Title	A randomized, split-face clinical study on comparative ultrasound analysis of two Hyaluronic Acid fillers for midface correction
Protocol number:	GLI.04.US.SL.015
Sponsor name and address:	Galderma Laboratories, L.P. 14501 North Freeway Fort Worth, TX 76177 USA
Test products:	Restylane® Contour Juvéderm® Voluma®
Investigator agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described study in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.
Principle Investigator:	
	Signature Date
Name:	Steve F. Weiner, MD
Address:	The Aesthetic Clinique 2050 West County Highway 30A Suite 114 Santa Rosa Beach, FL 32459 USA Telephone: 1-850-600-6997

A RANDOMIZED, SPLIT-FACE CLINICAL STUDY ON COMPARATIVE ULTRASOUND ANALYSIS OF TWO HYALURONIC ACID FILLERS FOR MIDFACE CORRECTION

APPROVAL SIGNATURE PAGE

Steven F. Weiner, MD Principle Investigator The Aesthetic Clinique	Date
Jessica Hicks, PhD Senior Medical Affair Advisor Galderma Laboratories, L.P.	Date
Matthew Meckfessel, PhD Director, Medical Affairs Galderma Laboratories, L.P.	Date

1. SYNOPSIS

Study Objective	To assess and compare tissue aggregation and visualization of two (2) Hyaluronic Acid fillers via ultrasound
Methodology	Randomized, split-face, subject-blinded, comparative study
Number of Subjects at the end	15 subjects to complete
Study duration	24 weeks
Test products	Restylane Contour Juvéderm Voluma
Conditions of use	Per on-label instruction
Study visits	Day 0, week 4, and week 24
Specific Inclusion Criteria:	o **Demographics and study skin conditions** - Any race and ethnicity (to be recorded) - Fitzpatrick skin type (to be recorded) - Women or men - Age: 22 to 65 years old - Subject with midface volume loss and contour deficiency o **Administrative** - Ability of giving consent for participation in the study - Agreement to adhere to the procedures and requirements of the study and to report to the institute on the day(s) and at the time(s) scheduled for the assessments.
Specific Exclusion Criteria:	o **Skin conditions** - History of allergy or hypersensitivity to lidocaine and/or injectable hyaluronic acid (HA) - Previous permanent or semi-permanent implant in proposed treatment area - Previous biodegradable tissue augmentation therapy in the proposed treatment area within 12 months prior to the baseline visit

	- History of other facial treatment/procedure at the study area (midface) in the previous 6 months that would potentially interfere with study injections (e.g., facial surgery, oral surgery, resurfacing, mesotherapy, lipolytic injections, *botulinum* toxin injections)
Procedure	○ **D0** **-** Subjects will report to the site as D0 visit, will be given an informed consent form, HIPAA form, photography release form, Code of Conduct form, and medical history form to complete. - Subjects will be screened on the basis of the selection criteria for study qualification. - Ultrasound will be performed on enrolled subject's cheeks, left and right side will be assessed separately. - 2D photography will be performed at neutral expression (3/4 left, front, 3/4 right) and at smiling (3/4 left, front 3/4 right). 3D photography will be performed at neutral expression on entire face. - Investigator will perform injection to the subjects, based on the predetermined randomization and the test products' instruction to achieve the maximum correction. - Immediately post-injection, ultrasound will be performed at the same location of the injection, on either side of the face. ○ **W4** - Subjects to return to the site at week 4 post-treatment (± 3 days). - Ultrasound, 2D and 3D photography will be performed similarly to D0. - Self-assessment questionnaire will be performed by the subjects. - If needed, subjects will be offered a touch up to correct uneven side upon study completion. ○ **W24** - Subjects to return to the site at week 24 post-treatment (± 3 days). - Ultrasound, 2D and 3D photography will be performed similarly to D0. - Self-assessment questionnaire will be performed by the subjects.
Statistical analysis	Comparison of filler aggregation, volume change, and self-assessment questionnaire.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
°C	Degrees Celsius
CRF	Case Report Form
etc.	et cetera
e.g.	for example (Latin; exempla gratia)
°F	Degrees Fahrenheit
GCP	Good Clinical Practice
HA	Hyaluronic Acid
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonization
ICT	Information and communication technologies
i.e.	that is (Latin; id est)
IEC	Independent Ethics Committee
IRB	Institutional Review Board
N or n	Number
%	percent
SAE	Serious Adverse Event
SD	Standard deviation
SOP	Standard Operating Procedure

4. BACKGROUND AND RATIONALE

The hallmark signs of aging in the mid-face are often characterized by the decrease in skin elasticity and thickness, loss of tissue volume and body mass, and redistribution of fat tissues. Overtime, they result in the formation of deep wrinkles, folds, sagging skin, and hollowing.[1] One of the most popular non-invasive aesthetic treatments for mid-face volume restoration is the use of hyaluronic acid (HA) fillers. Due to their safety, effectiveness, and reversibility by hyaluronidase, HA fillers can help correct facial wrinkles and folds, while improving facial contour and volume augmentation.[1-3]

Currently in the market, there are various types of HA fillers have been approved for the midface volume restoration. Among them are two well-known fillers: Restylane® Contour (Galderma, Uppsala, Sweden) and Juvéderm® Voluma® (AbbVie/Allergan Aesthetics, Irvine, CA). They each contain 20mg/mL of hyaluronic acid with different crosslinking gel technologies, resulting in varying biophysical properties. Restylane® Contour has moderate lifting capacity (G') and flexibility whereas Juvéderm® Voluma® has a higher lifting capacity (G') and low flexibility.

The mechanism that each HA filler integrates into the skin tissue reflects the overall appearance of the midface. This study is to investigate how the two HA fillers behave in the skin tissue using ultrasound.

5. STUDY OBJECTIVE AND CLINICAL HYPOTHESIS

5.1 Study Objective

To assess and compare tissue aggregation and visualization of two Hyaluronic Acid fillers via ultrasound.

5.2 Clinical Hypothesis

When each HA filler is injected and integrated into the tissue, it will add volume to the skin to achieve different lifting and contouring effect.

6. SELECTION AND DISPOSITION OF STUDY POPULATION

6.1 Number of Subjects

A minimum 15 subjects meeting inclusion/exclusion criteria listed below will be enrolled on the study to achieve 15 subjects who complete the study as planned.

6.2 Study Population Characteristics

Males and females of any skin type with diagnosis of midface volume loss and contour deficiency.

6.3 Inclusion Criteria

1. Subjects of 22 to 65 years of age.
2. Subjects with a clinical diagnosis of midface volume loss and contour deficiency, and in the opinion of the investigator, is otherwise a good candidate for treatment with HA fillers.
3. Subjects of any gender.
4. Subjects of any race and ethnicity.

5. Subjects of any Fitzpatrick skin type.
6. Subjects who are able and willing to provide written informed consent prior to any study related procedures.
7. Subjects who agree to be photographed at each visit.
8. Subjects apprised of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and applicable state Bill of Rights.
9. Subjects who agree to adhere to the procedures and requirements of the study, to report to the institute on the day(s) and at the time(s) scheduled for the assessments, and to complete all required visits.

6.4 Exclusion Criteria

1. Subjects with any diseases, condition or presentation that may, in the opinion of the investigator, may put the subject at risk, may confound study results, or may interfere with participation in the study.
2. Subjects who are pregnant or breast-feeding, or who plan to become pregnant or breast feed during the course of the trial.
3. Subjects that are relatives of the investigator or are themselves or a relative of any study staff or any Galderma employee.
4. Subjects who have participated in an investigational study within 30 days of enrollment; participated in biologic investigational studies within 90 days of enrollment, or subjects planning to participate in any other interventional clinical research study while enrolled in this trial.
5. Subjects with history of allergy or hypersensitivity to lidocaine and/or injectable HA
6. Subjects with previous permanent or semi-permanent implant in proposed treatment area
7. Subjects with previous biodegradable tissue augmentation therapy in the proposed treatment area within 12 months prior to the baseline visit
8. Subjects with history of other facial treatment/procedure at the study area (midface) in the previous 6 months that would potentially interfere with study injections (e.g., facial surgery, oral surgery, resurfacing, mesotherapy, lipolytic injections, botulinum toxin injections).
9. Use of concomitant medications that have the potential to prolong bleeding times such as anticoagulants or inhibitors of platelet aggregation (e.g., aspirin or other nonsteroidal anti-inflammatory drugs, Omega 3 or Vitamin E), within 14 days prior to injection. Omega 3 and Vitamin E were acceptable only as part of a standard multivitamin formulation.

6.5 Concomitant Therapies

All treatments and therapies used 30 days prior to enrollment (visit 1/baseline) or 90 days prior to enrollment for biologics and all treatments or therapies used during the course of the study must be recorded in the Case Report Form (CRF) or electronic Case Report Form (eCRF).

6.5.1. Authorized Therapies

Unless listed under the exclusion criteria (Section 6.4) or in Prohibited Therapies (Section 6.5.2), other therapies to treat ongoing conditions are authorized.

6.5.2. Prohibited Therapies

None other than as specified in the Inclusion/Exclusion criteria.

The decision to administer a prohibited medication/treatment should be made with the safety of the subject being the primary consideration. Whenever possible, Galderma Laboratories, L.P. should be notified before the prohibited medication/treatment is administered to discuss possible alternatives.

If a subject receives prohibited therapy during the study, the subject may be allowed (at the discretion of the investigator / Galderma Laboratories, L.P.) to continue in the study for safety evaluation purposes, only.

7. STUDY TREATMENT

The term “study treatment” refers to the study products (HA Fillers, see Section 7.1)

7.1 Product Identification and Use

Study product: Restylane® Contour	
Form	Transparent gel of HA with the addition of lidocaine hydrochloride 3 mg/mL
Mode of Administration	Injection
How supplied	Pre-filled plastic syringes containing 1 mL of gel. Each syringe is co-packed with two ultra-thin wall needles.
Lot numbers	19741
Storage and Handling	The syringes are to be stored in the original packaging, under controlled room temperature conditions 20°C to 25°C (68°F to 77°F), protected from freezing and sunlight.

Study product: Juvéderm® Voluma®	
Form	Sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenous gel implant of HA crosslinked with BDDE, formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.
Mode of Administration	Injection
How supplied	Individual treatment syringes with needles.
Lot numbers	VB20B20024
Storage and Handling	Store at room temperature (up to 25°C/77°F). DO NOT FREEZE.

7.2 Additional Products and Materials

The Sponsor will only provide Restylane® Contour for the study. The study overhead will cover any additional materials or supplies.

7.3 Study Product Accountability

Upon receipt of the study products, the investigator or designee will conduct an inventory. In accordance with federal regulations, the investigator must agree to keep all test article in a secure location with restricted access. Designated study personnel will provide the test article to the subjects in accordance with the protocol.

During the study, the investigator must maintain records of study treatment dispensation and collection for each subject. This record must be made available to the study monitor for the purposes of verifying the accounting of clinical supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. At the conclusion of the study, the investigator will be responsible for returning all unused study product (i.e., Restylane® Contour) unless otherwise instructed by the Sponsor. Shipping label and cost will be provided to the investigator by the Sponsor.

7.4 Method of Treatment Assignment

Before the start of the study, a randomization list will be prepared by the Sponsor utilizing a computer-generated software.

7.5 Treatments Administered

The study products contain lidocaine hydrochloride, but additional topical or local anesthesia or ice pack may be used at the discretion of the Investigator to enhance the experience of the subjects. Any additional topical or local anesthesia used will be recorded in the CRFs.

The injection tools (needles or cannulas) will be determined at the discretion of the Investigator. However, for each subject, the Investigator must use the same type of injection tool to perform injection for both sides of the face. Switching device within the subject will not be allowed in order to avoid any inconsistent comparison. Either needles or cannulas will be used per subject. The brand name, gauge and length of the cannulas and incision needles used by the Investigator will be recorded in the CRFs.

The study products will be injected into the midface at the supraperiosteal to subcutaneous layer in the prezygomatic space lateral to the plane of the medial canthus, along the plane of the zygomatic arch ~1cm medial to hairline (described in Figure 1 below).

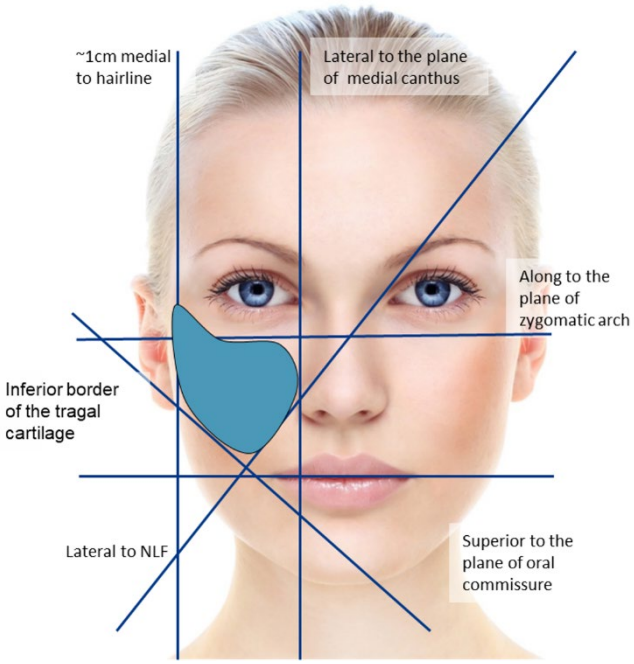

Figure 1. Description of injection boundary.

The amount of each study products needed varies between subjects and within subjects bilaterally, given the natural asymmetry of the face. However, subjects will be treated to optimal correction of the midface as agreed by the Investigator and subjects. The product volume injected during each treatment session for each subject will be recorded in the CRFs.

8. STUDY PROCEDURES

There will be three (3) visits during the course of the study:

1. Visit 1 – Screening/Baseline/Day 0
2. Visit 2 – Week 4 (Day 28)
3. Visit 3 – Week 24 (Day 168)

Test design / flow chart	**D0**	**W4**	**W24**
Informed consent	X		
Photo consent	X		
Demographics/Med History	X		
Concomitant Meds.	X		
Inclusion and exclusion criteria	X		
Randomization	X		
Case report form (CRF)	X	X	X
Injection per on-label instruction	X		
Touch up (if applicable)		X	
Ultrasound	X*	X	X

Standardized photography (2D and 3D)	X	X	X
Self-assessment questionnaire		X	X
AE Reporting	X	X	X

*Ultrasound at D0 will be performed before injection and immediately post-injection for each product.

8.1 Visits and Examinations

8.1.1. Screening/Baseline/Day 0 Visit (Visit 1)

1. Subjects will report to the testing clinical at D0 for baseline screening.
2. Prior to beginning of any study related activities, subjects will be informed about the purpose and nature of the study, the expected post-treatment events, and the potential risks involved with the treatments.
3. Subjects will be given an informed consent form, HIPAA form, photography release form, and Code of Conduct form to read.
4. Once subjects have completed reading, they will be interviewed to ensure their understanding of the aforementioned forms and be given the opportunity to ask any study related questions.
5. Subjects who agree to sign the aforementioned forms will be asked to complete a demographic information, medical history form, and concomitant medication form. Subjects declining to sign any of the forms will be dismissed from the study.
6. Subjects will be screened and qualified on the basis of the subject inclusion and exclusion criteria. Subjects failing to meet criteria will be dismissed from the study.
7. Subjects will have the below assessments by Investigator or a trained Clinic staff:
    a. Clinical 2D photography by VISIA at neutral expression (3/4 left, front, 3/4 right), at closed-mouth smile (3/4 left, front, 3/4 right), and at open-mouth maximum smiling (3/4 left, front 3/4 right)
    b. Clinical 3D photography by Vectra at neutral expression of full face
    c. Ultrasound on each cheek at neutral expression and at maximum smiling (left and right). Note: ultrasound assessment will be performed at the same area of the injection.
8. Clinic staff or Investigator will assign the appropriate test treatment to each side of the face based on the predetermined computer-generated randomization.
9. Investigator will instruct the subjects on each treatment administration procedure and perform the treatments.
10. Investigator or Clinic staff will record the details of the administration, amount of each treatment used for each cheek and any subsequent adverse events (AEs) in the CRF.
11. Immediately post-injection, subjects will have the below assessment by Investigator:
    a. Ultrasound on each cheek at neutral expression and at maximum smiling (left and right). Note: ultrasound assessment will be performed at the same area of the injection.
12. Subjects will be instructed on any standard care post-treatment and when to contact the Investigator in case of emerging AEs.
13. Subjects will be scheduled for a follow-up visit at Week 4 or Day 28 (±3 days) and dismissed from the Clinic.

Note: Subject screening /baseline/Day 0 must be on the same day.

Note: Whenever possible, the same investigator/staff that perform the baseline assessments and treatments should perform these assessments for each individual subject for the entire duration of the study. In the event of a change in the assigned investigator/staff for a given subject, the reason for change must be documented.

8.1.2. Visit 2 (Week 4 or Day 28 ±3 days)

1. Clinic staff or Investigator will record any AEs that are observed or reported.
2. Subjects will have the below assessments:
    a. Clinical 2D photography by VISIA at neutral expression (3/4 left, front, 3/4 right), at closed-mouth smile (3/4 left, front, 3/4 right), and at open-mouth maximum smiling (3/4 left, front 3/4 right)
    b. Clinical 3D photography by Vectra at neutral expression of full face
    c. Ultrasound on each cheek at neutral expression and at maximum smiling (left and right). Note: ultrasound assessment will be performed at the same area from Visit 1.
    d. Self-assessment questionnaire
3. Investigator will assess and offer the subjects an optional touch-up on the cheeks to reach the optimal aesthetic result.
4. If touch-up is needed, the same study treatment and type of injection tool used for each side of the face for the baseline treatment need to be used for this step. Investigator or Clinic staff will record the amount of the treatment used for the assigned cheek in the CRFs.
    a. Touch-up treatment was not to be performed if the subjects have a disease or condition described in the exclusion criteria, or an ongoing treatment-related AE that in the opinion of the Investigator would be worsened by a touch-up treatment.
5. Once completed, subjects will be scheduled for a follow-up visit at Week 24 or Day 168 (±3 days) and be dismissed from the Clinic.

8.1.3. Visit 3 (Week 24 or Day 168 ±3 days)

1. Clinic staff or Investigator will record any AEs that are observed or reported.
2. Subjects will have the below assessments:
    a. Clinical 2D photography by VISIA at neutral expression (3/4 left, front, 3/4 right), at closed-mouth smile (3/4 left, front, 3/4 right), and at open-mouth maximum smiling (3/4 left, front 3/4 right)
    b. Clinical 3D photography by Vectra at neutral expression of full face
    c. Ultrasound on each cheek at neutral expression and at maximum smiling (left and right). Note: ultrasound assessment will be performed at the same area from Visit 1.
    d. Self-assessment questionnaire
3. Once completed, subjects will be dismissed from the Clinic.

8.2 Discontinued Subjects

Any subject is free to discontinue his/her participation in this study at any time and for whatever reason, specified or unspecified, and without prejudice.

An investigator may decide to discontinue a subject from the study for safety reasons or when it is in the best interest of the subject. Galderma Laboratories, L.P. may also decide to prematurely terminate or suspend the study or the participation of a subject in the study. All data gathered on the subject prior to termination should be made available to Galderma Laboratories, L.P.

Criteria for the discontinuation of a subject during the study will include the following:

- Adverse Event
- Lack of Efficacy
- Pregnancy
- Subject Request
- Protocol Violation
- Lost to Follow-up
- Any unmanageable factor, in the Investigator's opinion, that may significantly interfere with the protocol or interpretation of results.

9. STUDY ASSESSMENTS

All images taken from the study will be saved and shared to the Sponsor via a data-protected platform.

9.1 Clinical Photography (VISIA)

Digital images of the subject's face will be taken at baseline (pre-injection), week 4 (pre-touch up), and week 24.

Clinic staff needs to ensure subjects to have a clean face with no makeup and to remove any jewelry from the area to be photographed. Subjects will be provided with a headband to keep hair away from the face. Subjects will be instructed to adopt neutral expression (3/4 left, front, 3/4 right), closed-mouth smile (3/4 left, front, 3/4 right), and open-mouth maximum smiling expression (3/4 left, front, 3/4 right) for each photograph.

A total of 9 full-face digital images will be taken of each subject's face using the VISIA CR photo-station (Canfield Imaging Systems, Fairfield, New Jersey) with a Canon digital SLR camera (manufacture name, location) under the standard lighting condition.

9.2 Clinical Photography (Vectra 3D)

Three (3) dimensional images of the subject's face will be taken at baseline (pre-injection), week 4 (pre-touch up), and week 24.

Clinic staff needs to ensure subjects to have a clean face with no makeup and to remove any jewelry from the area to be photographed. Subjects will be provided with a headband to keep hair away from the face. Subjects will be instructed to adopt neutral, nonsmiling expression with their eyes gently closed, and in a relaxed positioned for each scan.

Photography will be performed using the Vectra H2 Imaging system (Canfield Scientific, Inc., Canfield, NJ). The Vectra H2 utilizes raised flash to provide raked lighting to better capture and view skin topography and contours. Its software allows 3D viewing of the images and quantitative assessment of 3D parameters of the face.

Change in volume on each cheek will be analyzed by the Vectra H2 software (left and right cheek separately).

The 3D images will be uploaded to a secure database that can be accessed by the Sponsor remotely.

9.3 Ultrasound

Ultrasound measurements will be performed at baseline (pre-injection and immediately post-injection), week 4 (pre-touch up), and week 24. A single ultrasound measurement will be taken on each subject's left and right cheek, at neutral expression and at maximum smiling. The placement of the ultrasound probe needs to be at the same location of the product injection and for both visits to ensure consistent assessment.

Ultrasound measurements will be performed using an 18 MHz GE Venue Fit or 42 MHz Vevo® MD ultrasonic transducer interfaced to a system. The probe will have a standard setting of gain, depth, and velocity scale to assess placement/depth of filler, size of filler aggregates, and vascularity around aggregates.

9.4 Self-Assessment Questionnaire

Subjects will complete self-assessment questionnaire at week 4 (day 28) and week 24 (day 168). See Appendix I: Self-assessment questionnaire.

10. STATISTICAL ANALYSIS

Data of completing subjects will be included for all statistical analyses. Descriptive statistical summary will be performed including N, mean, median, standard deviations, minimum, and maximum of values at all applicable time points and for both treatments.

For each study treatment, mean of the change from baseline will be estimated at applicable post-baseline time point. The null hypothesis, that the mean change from baseline is zero, will be tested using methods described in the Statistical Analysis Plan table.

The following will be calculated and reported for each evaluation parameter at applicable post-baseline time point:

Percent mean change from baseline = $\frac{(\text{visit mean score} - \text{baseline mean score})}{\text{baseline mean score}}$ x 100

Percent of subjects improved/worsened = $\frac{(\text{number of subjects improved/worsened from baseline}}{\text{total number of subjects}}$ x 100

Comparison between the study treatments will be made in terms of changes from baseline. The null hypothesis, that the mean change from baseline is equal between the 2 study treatments at post-baseline time point, will be tested using methods described in the Statistical Analysis Plan table.

Statistical Analysis Plan

Evaluation	Change from Baseline	Comparisons between study treatments	Notes/Interpretation
Ultrasound measurement o Aggregate size	Paired t-test; If normality fails, a Wilcoxon signed-rank test will be used.	Wilcoxon rank-sum test or sample t-test	N/A

Volume change by 3D imaging analysis	Paired t-test; If normality fails, a Wilcoxon signed-rank test will be used.	Wilcoxon rank-sum test or sample t-test	A higher value reflects an improvement in skin volume.

Questionnaires will be tabulated, and the percentage of all response options will be reported for each question.

11. ADVERSE EVENTS

Throughout the course of the study, all adverse events will be monitored and reported on an adverse event CRF/eCRF without omitting any requested and known information. When AEs occur, the main concern is the safety of the study subjects. At time of the informed consent signature, each subject must be given the name and phone number of investigational site personnel for reporting AEs and medical emergencies.

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the standard questions:

- “Have you had any health problems since your last study visit?”
- “Have there been any changes in the medicines you take since your last study visit?”

AEs should be reported for any clinically relevant change, as determined by the Investigator, in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change from baseline in a subject's medical health following exposure to the study treatment.

Changes from baseline in any protocol-specific parameter evaluated during the study are to be reviewed by the Investigator. In addition, the subject’s responses to any questionnaire utilized during the study are to be reviewed by the investigator. Any untoward (unfavorable and unintended) change from baseline in a protocol-specific parameter or question response that is clinically relevant, in the opinion of the investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

11.1 Definitions

11.1.1. Adverse Events (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a subject taking part in the clinical study, and which does not necessarily require a causal relationship with the investigational product and/or a clinical trial procedure.

An AE can be any unfavourable and unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of the investigational product, whether or not related to this product.

When an AE has a likely or very likely causal relationship with the investigational product and/or a clinical trial procedure, it is named undesirable effect or related AE (see Section 3).

11.1.2. Local tolerability signs and symptoms (only applicable for cosmetic safety studies)

In cosmetic studies, local skin tolerability includes some expected functional and/or physical signs on the application area, observed by the Investigator or reported by the subjects (see Appendix). Those signs are collected in the final report based on scales or a diary. If the severity of a local skin tolerability sign or symptom, is such that the product application is

permanently discontinued and/or a corrective concomitant treatment (except moisturizer or emollient) is prescribed, it is recorded as an undesirable effect (related AE).

11.1.3. Serious Adverse Events (SAE) and serious undesirable effect/related SAE

A Serious Adverse Event (SAE) is any adverse event which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Notes:

The term “immediate vital risk” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. Hospitalization solely for the purpose of a diagnostic test (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical trial, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination) should not be considered as a SAE.

A serious undesirable effect/related SAE is defined as any SAE which the Investigator classifies as having a reasonable possibility for a causal relationship with the investigational product and/or the clinical trial procedure.

11.2 Severity Assessment

For all AEs occurring during the clinical trial, the Investigator is to classify and report the intensity of AEs using the following definitions as a guideline:

- Mild: awareness of signs and symptoms, but easily tolerated
- Moderate: discomfort, enough to cause interference with usual activity
- Severe: incapacitating, with inability to work or perform usual activity.

11.3 Causality Assessment

The Investigator is to assess the causal relationship (causality) between an adverse event and the investigational product and/or the clinical trial procedure according to the following definitions (Decision of 25 November 2013 on Guideline on Annex I to Regulation (EC) No 1223/2009 (2013/674/EU) - Causality assessment of undesirable effect caused by cosmetic products):

- Very likely
- Likely
- Not clearly attributable
- Unlikely
- Excluded

Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, positive de-challenge or re-challenge, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

11.4 Collection, Management and Reporting Procedures

The period of collection of adverse events starts from the time of signature of the Informed Consent Form (ICF) by the subject *(and/or, for subjects who are minor, by the parents/legal representatives)* until the end of the subject's participation in the clinical study.

If a Serious Adverse Event (SAE) is on-going at the final clinical trial visit, it should be followed by the Investigator until it has resolved or has reached a stable condition.

After the subject completes the clinical study, the Investigator should also inform the Sponsor (see Sponsor's contact details below) if he/she becomes aware of an SAE involving a subject who has participated in the clinical study.

At each post-enrollment visit, the Investigator will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example "*Have you noticed any change in your health since the last visit?*" Direct questioning and examination will be performed when appropriate.

The Investigator will obtain and maintain in the subject's files all pertinent medical records, and (if applicable) information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the Investigator will contact the subject's personal physician or hospital staff to obtain further details.

As a minimum, Investigators are requested to report in the Case Report Form (CRF) and in the report all <u>related</u> adverse events (i.e. undesirable effects) and all Serious Adverse Events, <u>whether related or not.</u>

11.4.1. Management and reporting procedures for undesirable effects (i.e. related adverse events

Undesirable effects should be recorded in the CRF and summarized in the report in a summary table with at minimum the subject number, AE number, AE diagnosis or signs and symptoms, location, date of onset, seriousness, severity, action taken, relationship, date of resolution and concomitant treatment associated as well as a detailed narrative of the event.

In addition, based on his/her medical judgment, the Investigator will assess whether an undesirable effect requires immediate (i.e. within 24 hours) reporting to the Sponsor. In such cases, the summary table will be sent to the Sponsor, along with the AE narrative and any other relevant information (concomitant treatments, product weighing, …).

All undesirable effects should be appropriately documented, i.e. any relevant information such as demographics, medical history and concomitant therapies should be recorded in the CRF.

The Investigator is to monitor and record the progress of the adverse effect until the last subject's study visit.

The Investigator is to update the AE narrative as appropriate, each time follow-up information is collected and when the final outcome of the adverse effect is known.

11.4.2. Management and reporting procedures for Serious Adverse Events

The Investigator is to take the following steps:

1. Take prompt and appropriate medical action, if necessary. The safety of clinical trial subjects is the first priority
2. Ensure the AE is classified as an SAE. Immediately inform the Sponsor's representative of the event by email or fax (see contact details below) and discuss further actions to be taken:

   e-mail: pharmacovigilance@galderma.com
3. Complete the Serious Adverse Event (SAE) form provided by the Sponsor's representative **Within 24 hours**, fax or send by e-mail **to the Sponsor's representative** the completed SAE form, accompanied any other relevant information (e.g. test results or medical records).
4. Monitor, record and send to Sponsor's representative the progress of the event until it resolves or reaches a stable outcome, with or without sequelae (send the updated SAE form with follow-up information and any other relevant information to Sponsor's representative).
5. Obtain and maintain in the subject's file all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
6. If applicable, comply with the regulatory requirement(s) related to the reporting of SAEs to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

11.5 Pregnancy

Pregnancy itself is not to be considered as an adverse event. If a pregnancy occurs during the clinical trial, **the product application should be stopped immediately**, the subject should be withdrawn from the clinical study and Sponsor's representative (see Sponsor's contact details above) should be informed **within 24 hours.**

Pregnancy must be recorded as a reason for discontinuation in the exit form of the CRF.

No specific follow-up of pregnancy is required, except if it is a regulatory requirement in the country(ies) where the clinical trial is conducted.

12. ETHICAL AND REGULATORY PROCEDURES

12.1 Research Standards/Good Clinical Practice

This study will be conducted in accordance with all applicable guidelines for the protection of human subjects for research as outlined in 21 CFR 50 the accepted standards for Good Clinical Practice (GCP), and the standard practices of SGS Stephens in accordance with the protocol and amendment(s) as applicable.

12.2 Quality Assurance/Audit/Inspection

To ensure compliance with GCP and all applicable regulatory requirements, Galderma Laboratories, L.P. may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. The investigator must agree to grant the auditor(s) and inspector(s) direct access to all

relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

12.3 Institutional Review Board

This study (protocol, ICF and all addenda) will be reviewed and approved by Sterling IRB. The study will not be activated and subjects will not be consented, receive any study products, or participate in any study procedures until the IRB has approved the protocol and the ICF. In addition, the IRB will review the study before any significant change in the protocol is initiated. After each review, the IRB's approval will be documented in a letter to the Investigator and a copy of the IRB approval letter will be forwarded to the Sponsor.

13. STUDY CONDUCT CONDISERATIONS

13.1 Clinical Monitoring

The conduct of the study will be closely monitored by representatives of Galderma Laboratories, L.P. following GCP, ICH guidelines, applicable SOPs, guidelines, and all local regulations. The clinical investigation will be monitored to ensure that: the rights and well-being of the subjects are protected; the reported data are accurate, complete and verifiable from applicable source documents; and the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements. The investigator will allow the Galderma Laboratories, L.P. representatives to have access to all study records, CRF/eCRFs, corresponding subject medical records, and any other documents considered source documentation. The investigator also agrees to assist the representatives, if required, which can include AE reporting. All study monitoring details will be detailed in the Clinical Monitoring Plan.

13.2 Data Collection

Investigators must keep accurate records of all subjects' visits and all procedures done, being sure to include all pertinent study related information from which CRF/eCRF data will be recorded. Data for this study may be recorded in the subject's chart (e.g. source documents / electronic records) or if approved by the Galderma Laboratories, L.P. directly into CRF/eCRFs. If electronic records are maintained, the method of verification must be determined in advance of starting the study. The process of administering the informed consent must also be documented. Any and all side effects and AEs with the concomitant therapies associated must be thoroughly documented. Results of any diagnostic tests conducted during the study should be included in the source documentation. Pertinent telephone conversations with the subjects and/or Galderma Laboratories, L.P. concerning the study will be documented and kept on file.

It is required that the author of an entry in the source documents be identifiable. Direct access to all source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF/eCRF are consistent with the original source.

Only designated individuals may complete the CRF/eCRFs. The principal investigator will review the reported data and certify that the CRF/eCRFs are accurate and complete.

After monitoring has occurred at the clinical site(s) and the CRF/eCRFs have been reviewed, additional data clarifications and/or additions may be needed including AE reporting. Data clarifications and/or additions are documented and are part of each subject’s CRF/eCRFs.

13.3 Record Retention

The investigator is required to maintain up-to-date, complete regulatory documentation as indicated by Galderma Laboratories, L.P. and the investigator's files will be reviewed as part of the ongoing study monitoring. The records must be easily accessible when needed (e.g., for a Galderma Laboratories L.P.'s audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site personnel. Financial information is not subject to regulatory inspection and should be kept separately.

Galderma Laboratories, L.P. will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, Galderma Laboratories, L.P. SOPs, and/or institutional requirements.

The investigator should take measures to prevent accidental or premature destruction of these documents. If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Galderma Laboratories, L.P. must be notified in writing of the name and address of the new custodian.

13.4 Changes in Study Conduct/Amendments

No amendment will be done for modification(s) due to change in logistical or administrative aspect of the study (e.g., change in monitors, change of telephone numbers). In such a case, the appropriate institution(s) and/or person(s) will be notified of the changes.

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by Galderma Laboratories, L.P. and must be approved by the IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all Subjects/subjects currently enrolled in the study may be required by the IRB to sign the approved, revised informed consent form.

13.5 Confidentiality

All the data provided to the investigator and his/her staff and all data obtained through this Galderma Laboratories, L.P. protocol will be regarded as confidential and proprietary in nature and should not be disclosed to any third party without Galderma Laboratories, L.P.'s written consent"

14. REFERENCES

1. Callan P, Goodman GJ, Carlisle I, et al. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of midface volume deficiency: a 24 month study. *Clin Cosmet Investig Dermatol*. 2013;6:81–89.
2. Cohen JL, Dayan SH, Brandt FS, et al. Systematic review of clinical trials of small- and large-gel-particle hyaluronic acid injectable fillers for aesthetic soft tissue augmentation. *Dermatol Surg*. 2013;39:205–231.

3. Weiss RA, Moradi A, Bank D, et al. Effectiveness and safety of large gel particle hyaluronic acid with lidocaine for correction of midface volume deficit or contour deficiency. *Dermatol Surg*. 2016;42(6):699-709.

APPENDIX I: SELF-ASSESSMENT QUESTIONNAIRE

VISIT 2 (DAY 28 OR WEEK 4)

Preference questions	Left	Right	No Difference
a) Which cheek do you prefer?	☐	☐	☐
b) Which cheek has the best contour?	☐	☐	☐
c) Which cheek looks more natural?	☐	☐	☐

Thinking about the left side of your face…	**Strongly Agree**	**Agree**	**Neutral (neither agree nor disagree)**	**Disagree**	**Strongly Disagree**
a) I love how my cheek looks in selfies/photos	☐	☐	☐	☐	☐
b) I am camera-ready with my natural contour	☐	☐	☐	☐	☐
c) My cheek feels natural	☐	☐	☐	☐	☐
d) My cheek makes me feel good about myself	☐	☐	☐	☐	☐
e) I am happy with my contoured cheek	☐	☐	☐	☐	☐
f) My cheek looks natural when smiling	☐	☐	☐	☐	☐

Thinking about the right side of your face…	**Strongly Agree**	**Agree**	**Neutral (neither agree nor disagree)**	**Disagree**	**Strongly Disagree**
a) I love how my cheek looks in selfies/photos	☐	☐	☐	☐	☐
b) I am camera-ready with my natural contour	☐	☐	☐	☐	☐
c) My cheek feels natural	☐	☐	☐	☐	☐
d) My cheek makes me feel good about myself	☐	☐	☐	☐	☐
e) I am happy with my contoured cheek	☐	☐	☐	☐	☐

f) My cheek looks natural when smiling	☐	☐	☐	☐	☐

Testimonials (please provide any comments on your experience, treatments, satisfaction/dissatisfaction, or anything related to this study)

_____

_____

_____

_____

_____

VISIT 3 (WEEK 24 OR DAY 168)

Preference questions	Left	Right	No Difference
a) Which cheek do you prefer?	☐	☐	☐
b) Which cheek has the best contour?	☐	☐	☐
c) Which cheek looks more natural?	☐	☐	☐

Forced Preference questions	Left	Right
a) If you have to choose, which cheek do you prefer?	☐	☐
b) If you have to choose, which cheek has the best contour?	☐	☐
c) If you have to choose, which cheek looks more natural?	☐	☐

Thinking about the left side of your face…	**Strongly Agree**	**Agree**	**Neutral (neither agree nor disagree)**	**Disagree**	**Strongly Disagree**
a) I love how my cheek looks in selfies/photos	☐	☐	☐	☐	☐
b) I am camera-ready with my natural contour	☐	☐	☐	☐	☐

c) My cheek feels natural	☐	☐	☐	☐	☐
d) My cheek makes me feel good about myself	☐	☐	☐	☐	☐
e) I am happy with my contoured cheek	☐	☐	☐	☐	☐
f) My cheek looks natural when smiling	☐	☐	☐	☐	☐

Thinking about the right side of your face…	**Strongly Agree**	**Agree**	**Neutral (neither agree nor disagree)**	**Disagree**	**Strongly Disagree**
a) I love how my cheek looks in selfies/photos	☐	☐	☐	☐	☐
b) I am camera-ready with my natural contour	☐	☐	☐	☐	☐
c) My cheek feels natural	☐	☐	☐	☐	☐
d) My cheek makes me feel good about myself	☐	☐	☐	☐	☐
e) I am happy with my contoured cheek	☐	☐	☐	☐	☐
f) My cheek looks natural when smiling	☐	☐	☐	☐	☐

Testimonials (please provide any comments on your experience, treatments, satisfaction/dissatisfaction, or anything related to this study)

_____

_____

_____

_____

_____