Rivkin A. New fillers under consideration: What is the future of injectable aesthetics? Facial Plast Surg. 2009; 25:120-123.

Sarnoff DS, Saini R, Gotkin RH. Six steps to the “Perfect” lip. J Drug Dermatol. 2012;11(9):1081-1088.

Segall L, Ellis D. Therapeutic options for lip augmentation. Facial Plast Surg Clin North Am. 2007;15:485-490.

Smith L, Cockerham K. Hyaluronic acid dermal fillers: can adjunctive lidocaine improve patient satisfaction without decreasing efficacy or duration? Patient Preference Adherence. 2011; 5:133-139.

Solish N, Swift A. An open-label, pilot study to assess the effectiveness and safety of hyaluronic acid gel in the restoration of soft tissue fullness of the lips. J Drugs Dermatol. 2011; 10(2):145-149.

Weinkle SH, Bank DE, Boyd CM, Gold MH, Thomas JA, Murphy DK. A multi-center, double-blind, randomized controlled study of the safety and effectiveness of Juvéderm® injectable gel with and without lidocaine. J Cosmet Dermatol 2009; 8:205-210.

14. Protocol Amendment Summary

Version Date/Amend. No.	Changes to Protocol
July 24, 2015/1	<ul style="list-style-type: none">• Updated Sponsor address on Title page■ [REDACTED]■ [REDACTED]• Clarification of Section 6.3 Instructions for the Subjects to discuss routine alternative treatments and to include available alternative treatments• Clarification of Section 10.3 Pregnancy to align with exclusion criteria• Updated Section 12.4.4 to remove Sponsor address• Updated Section 12.7 to remove the requirement for lactate dehydrogenase and glucose testing

Approval Date: 29-Jul-2015

July 29, 2015/2	<ul style="list-style-type: none">• Updated Section 7.2 to clarify timing of vital signs measurements and urine pregnancy tests• Updated Section 12.7 to clarify chemistry tests and storage of samples
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Approval Date: 29-Jul-2015

ALLERGAN

Protocol VOLBELLA-005 Amendment 2

Date (DD/MMM/YYYY)/Time (PT)

████████████████████

Signed by:

██████████

Justification

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