

Study Protocol

A Randomized, Evaluator-Blinded, No-Treatment-Controlled Study of the Effectiveness and Safety of *Restylane*[®] in the Augmentation of Soft Tissue Fullness of the Lips

Medicis Protocol Number MA-1300-15

Original Protocol Date: December 10, 2008
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Amendment 3 Date: June 2, 2009

Sponsor:
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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
CFR	Code of Federal Regulations
BDDE	1,4 butanediol diglycidyl ether
CRF	Case Report Form
EES	Norway, Iceland, and Liechtenstein
FDA	US Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
IDE	Investigational Device Exemption
IND	Investigational New Drug
IPR	Independent Photographic Reviewer
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Medicis Lip Fullness Scale
OTC	Over-the-Counter
SAS	Statistical Analysis System
TEAE	Treatment-Emergent Adverse Event

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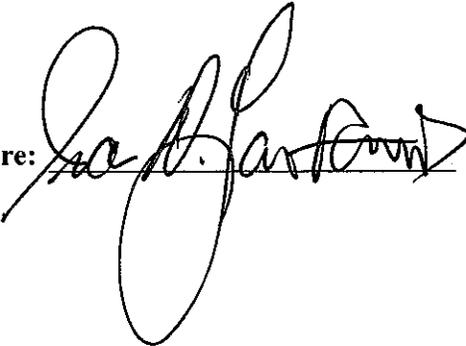
3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

3.1. SPONSOR SIGNATURES

Protocol Number: MA-1300-15
Date: December 10, 2008
Version: Original
Date: February 20 2009
Version: Amendment 1
Date: April 28, 2009
Version: Amendment 2
Date: June 2, 2009
Version: Amendment 3
Title: A Randomized, Evaluator-Blinded No-Treatment-Controlled Study of the Effectiveness and Safety of *Restylane*[®] in the Augmentation of Soft Tissue Fullness of the Lips
Test Product: *Restylane*[®]
Clinical Laboratories (if Central): N/A
Sponsor Medicis Global Services Corporation (MGSC)
7720 N. Dobson Road
Scottsdale, Arizona 85256

The signatures of the Sponsor below constitute approval of this protocol and provide the necessary assurances that this study will be conducted according to all conditions of the protocol, the Investigator Contractual Agreements and applicable laws and regulations, including all statements regarding confidentiality.

Sponsor's
Senior Vice President, Research
and Development:
Ira D. Lawrence, MD

Signature:  Date: 6/2/09

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3.2. INVESTIGATOR SIGNATURE

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Version: Original
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Test Product: *Restylane*[®]
Sponsor Medicis Global Services Corporation (MGSC)
7720 N. Dobson Road
Scottsdale, Arizona 85256

The signature of the Investigator below constitutes agreement with this protocol and that the Investigator will conduct this study according to all conditions of the protocol, the Investigator Contractual Agreements and applicable laws and regulations, including all statements regarding confidentiality.

Investigator:

Affiliation (if any):

Address:

Investigator Signature: _____ **Date:** _____

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4. ETHICS

4.1. INSTITUTIONAL REVIEW BOARD (IRB)

The Principal Investigator will provide the IRB with all appropriate materials to permit their review and approval of the protocol. No study subject will be admitted to this study until written IRB approval of the protocol and the informed consent template has been obtained by the Investigator. The Investigator should file all related correspondence with the IRB. Copies of IRB approvals will be forwarded to Medicis. The study product for this study will not be delivered to the study centers until copies of IRB approvals for the site have been supplied by the Investigators to Medicis.

Appropriate reports on the progress and conclusion of this study by the Principal Investigator must be made to the IRB at least annually in accordance with applicable government regulations. The Investigator is responsible for checking what additional local reporting procedures may be applicable and complying with such requirements. Federal regulations also provide for expedited reporting of certain events to the IRB and the FDA. See [section 12.4](#). The Investigator is responsible for such expedited reporting. Additionally, the Investigator is responsible for any additional expedited reporting requirements that may be imposed by his or her IRB.

4.2. ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and later revisions (insofar as such revisions are consistent with US treaty obligations and in accordance with US law), with the Common Rule (Part 46 of Title 45 of the U.S. Code of Federal Regulations) and with Parts 50 and 56 of Title 21 of the U.S. Code of Federal Regulations.

4.3. STUDY SUBJECT INFORMED CONSENT

The informed consent process is intended to give a study subject or patient or his or her designated representative all the information (s)he would reasonably want to know about a study, to ensure that the study subject understands the information and to give the study subject an opportunity to agree to participate in the study. A properly executed written informed consent, which has been approved by the IRB and is in compliance with 21 CFR Part 50, shall be obtained from each study subject before screening or enrollment to this study. The subjects must be informed about their right to withdraw from the study at any time, and that such withdrawal will not affect their future medical care, treatment or

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benefits to which the subject is otherwise entitled. If photographs are obtained, the informed consent must contain information specific to their ownership, handling and how privacy will be protected, if applicable. The study subject should also be informed if privacy rights under this study are exempt from the confidentiality provisions of the Health Insurance Portability and Access Act of 1996 pursuant to 45 CFR § 512(b)(iii) and, if so, what components of study subject confidentiality will be maintained and by whom.

The Investigator shall provide a copy of the signed and dated informed consent to the study subject and will keep the original, signed form in the study subject's study file. The Investigator will confirm the receipt of informed consent from each subject by a recording in the CRF.

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5. BACKGROUND, RATIONALE, AND RISK ANALYSIS

5.1. BACKGROUND

Restylane[®] is a transparent, viscous gel composed of hyaluronic acid biosynthesized by *Streptococcus* species of bacteria, chemically cross-linked with 1,4 butanediol diglycidyl ether (BDDE), and suspended in physiologic buffer at pH = 7 and concentration of 20 mg/mL.^{1,2,3,4} The gel is physically separated into variably shaped particles. *Restylane* is free of animal protein or other potential agents of xenogeneic disease transmission. *Restylane* is approved by the US Food and Drug Administration and is intended for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Voluminous lips are a sign of youth and fertility⁵. Many women's lips have grown wrinkled and thinner with age, because collagen and elastin, the fibrous proteins that keep lips full, gradually waste away. Currently, *Restylane* labeling in the U.S. contains a precaution that the safety and effectiveness of usage for lip augmentation has not been established in controlled clinical studies. This study will assess the safety and effectiveness of *Restylane* when used to augment lip fullness, using a five grade assessment tool of Medicis Lip Fullness Scales with photoguides for each lip (one scale for upper lip and one scale for lower lip).

Aesthetic dermatologists with significant experience with *Restylane* in the United States anecdotally report the successful use of *Restylane* for lip augmentation. The Sponsor believes it is important, given these clinical impressions, to acquire information on the safety and effectiveness of *Restylane* when used for lip augmentation.

5.2. RESTYLANE POST-MARKETING EXPERIENCE

Review of the distribution and type of post-marketing adverse event reports in the United States are consistent with current labeling. There are a variety of reasons why calculation of the relative adverse event for lip augmentation versus labeled use cannot be done from these data. For instance, reports of adverse event for an off-label use may be increased relative to labeled use because of concern about this usage, especially given the labeling statement, which may increase the relative reporting rate. The sample size in this study may permit identification of whether the more frequently reported events (e.g., pain and swelling) are more common following use of *Restylane* in the lips.

Adverse events reported in the manufacturer's (Q-Med AB, Uppsala, Sweden) worldwide post-marketing surveillance database of events (excluding the U.S.) reported in the lip with potential relationship to *Restylane* resulted in 70 reports for review.

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The most frequently-reported adverse event in the safety surveillance database referring to Restylane use in the lip was “device ineffective:” (21 cases). Injection site swelling and injection site inflammation were both reported in 8 cases. Implant site pain and implant site swelling were both reported in 4 cases. Reported mass formation included 4 injection site nodules, 3 implant site masses, 2 injection site masses, and 3 implant site papules. There were 3 cases each of injection site infection and injection site necrosis. There were no events reported in conjunction with lip administration that were not also observed in nasolabial fold administration.

5.3. CLINICAL DOCUMENTATION

A 20 subject pilot study (MA-1300-13K) was undertaken to evaluate the safety and effectiveness of a single, open-label *Restylane* treatment in lip fullness augmentation. The results of this pilot study justified further assessment of the use of *Restylane* for lip augmentation by displaying promising effectiveness results and absence of safety issues.

Subjects were uniformly satisfied with their lip improvement: all (100%) subjects indicated lip improvement through Week 12 and 74% of subjects maintained their assessment of improvement through Week 24. Similarly, 100% of Treating Investigator assessments indicated lip improvement through Week 12 and 84% improvement through Week 24. Exploratory analyses of measurements taken by four different imaging systems provided correlations that demonstrated useful trends for future evaluation in studies of lip augmentation. A number of lip measurements showed statistically significant changes from baseline across study time points.

A single treatment with *Restylane* administered for lip fullness augmentation was well-tolerated. Seven treatment-emergent adverse events (TEAEs) were experienced by 4 (20%) subjects. Only two of these events (both mild bruising) were considered to be caused by the injection procedure.

Mass formation was reported in diaries by 90% of subjects treated in the lip pilot study. The Principal Investigator of the study stated that subjects had been specifically instructed to record any product palpability as mass formation in the diary, whether or not the palpability was a mass formation or the intended feel of the product. Clinically, the Principal Investigator did not report any mass formation during the study. Intended palpability of the product was detected by the Principal Investigator through Week 2 of the study in up to 35% of subjects. Intensity and duration of bruising, redness, swelling, pain, tenderness, itching and mass formation were comparable between the study of lip augmentation and historic data involving *Restylane* in the treatment of nasolabial folds. As assessed by subject diaries, the severity of most symptoms was tolerable and most events resolved after one week.

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5.4. RATIONALE

A study of the safety and effectiveness of *Restylane* in lip fullness augmentation is important to establish whether aesthetic lip augmentation can be successfully achieved using *Restylane*, with acceptable risks. By using a standardized evaluation tool, the results of lip fullness augmentation reported by US physicians anecdotally can be confirmed by accurate measurements.

This study is to evaluate 180 subjects, including 30 subjects with Fitzpatrick skin types IV, V, or VI. The group of 150 subjects with Fitzpatrick skin type I, II, or III must have the required Medicis Lip Fullness Scales (MLFS) lip thinness score for both upper and lower lips to be enrolled. They will then be randomized in a 3:1 ratio to *Restylane* treatment or no treatment. The group of subjects with Fitzpatrick skin types IV, V, or VI must have the required MLFS lip thinness score for at least one lip (either upper or lower) to be enrolled. They will then be randomized in a 3:1 ratio to *Restylane* treatment or no treatment. Both the treated group and the untreated control group will be assessed by a Blinded Evaluator at 8 weeks and thereafter and the assessments will be used to demonstrate the superiority of *Restylane* for the augmentation of lip fullness.

5.4.1. MEDICIS LIP FULLNESS SCALE VALIDATION

The objective of the validation study was to evaluate the 5-grade MLFS regarding the within- and between-evaluator agreement. There were two separate Lip Fullness Scales, one for the upper lip and one for the lower lip. The within-observer agreement refers to the ability of each evaluator to reproduce their original score at a subsequent time, having allowed reasonable amount of time to elapse so that memory was not a likely factor. Between-observer agreement is the degree to which the evaluators independently provided an identical score for the same subject.

The validation study included photographs of 85 subjects that were assessed independently by five board certified dermatologists or plastic surgeons (Evaluators). Diverse age groups, genders, and ethnicities were represented in the subjects used to photographically evaluate the MLFS in order to evaluate lip fullness in a varied population. The same photographs were used for upper lip scale validation and lower lip scale validation. Each photograph displayed a frontal (AP) view of the lips slightly parted. The photographs used were intended to reflect the range of the scale, ratings 1 to 5. Each photograph had a unique identification number, but they were not arranged in any specific order. Assessments were made by each of the Evaluators on two occasions, at least 2 weeks apart. The same set of photographs was used for both occasions, however they were provided to the Evaluators in a different order at each time.

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Five evaluators evaluated each of the 85 photographs at two occasions. The agreement of these matched data was assessed using two measures utilizing the original data on the 5-grade MLFS (separately for the upper and lower lip):

1. The overall proportion of the observed agreement, i.e. the sum of the number of ratings in the main diagonal of the square matrix, divided by the total number of observations.
2. A weighted kappa coefficient and associated 95% confidence interval. A value of the weighted kappa coefficient ≥ 0.75 is considered as excellent agreement, whereas a value ≤ 0.40 signifies poor agreement.

Weighted Kappa coefficients for intra-rater reliability were graded according to the following categories:

- 0 - 0.19 = Poor Agreement
- 0.20 - 0.39 = Fair Agreement
- 0.40 - 0.59 = Moderate Agreement
- 0.60 - 0.79 = Substantial Agreement
- 0.80 - 1.0 = Almost Perfect Agreement

The overall within-observer weighted kappa value stratified by rater was 0.81 for both the upper lip and lower lip, separately. This score indicated almost perfect agreement within the 5 raters for their ability to independently provide an identical score for the same subject during two temporally discrete occasions. The overall exact agreement was consistent for both upper and lower lips (70% and 71%, respectively).

The variation of weighted kappa coefficients for between-observer agreement was consistent between lips, with scores varying from 0.60 to 0.83 (upper) and from 0.60 to 0.82 (lower), indicating substantial to almost perfect agreement between raters for each lip fullness scale.

Additionally, the MLFS was rated in live subject: 39 subjects reflecting the range of the scale ratings 1 to 5 for the upper lip and 39 subjects reflecting the range of the scale ratings 1 to 5 for the lower lip.

The overall live vs photo weighted kappa value stratified by rater was 0.65 for the upper lip. The weighted kappa values varied between 0.62 and 0.68 among the different raters.

The overall live vs photo weighted kappa value stratified by rater was 0.64 for the lower lip. The weighted kappa values varied between 0.61 and 0.68 among the different raters.

Based on the results of the photographic assessments of intra- and inter-observer ratings using weighted kappa coefficients and the intra-observer ratings between the live and

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photographic assessments, it was demonstrated that the MLFS can be used consistently by different evaluators and by the same evaluator at different time points. It is concluded that the 5-point MLFS is considered suitable for use in clinical studies to grade lip fullness.

5.5. RISK-BENEFIT ASSESSMENT

Currently, *Restylane* is approved for use and considered safe and effective for soft tissue augmentation to correct wrinkles and folds such as nasolabial folds. Prospective human experience and existing preclinical and human prospective studies on the use of the *Restylane* family of chemically identical products provides substantial support for the safety of *Restylane*. Surveillance data for *Restylane* do not, at this point, confirm any increased risk or special risk related to this off-label use.

The FDA's Manufacturer and User Facility Device Experience Database (MAUDE) is a dataset that includes information about problems that have occurred with medical devices. The data comes from voluntarily report adverse events from user facilities (hospitals, clinics, consumers, etc.) as well as problems reported by product distributors and manufacturers, as required by the FDA.

The MAUDE Database was searched using the criteria "Restylane" and "lip". A total of 28 reports were identified. Of the 28 reports, 19 reports indicated an administration and an adverse event in/around the lip area with *Restylane*. These events included masses such as papules and lumps, discoloration such as erythema and bruising, infection-related events such as Herpes zoster and abscess, swelling such as allergic reaction and facial swelling, ischemia-related events such as scars and necrosis, and other events such as soreness and dryness.

Most events found in the MAUDE database search are analogous to adverse events described in the *Restylane* label for the nasolabial fold indication. Swelling, pain, inflammation, discoloration, and papules have been observed with *Restylane* use, but the rate of these events in the lips is difficult to determine since the number of lip augmentation procedures performed during that time is unknown.

Medicis anticipates a lip augmentation safety profile similar to the safety profile in the nasolabial fold regarding type, duration, severity, and time to onset of adverse events. Although some events may occur at different rates specific to the lip's anatomical configuration, there is no expectation that the lips pose a greater adverse event risk than the currently marketed indication.

The weakening of tissue continuity and loss of fat volume around the mouth leads to a significant aesthetic defect giving an aged appearance. This loss of lip structure may be

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susceptible to repair with *Restylane*. This study also includes evaluation of subject satisfaction with lip augmentation as an improvement of quality of life, through measurement with the Global Aesthetic Improvement Scale (GAIS). Given the anticipated low level or transient and acceptable risk, the risk-benefit assessment of the use of *Restylane* for lip augmentation appears to offer a substantial clinical benefit at reasonable risk.

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6. STUDY OBJECTIVES

6.1. PRIMARY OBJECTIVES

The primary effectiveness objective is:

- to identify whether *Restylane* is more effective in lip augmentation than no treatment as determined by the Blinded Evaluator assessment of lip fullness at 8 weeks after the first treatment as compared to the Treating Investigator's assessment of the baseline condition, separately in the upper and lower lips (co-primary endpoints). The Treating Investigator and Blinded Evaluator will score upper and lower lip fullness using separate five grade Medicis Lip Fullness Scales (MLFS) with photoguides for each (one scale for upper lip and one scale for lower lip): 1 – Very Thin; 2 – Thin; 3 – Medium; 4 – Full; 5 – Very Full. Treatment success will be defined as at least a one grade increase in the MLFS for the Blinded Evaluator assessments at Week 8 (as compared to the Treating Investigator's baseline assessment of the MLFS) in the analyses of BOTH the upper and lower lips.

The primary safety objective is:

- to define the incidence of all adverse events, including subject complaints reported during the first fourteen days after treatment as recorded in the Subject Diary, safety assessments at the 72 hour visits, Treating Investigator assessments at 2, 4, 8, 12, 16, 20, 24 weeks as well as 2 and 4 weeks after the 6-Month treatment; and any systemic adverse events.

6.2. SECONDARY OBJECTIVES

Secondary effectiveness objectives include:

- assessment of lip fullness augmentation after treatment with *Restylane* as compared to no treatment, as measured by the Blinded Evaluator at 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks, as well as 2 and 4 weeks after the 6-Month treatment, as correlated to baseline, with response determined by at least one grade increase from baseline in the upper and lower lips using the MLFS.
- assessment of lip augmentation after treatment with *Restylane* as compared to no treatment, as determined by the Treating Investigator at each time point after treatment as compared to baseline condition, with response determined by at least one grade increase from baseline in the upper and lower lips using the MLFS.
- identification of subject satisfaction with lip fullness augmentation at each time point after treatment with *Restylane* as compared to no treatment, with response determined by a score of 1 or greater on the Global Aesthetic Improvement Scale (GAIS) score

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from baseline in the upper and lower lips. GAIS: -3 = Very Much Worse; -2 = Much Worse; -1 = Worse; 0 = No Change; 1 = Improved; 2 = Much Improved; 3 = Very Much Improved (with improvement assessed from the baseline condition).

- identification of lip fullness augmentation at each time point after treatment with *Restylane* as compared to no treatment with response determined by a score of 1 or greater on the GAIS as assessed by the Treating Investigator in the upper and lower lips.
- assessment of lip fullness augmentation after treatment with *Restylane* as compared to no treatment, as measured by Independent Photographic Reviewers (IPR) after assessment of imaging at each time point, with response determined by at least one grade increase from baseline in the upper and lower lips using the MLFS.
- correlation among the degree of response per the MLFS (1+, 2+, 3+, 4+ grade increase) and the GAIS scores for the Treating Investigator separately in the upper and lower lips, to assess the trend between the two scales.
- correlation among the degree of response per the MLFS (1+, 2+, 3+, 4+ grade increase) for the Treating Investigator with the GAIS scores for the subject, separately in the upper and lower lips, to assess the trend between the two scales.
- agreement among the proportion of responders between the MLFS (with response determined by at least a one grade increase) and the GAIS (with response determined by a score of 1 or greater) for the Treating Investigator, separately in the upper and lower lips.
- agreement among the MLFS between the Treating Investigator, Blinded Evaluator, and IPR assessments, separately in the upper and lower lips.

Secondary safety objectives include:

- lip texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation as evaluated by the designated study staff member.

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7. STUDY DESIGN

7.1. STUDY DESIGN

This will be a randomized, evaluator-blind study of 180 subjects who are seeking lip fullness augmentation from up to 15 investigational centers. Subjects who meet all inclusion/exclusion criteria will be randomized at entry in a 3:1 ratio to *Restylane* treatment or no treatment. The study will recruit a minimum of 30 subjects with darker skin types based on classification of Fitzpatrick skin types IV, V, or VI. See [Section 7.2](#) for skin type definitions. Each lip qualified by MLFS score will be analyzed for effectiveness and all lips will be analyzed for safety. Subjects randomized to treatment will be re-treated at 6 months and subjects randomized to no treatment will receive their first treatment at 6 months. The safety of all patients will then be monitored for one month after the 6-month treatment

Screening:

Eligibility criteria will be assessed and informed consent will be obtained at the Screening visit (Visit 1). Subjects with Fitzpatrick skin types I, II, or III must have a score of 1 (Very Thin) or 2 (Thin) on BOTH upper and lower lips on the MLFS as assessed at baseline by the Treating Investigator to be eligible for enrollment. The MLFS score for the upper lip and lower lip do not have to be equal as long as each score is 1 (Very Thin) or 2 (Thin). The group of subjects with Fitzpatrick skin types IV, V, or VI must have the required MLFS score for at least one lip (either upper or lower) as assessed at baseline by the Treating Investigator to be enrolled.

The Screening and treatment visit may be performed as one visit. If performed as separate visits, the Screening visit will be conducted no more than 28 days prior to randomization.

If the subject meets all inclusion/exclusion criteria, the subject will then be randomized to treatment or no-treatment (Visit 2). Both lips may be treated for effectiveness if each lip meets the MLFS lip thinness requirement, but each lip will be analyzed separately. In subjects with Fitzpatrick skin types IV, V, or VI where only one of the lips meets MLFS eligibility for treatment, the other lip may be treated as well to achieve or maintain overall symmetry. This will be at the discretion of the Investigator in consultation with the subject. An analysis will be performed for the effectiveness outcomes observed for each lip (i.e., upper or lower) that meets the MLFS inclusion criteria of 1 [Very Thin] or 2 [Thin]. Analyses will be performed in all subjects and in the subset of subjects with Fitzpatrick skin types of IV, V or VI. The subsets of upper and lower lips that are

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treated, but not qualified by MLFS will be analyzed for safety only. All lips will be analyzed for safety.

At screening, subjects with any abnormal rating of lip texture, firmness, function, or sensation will be excluded from the study. Subjects with mild abnormality of symmetry will be permitted to enroll, but subjects with moderately or severely abnormal ratings of symmetry will be excluded from the study. Subjects unable to pronounce three or more pre-selected words to evaluate lip movement will be excluded from the study (see [Sections 12.6.1](#) and [12.6.2](#)).

Randomization at Baseline:

Pre-treatment photographic imaging will be obtained to document baseline condition. At the treatment session, each of the eligible subjects randomized to treatment will be treated with *Restylane* for optimal lip augmentation. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects randomized to the control group will receive no treatment at baseline.

A Subject Diary will be dispensed for daily completion over the first two weeks after randomization. The Diary requires recording of the presence (none) or, if so, the extent (tolerable, affects daily activities, disabling) of each of the following listed events around the lips: bruising, redness, swelling, pain, tenderness, itching, or other.

The subject will be scheduled for a follow-up visit on Day 3 (72 hours) (Visit 3) for adverse event assessment, assessment of lip texture, lip firmness, lip symmetry, lip movement, lip function, lip sensation, palpability, mass formation, and recording of concomitant medication, and photographic imaging.

A clinic visit will be scheduled for two weeks, and subjects will be instructed to return the Diary at the 2-Week visit.

Subjects will return at 2 weeks for Diary collection, safety assessments, GAIS assessments by the Treating Investigator and subject, and MLFS assessments of the lips by the Treating Investigator, as well as photographic imaging. Touch-up with *Restylane* (as randomized) will be provided at 2 weeks, if appropriate to achieve optimal correction. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved. Baseline photographs can be employed to assist in this determination for the live assessment. If touch-ups are given at the 2 Week Follow-Up

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visit (Visit T), another 2 Week Follow-Up visit (Visit 4) must be scheduled 2 weeks after the touch-up treatment visit. Visit 4 will then be calculated from the touch-up visit.

At Visits 4-10 (Weeks 2, 4, 8, 12, 16, 20, and 24) the Treating Investigator will score upper and/or lower lip fullness for the randomized lip(s) using separate five grade Medicis Lip Fullness Scales (MLFS) with photoguides for each (one scale for upper lip and one scale for lower lip): 1 – Very Thin; 2 – Thin; 3 – Medium; 4 – Full; 5 – Very Full. In addition, at Week 8 and thereafter, the Blinded Evaluator will score upper and/or lower lip fullness using the MLFS to assess the randomized lip(s). The Blinded Evaluator MLFS at Week 8 in the upper and lower lips are the co-primary effectiveness endpoints. The Treating Investigator and subject will assess improvement from baseline at each time point using a 7-point Global Aesthetic Improvement Scale (GAIS) (-3 = Very Much Worse; -2 = Much Worse; -1 = Worse; 0 = No Change; 1 = Improved; 2 = Much Improved; 3 = Very Much Improved). Photographs of baseline condition may be used to refresh recollection.

6-Month Treatment:

At Week 24 (Visit 10), subjects who were initially randomized to treatment will receive a second treatment with *Restylane*. If the subject does not want to be re-treated, the reason for this decision will be documented. Subjects who were initially randomized to no treatment will receive their first treatment with *Restylane* (both lips for subjects with Fitzpatrick skin types I, II, and III or eligible lip(s) for subjects with Fitzpatrick skin types IV, V, or VI). All subjects will be treated with *Restylane* for optimal lip augmentation. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved. Investigators will be asked to assess subjects with prior randomized treatment for signs of difficulty upon repeat injection, such as difficulty during injection due to presence of scar tissue or previous filler (see [Section 12.6.5](#)). A Subject Diary will be dispensed for daily completion over the first two weeks after 6-Month treatment and re-treatment.

The subject will be scheduled for a follow-up visit (72 hours) after the 6-Month treatment (Visit 11) for adverse event assessment, assessment of lip texture, lip firmness, lip symmetry, lip movement, lip function, lip sensation, palpability, mass formation, and recording of concomitant medication, and photographic imaging. A clinic visit will be scheduled for two weeks and subjects will be instructed to return the Diary at the two-week visit.

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Subjects will return 2 weeks later (Visit T 2) for Diary collection, safety assessments, GAIS assessments by the Treating Investigator and subject, and MLFS assessments of the lips by the Treating Investigator, as well as photographic imaging. Touch-up with *Restylane* will be provided at 2 weeks, if appropriate to achieve optimal correction. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved. Baseline photographs can be employed to assist in this determination for the live assessment. If touch-ups are given at the 2 Week follow-up visit, another 2 Week Follow-Up visit (Visit 12) must be scheduled 2 weeks after the visit T 2. Visit 12 will then be calculated from the touch-up visit (T 2). Subjects will be scheduled to return 4 weeks after the 6-Month treatment or touch-up (Visit 13) and will receive MLFS assessment by the Treating Investigator, GAIS assessment by Treating Investigator and subject, and all safety assessments including evaluation of lip texture, firmness, symmetry, movement function, sensation, and mass formation.

Safety and Effectiveness Assessments:

All safety evaluations will be performed by a study staff member (other than the Treating Investigator and Blinded Evaluator) that is qualified by training and experience to perform safety assessments. Lip texture, firmness and symmetry will be scored at screening, 72 hours, and at Weeks 2, 4, 8, 12, 16, 20, 24, 72 hours post-treatment, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment. These parameters will be rated as “Normal” or “Abnormal.” All abnormal ratings will be further assessed as mild, moderate, or severe (see [Section 12.6.1](#)) and all test scores will be recorded. Subjects will be assessed for lip movement, function, and sensation (see [Section 12.6.2](#)) at screening, 72 hours, and at Weeks 2, 4, 8, 12, 16, 20, 24, 72 hours post-treatment, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment. Lip movement will be tested by assessing the ability of the subject to pronounce a pre-selected series of words. Lip function will be tested by assessing the subject’s ability to suck liquid through a straw.

Lip sensation will be tested using two methods: 1) Monofilament test - assessing the subject’s ability to feel the sensation of a 0.4G monofilament on 3 points on the upper lip and 3 points on the lower lip, and 2) Cotton Wisp test - assessing the subject’s ability to feel the sensation of a cotton wisp on 3 points on the upper lip and 3 points on the lower lip. The 3 different points on the upper and lower lips will be tested randomly. Subjects will be blindfolded and asked to acknowledge sensation or lack of sensation at each point.

Device palpability will be assessed at each scheduled post-treatment visit and will be assessed whether or not the palpability is the normal expected feel. Mass formation will

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be assessed at all visits. Unexpected feel or mass formation will be recorded as an adverse event.

Lip fullness augmentation will also be assessed after the study completion using photographic images from all time points as compared to baseline condition by an Independent Photographic Review (IPR) consisting of three off-site reviewers. Sets of lip images for baseline, 72 hours, 2, 4, 8, 12, 16, 20, 24 weeks, 72 hours post-treatment, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment will be presented to the IPR in pairs with one set being the baseline and the IPR evaluator asked to score lip augmentation using the MLFS.

7.2. STUDY SUBJECT ASSIGNMENT, RANDOMIZATION, & BLINDING

Study participants meeting all inclusion/exclusion criteria will be randomly assigned to one of two groups in a 3:1 ratio:

- Treatment with *Restylane* for lip augmentation
or
- No treatment – control

A group of 150 subjects with Fitzpatrick skin types I, II, or III must have the required MLFS score for both upper and lower lips to be enrolled. A minimum of 30 subjects with darker skin types based on classification of Fitzpatrick skin types IV, V, or VI (see below) will be included in enrollment. This group of subjects must have the required MLFS score for at least one lip (either upper or lower) to be enrolled.

Fitzpatrick Skin Type Scale	
Skin Type	Description
I	Extremely fair, always burns, never tans
II	White, always burns, sometimes tans
III	White, sometimes burns, always tans
IV	Olive or light brown, rarely burns, always tans
V	Brown, never burns
VI	Heavily pigmented or black, never burns

The randomization will be prepared by a statistician and will be stratified by Fitzpatrick skin type (I-III, IV-VI). Study participants that qualify for inclusion will be randomized. Randomization will be assigned centrally. At the time for randomization, the subject's initials, date of randomization, randomized treatment, and the signature of the Investigator must be documented. The Blinded Evaluator will be blinded to treatment assignment. Blinded Evaluators and IPR will not have access to the randomization code

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or the Treating Investigator/subject CRFs since these documents refer to treatment information and treatment schedules.

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7.3. SCHEDULE OF EVENTS

A table outlining the schedule of procedures for this study is included in [Appendix A](#).

7.4. DURATION OF SUBJECT PARTICIPATION

The total duration of a subject's participation in the study will be up to 9 months from the time of initial screening until the final follow-up visit.

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8. ELIGIBILITY

8.1. SELECTION OF STUDY POPULATION

This is a multi-center US study with a planned enrollment of up to 180 subjects at up to 15 study centers. Subjects meeting all inclusion/exclusion criteria will be randomized at entry in a 3:1 ratio to *Restylane* treatment or no treatment. A group of 150 subjects with Fitzpatrick skin types I, II, or III must have the required MLFS score for both upper and lower lips to be randomized. A minimum of 30 subjects with Fitzpatrick skin type IV, V or VI who meet the MLFS score requirement of 1 (Very Thin) or 2 (Thin) on either upper, lower, or both lips will be randomized into the group evaluated for both safety and effectiveness.

8.1.1. INCLUSION CRITERIA

Individuals eligible for inclusion in the study:

1. Males or non-pregnant, non-breast feeding females, 18 to 65 years of age.
2. Subjects seeking augmentation therapy for the lips.
3. Subjects with Fitzpatrick skin types I, II, or III with a score of 1 (Very Thin) or 2 (Thin) on BOTH upper and lower lips on the MLFS as assessed at baseline by the Treating Investigator. The MLFS score for the upper lip and lower lip do not have to be equal as long as each score is 1 (Very Thin) or 2 (Thin). Subjects with Fitzpatrick skin types IV, V, or VI with a score of 1 (Very Thin) or 2 (Thin) on either upper or lower or both lips on the MLFS as assessed at baseline by the Treating Investigator are eligible for enrollment.
4. Subjects with the willingness to comply with the requirements of the study, including sequential photography or imaging for which copyright will be held by the Sponsor.
5. Subjects willing to abstain from any other facial plastic surgical or cosmetic procedures for the 9 months of the study (e.g., laser or chemical resurfacing, facelift, etc). Subjects may have facial cosmetic procedures outside the area of assessment (e.g., botulinum toxin above the orbital rim, etc.) either before or contemporaneously with lip augmentation.
6. Subjects willing to give written informed consent to participate in the study including release of copyright of facial images.

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7. Women of childbearing potential must be willing to use an acceptable form of birth control during the study period.
8. Women must be willing to take a urine pregnancy test at baseline and at the 6-Month visit.

8.1.2. EXCLUSION CRITERIA

The presence of any of the following will exclude the potential study participant from entry into the study:

1. A history of allergy or hypersensitivity to injectable hyaluronic acid gel.
2. A history of the presence of any disease on entry which may result in changes in facial contour or edema of the face during the course of the study, such as inflammation, infection, facial psoriasis, herpes zoster, acanthosis, cancer, precancer, actinic keratosis, etc.
3. A history of the use of any biodegradable or non-biodegradable tissue augmentation therapy or aesthetic facial surgical therapy below the level of the lower orbital rim, e.g., injection or other form of implantation of tissue augmenting substances, fillers, fat augmentation, Botox[®] injections, facelift, or dental work in the preceding eight months, or plans to use these substances or have these procedures during the study.
4. The presence of any contraindication to the implant procedures, including use of platelet inhibiting agents (e.g., aspirin) or other anticoagulant, in a relevant period before study entry.
5. A history of severe allergies or multiple allergies manifested by anaphylaxis or a history of a hypotensive crisis in response to radio-contrast media or other osmotic agent.
6. The presence of any condition, which in the opinion of the Investigator, makes the subject unable to complete the study per protocol (e.g., subjects not likely to avoid other facial cosmetic treatments; subjects not likely to stay in the study for up to 9 months because of other commitments, concomitant conditions, or past history; subjects anticipated to be unreliable; or subjects who have a concomitant condition that might confuse or confound study treatments or assessments).
7. The presence of known allergies or hypersensitivity reactions to local topical anesthetics or nerve blocking agents (if such products are intended to be used for that subject).

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8. The presence of cancerous or pre-cancerous lesions in the area to be treated.
9. A history of prior surgery to the upper or lower lip
10. A history of prior significant trauma, such as dog bite or laceration, to the upper or lower lip resulting in formation of a scar.
11. Presence of facial hair that could interfere with MLFS evaluation.
12. A history of herpes labialis and an outbreak within 4 weeks of study entry or with four or more outbreaks in the 12 months prior to study entry.
13. The presence of mild, moderate, or severe abnormal rating for texture or firmness (see [Section 12.6.1](#)) or detection of any abnormal lip structure, such as a scar or lump.
14. The presence of moderate or severe abnormal rating for lip symmetry (see [Section 12.6.1](#)).
15. The presence of abnormal rating in lip movement, with inability to pronounce three or more of the pre-selected words (see [section 12.6.2](#)).
16. The presence of abnormal rating in lip function, with inability to effectively suck water through a straw (see [section 12.6.2](#)).
17. The presence of abnormal rating in lip sensation, with inability to feel a 0.4G monofilament or a cotton wisp at any site on the lip (see [section 12.6.2](#)).
18. The presence of any mass formation at screening.
19. Current use of immunosuppressive therapy.
20. A history of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), dermatomyositis (DM) or scleroderma.
21. Participation in any interventional clinical research study within 30 days prior to randomization.

8.2. SCREEN PROCEDURES

The following screening procedures will be performed no more than 28 days prior to the first administration of the study product.

Obtain written informed consent before initiating any study specific procedures.

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Record the subject's medical history. Significant and/or related surgical events and medical conditions will be recorded on the medical history CRFs for all enrolled subjects.

Detailed information regarding the medication taken within 30 days will be recorded on the Concomitant/Prior Medication CRFs. This will include all prescription medications and OTC products taken within 30 days, prior to the first administration of the study product. If medications related to a pre-existing (concomitant) disease unrelated to the study entry criteria are being taken, the nature, degree and/or severity of this concomitant disease will be documented on the Medical History CRF.

Subjects with Fitzpatrick skin types I, II, or III must have a score of 1 (Very Thin) or 2 (Thin) on BOTH upper and lower lips on the MLFS as assessed at baseline by the Treating Investigator to be eligible for enrollment. The group of subjects with Fitzpatrick skin types IV, V, or VI must have the required MLFS for at least one lip (either upper or lower) as assessed at baseline by the Treating Investigator to be enrolled.

At screening, subjects with any abnormal rating of lip texture, firmness, function, or sensation will be excluded from the study. Subjects with mild abnormality of symmetry will be permitted to enroll, but subjects with moderately or severely abnormal ratings of symmetry will be excluded from the study. Subjects unable to pronounce three or more pre-selected words to evaluate lip movement will be excluded from the study (see [Sections 12.6.1](#) and [12.6.2](#)).

8.3. STUDY SUBJECT IDENTIFICATION

Study subjects will be identified by a two-digit investigator site number (YY) and a 3-digit subject number (XXX) as follows: YY-XXX. Subject initials will be recorded as well (AAA). If the subject does not have a middle initial, a hyphen will be used as a substitute (e.g., A-A). Subject confidentiality will be maintained by use of this method of study subject identification. Subjects must be informed that digital photography, obtained and transferred to the Sponsor, may contain individual subject identifying facial features.

8.4. STUDY SUBJECT WITHDRAWAL OR PREMATURE TERMINATION

8.4.1. VISIT FAILURE

If a subject fails to return for a follow-up visit, reasonable efforts must be made to determine the reason(s) why the subject failed to return for a necessary visit and the reason(s) must be recorded in the source documentation. The study protocol provides for visit windows, therefore, an effort should be made to re-schedule the visit within the visit window. Additionally, if study procedures can be completed telephonically (in the view

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of the Investigator) or by some other means, an attempt should be made to complete all those portions of the study visit by alternative means of communication with the study subject.

8.4.2. CRITERIA FOR PREMATURE WITHDRAWAL / DISCONTINUATION

The reasons for a subject discontinuing from the study will be recorded in the CRF. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completing the protocol. Subjects must be permitted to withdraw from the study at any time for any reason. Subjects may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, compliance or other reasons. In general, subjects should not be withdrawn by Investigators prior to completion of the study unless there is documentation of any of the following:

- The protocol treatment administration has not been completed and the Investigator believes that the study subject has experienced significant or disabling treatment related adverse event(s) that can be diminished or avoided by study subject withdrawal. Generally, this would not be the case when treatment is administered only in the early part of the study and follow-up is composed of data collection only.
- Study subject withdrawal is otherwise in the best interests of the health of the study subject. A withdrawal for medical reasons should document the specific condition for removing the subject and set forth the anticipated harm or detriment.
- Lost to follow-up (See 8.4.1)
- A protocol violation that precludes both further safety and effectiveness assessment.

In general, study subject withdrawal after study treatment completion should be avoided because follow-up study procedures permit careful oversight and management of the study subject. Since the statistical analysis is designed as an intent-to-treat analysis, including safety data from all study subjects exposed to the product, study subjects should not be withdrawn for protocol violations, such as treatment of study subjects discovered to have been ineligible, unless ongoing study treatment is deemed potentially harmful or unsuitable because of the protocol violations. All protocol violations must be documented, including the basis for the violation. A discontinuation must be reported immediately to the Sponsor if it is due to a serious adverse event.

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The final safety evaluation required by the protocol will be performed at the time of the study discontinuation, if possible.

A withdrawn subject may not be replaced without approval of the Sponsor.

8.4.3. SCREEN FAILURES

The Informed Consent Form signed by the subject should be kept with the source document for subjects who do not pass the screening procedures. The documentation should include identification of the eligibility criterion or criteria that was not met. When the protocol includes screening procedures that are not a part of the routine care of the study subject, failure of the study subject to pass the screening procedure should not be identified as a withdrawal unless the study subject has received the study treatment. In such cases, the specified form for the subject log should be completed and documentation should include identification of the eligibility criterion or criteria that was not met.

8.4.4. DOCUMENTATION

All subject withdrawals will be fully documented in the CRF. A withdrawn subject may not be replaced without written approval of the Sponsor. In cases of subject withdrawal, completion of all study safety evaluations through to the end of the study should be obtained when possible.

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9. TREATMENTS AND STUDY PRODUCTS

9.1. PRODUCT IDENTITY AND TREATMENTS ADMINISTERED

9.1.1. RESTYLANE

Restylane is composed of a clear, colorless and transparent gel which consists of 20 mg/ml hyaluronic acid biosynthesized by *Streptococcus sp.* of bacteria, chemically-crosslinked with BDDE, and suspended in physiological buffer at pH=7. The gel is sterile, viscoelastic and free from products of animal origin. Pre-testing for hypersensitivity is not required. *Restylane* is packaged in sterile 1.0 mL syringes and supplied with a sterilized 30G x ½ inch needle. For this study, commercial *Restylane* supplies will be used but will be over-labeled as an investigational device.

9.2. CLINICAL SUPPLIES

9.2.1. PACKAGING AND LABELING

Each box of *Restylane* contains one syringe in a blister pack. *Restylane* will be provided with approved labeling. Approved labeling does not include use for lip augmentation. *Restylane* boxes will be labeled on the outer container with the following text: "CAUTION - Investigational Device. Limited by Federal law to investigational use." *Restylane* is manufactured, packed and labeled by Q-Med AB, Uppsala, Sweden.

9.2.2. DISPENSING

The Treating Investigator should use the amount of dermal filler (*Restylane* as randomized) necessary to achieve an optimal correction of the lips for each randomized subject. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject.

9.2.3. STORAGE

The *Restylane* syringe can be stored at a temperature of up to 25°C, and should be protected from sunlight and freezing. Opened packages or syringes should not be re-used.

9.3. ACCOUNTABILITY

The product will be released to the Investigator after approvals of the study protocol have been received by the Sponsor from the Institutional Review Board or Ethics Committee. Product accountability must be maintained for *Restylane* provided for this study. The Principal Investigator is responsible for ensuring that accurate records of the receipt of all investigational products shipped by the Sponsor, including date received, lot number, and

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amount received, are maintained. Dispensing records of all investigational products will also be maintained including the date, amount dispensed, and the subject receiving the investigational products. All unused investigational products must be returned to the Sponsor or designee or destroyed immediately after the study is completed. Products deliberately and/or accidentally destroyed at shipment or at a study center should be accounted for and documented. Used syringes and needles or other study medical supplies, if applicable, should be destroyed according to the procedures at the clinic, unless instructed otherwise. Disposal of biohazardous material, i.e., contaminated syringes and needles, must conform to applicable laws and regulations. The study products must not be used outside the study. All clinical supplies must be accounted for at the termination of the study and a written explanation provided for discrepancies.

9.4. DOSE ADMINISTRATION

9.4.1. INJECTION TECHNIQUE - RESTYLANE

The treatment site should be cleaned with a suitable antiseptic solution. If anesthetic is used (topical, infiltrative or regional block) the area should be cleaned after anesthesia is obtained. *Restylane* is administered using a thin gauge needle. Before injecting, the air is removed from the syringe up to the point where a droplet is visible at the tip of the needle.

Restylane is to be administered by submucosal injection.

Care should be taken to avoid intramuscular injection. This can often be recognized by an increased force of injection required compared to submucosal injection. Injection techniques may include linear retrograde threading, linear antegrade threading and the serial puncture technique.

To enhance the vermilion of the lip, the retrograde linear threading technique is most advisable. The needle is inserted along the intended path and depth of implantation, typically from lateral towards the medial. *Restylane* is then injected while pulling the needle slowly backwards. Injection should stop just before the needle is pulled out from the skin to prevent superficial deposition of the implant. Lips should be fully corrected, but not overcorrected. The injection site should be massaged to conform to the contour of the surrounding tissues. This procedure can be repeated at or near the same site as needed to develop the intended enhancement of the lip. Additional implant material can be deposited into the body of the lip using the serial puncture or antegrade threading technique. Care should be taken to avoid excess deposition of material into individual areas. After each injection, the lip should be observed to assess the degree of enhancement and the uniformity of the implant. The lips should be gently palpated to ensure an even deposition of the implant. Palpated “skip areas” should be treated with

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additional implant material or by gentle massage/kneading of the area until a uniform implant is palpable. It is recommended that the dose should not exceed 1.5 mL per upper lip and 1.5 mL per lower lip. The injector should place implant to achieve the desired level of enhancement at the visit. DO NOT OVERCORRECT.

If the treated area is excessively swollen directly after the injection, topical cooling via melting ice, “cold packs” or endothermic chemical cooling packets can be applied on the site for a short period, as per physician instructions. Method of injection (linear antegrade, linear retrograde, serial puncture, or other) and depth of injection (sub-mucosal or other) will be recorded. Total volume injected, as well as volume per lip injected, will also be collected.

9.4.2. PATIENT INSTRUCTIONS – RESTYLANE

It is recommended that the following information be shared with patients.

To report an adverse reaction, phone the study site. The study site will provide contact information to the subject.

Avoid touching your lips within the first 6 hours after treatment unless otherwise instructed by your physician.

Six hours after treatment your lips can be gently washed with soap and water and make-up can be lightly applied.

There may be slight bruising, redness, swelling, pain, tenderness and/or an itching sensation in the treated area immediately after the injection. This is a normal symptom of the injection that is temporary and generally disappears within a few days. If the symptom continues or worsens contact your study physician.

All symptoms in the treated area should be recorded in the Diary.

Do not expose the treated area to intense heat or extreme cold until the swelling and redness have resolved, unless otherwise instructed by your study physician.

Restylane is generally “palpable” without being visible, which means that you should be able to feel the product under your skin. The only visible effect should be the general increase in fullness of the lips.

9.5. TIMING OF DOSE FOR EACH STUDY SUBJECT

Treatment should be administered one or two times (6 months apart), based on randomization. A touch-up session at two weeks after treatment may be used to assure optimal correction. Optimal lip augmentation is defined as the best possible aesthetic

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result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved.

9.6. PRIOR AND/OR CONCOMITANT STUDY THERAPY

Prior and/or concomitant study therapy should be documented. Prohibited medications and facial cosmetic therapy which should preclude subject enrollment are set forth in the exclusionary criteria. Investigators may choose to use pre-operative prophylactic antibiotics as part of their normal practice in the placement of soft tissue fillers or dermal implants. Pre-operative antisepsis, and other standard peri-operative therapy will be permitted prior to implantation. Assessment should be made of the subject's analgesic needs, and local anesthetics (topical, infiltrative, or regional blocks) may be administered.

9.7. ASSESSMENT OF TREATMENT COMPLIANCE

The treatment is administered by the Treating Investigator and thus assessment of compliance is unnecessary.

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10. CONCOMITANT MEDICATION/CONDITIONS

Medications present upon entry should also be documented in the CRF. Documentation should include medications that study subjects may take on an elective basis and the general frequency of such medications also recorded or an explanation provided as to the reason for the change or addition of a medication. Medication used for anesthesia should be recorded as concomitant medication as well. To ensure the capture of the foregoing information on pre-existing conditions, sites should also be attentive to the need to document without limitation and whenever discovered: (1) all chronic, episodic or 'as needed' medications used before study enrollment; (2) prior episodic or 'as needed' therapeutic interventions, procedures or hospitalizations; and, (3) recent or planned surgical procedures.

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11. EFFECTIVENESS ASSESSMENTS

11.1. MEDICIS LIP FULLNESS SCALES (MLFS)

This study will assess the magnitude of lip fullness augmentation by *Restylane* using two separate five grade Medicis Lip Fullness Scales (MLFS) with photoguides (one scale for upper lip and one scale for lower lip). Accompanying photographs depicting the following ratings will be used to determine lip fullness for the lower lip and upper lip separately:

- 1 – Very Thin
- 2 – Thin
- 3 – Medium
- 4 – Full
- 5 – Very Full

Subjects with Fitzpatrick skin types I, II, or III must have a score of 1 (Very Thin) or 2 (Thin) on BOTH upper and lower lips on the MLFS as assessed at baseline by the Treating Investigator to be eligible for enrollment. The MLFS score for the upper lip and lower lip do not have to be equal, as long as each score is 1 (Very Thin) or 2 (Thin). The group of subjects with Fitzpatrick skin types IV, V, or VI must have the required MLFS score for at least one lip (either upper or lower) as assessed at baseline by the Treating Investigator to be enrolled. Treatment success will be defined as a one grade increase in either the upper or lower lip. The MLFS will be used to rate lip fullness by the Treating Investigator at Visit T, Weeks 2, 4, 8, 12, 16, 20, 24, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment. It will be used by the Blinded Evaluator at Week 8 and thereafter and IPR at all visits.

11.1.1. INDEPENDENT PHOTOGRAPHIC REVIEW (IPR)

Three Independent Reviewers (IPRs), blinded to the subject's randomized treatment, will perform photographic assessments of each subject's lip fullness (upper and lower) using the MLFS (see section 11.1). The IPRs will use the MLFS for comparison with photographs of each subject's lips at all study time points. For the IPR photographic assessment, a responder will be defined as a subject who has a rating of at least one grade increase from baseline on the MLFS. The IPR score will be determined as the median of the scores of the three reviewers.

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11.2. TREATING INVESTIGATOR GLOBAL AESTHETIC IMPROVEMENT SCALE (GAIS)

The Treating Investigator will rate the lip fullness for global aesthetic improvement, i.e. improvement from baseline appearance, at each post-baseline time point (except the 72-hour safety visits) using the following categorical scale.

Global Aesthetic Improvement Scale (GAIS)

Score	Rating	Definition
3	Very Much Improved	Optimal cosmetic result for the implant in this subject.
2	Much Improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject.
1	Improved	Obvious improvement in appearance from the initial condition.
0	No Change	The appearance is essentially the same as baseline.
-1	Worse	The appearance is worse than the original condition.
-2	Much Worse	Marked worsening in appearance from the initial condition.
-3	Very Much Worse	Obvious worsening in appearance from the initial condition.

The baseline archival photographs (obtained prior to injection of the implants at baseline) may be reviewed at each visit to aid in the assessment.

The GAIS assessment will be performed separately for both the upper and lower lip.

11.2.1. SUBJECT GLOBAL AESTHETIC IMPROVEMENT SCALE (GAIS)

The subjects will rate the global aesthetic improvement of the lip fullness, relative to pre-treatment appearance, using the following categorical scale:

Global Aesthetic Improvement Scale (GAIS): Subject

3	Very Much Improved	<input type="checkbox"/>
2	Much Improved	<input type="checkbox"/>
1	Improved	<input type="checkbox"/>
0	No Change	<input type="checkbox"/>
-1	Worse	<input type="checkbox"/>
-2	Much Worse	<input type="checkbox"/>
-3	Very Much Worse	<input type="checkbox"/>

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The subject will be instructed to select the one rating that best describes the degree to which the appearance of their lip(s) have changed relative to baseline. The subject can review the archival photograph (obtained at baseline) at each visit to aid in the assessment.

The assessment will be performed at two weeks after baseline and at each subsequent visit (except the 72-hour safety visits) for the upper and/or lower lip.

The GAIS assessment will be performed separately for both the upper and lower lip.

11.3. APPROPRIATENESS OF MEASUREMENTS

Ideal successful achievement of an optimal cosmetic result in a subject is attained when an objective observer identifies an improved grade. This assessment must primarily be conducted live. Identification of success must also be viewed by the subject as a subjective improvement, i.e., subject satisfaction. Thus, the endpoints identify both whether the subject identifies improvement and whether an objective evaluator believes the end result to be superior to the original condition. Additionally, as supportive assessments, a panel of three independent reviewers will evaluate photographs of each time point in pairs, with one set being the baseline and the other being the non-designated time points during the study, in order to evaluate lip augmentation using the MLFS.

11.4. PRIMARY EFFECTIVENESS VARIABLE(S)

- to identify whether *Restylane* is more effective in lip augmentation than no treatment as determined by the Blinded Evaluator assessments of lip fullness at 8 weeks after the first treatment as compared to the Treating Investigator's assessment of the baseline condition, separately in the upper and lower lips (co-primary efficacy endpoints). The Treating Investigator and Blinded Evaluator will score upper and lower lip fullness using separate five grade Medicis Lip Fullness Scales (MLFS) with photoguides for each (one scale for upper lip and one scale for lower lip): 1 – Very Thin; 2 – Thin; 3 – Medium; 4 – Full; 5 – Very Full. Treatment success will be defined as a statistically significant difference ($\alpha < 0.05$) in the proportion of subjects with at least a one grade increase in the MLFS for the Blinded Evaluator assessments (as compared to the Treating Investigator's baseline assessment of the MLFS) between the *Restylane* and no treatment groups for the co-primary efficacy analyses of the upper and the lower lips.

11.5. SECONDARY EFFECTIVENESS VARIABLES

Secondary effectiveness variables include:

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- assessment of lip fullness augmentation after treatment with *Restylane* as compared to no treatment, as measured by the Blinded Evaluator at 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, as well as 2 and 4 weeks after the 6-Month treatment, as correlated to baseline, with response determined by at least one grade increase from baseline in the upper and lower lips using the MLFS.
- assessment of lip augmentation after treatment with *Restylane* as compared to no treatment, as determined by the Treating Investigator at each time point after treatment as compared to baseline condition, with response determined by at least one grade increase from baseline in the upper and lower lips using the MLFS.
- identification of subject satisfaction with lip fullness augmentation at each time point after treatment with *Restylane* as compared to no treatment, with response determined by a score of 1 or greater on the Global Aesthetic Improvement Scale (GAIS) score from baseline in the upper and lower lips. GAIS: -3 = Very Much Worse; -2 = Much Worse; -1 = Worse; 0 = No Change; 1 = Improved; 2 = Much Improved; 3 = Very Much Improved (with improvement assessed from the baseline condition).
- identification of lip fullness augmentation at each time point after treatment with *Restylane* as compared to no treatment, with response determined by a score of 1 or greater on the GAIS as assessed by the Treating Investigator in the upper and lower lips.
- assessment of lip fullness augmentation after treatment with *Restylane* as compared to no treatment, as measured by Independent Photographic Reviewers (IPR) after assessment of photographic imaging at each time point, with response determined by at least one grade increase from baseline in the upper and lower lips using the MLFS.
- correlation among the degree of response per the MLFS (1+, 2+, 3+, 4+ grade improvement) and the GAIS scores for the Treating Investigator, separately in the upper and lower lips, to assess the trend between the two scales.
- correlation among the degree of response per the MLFS (1+, 2+, 3+, 4+ grade increase) for the Treating Investigator with the GAIS scores for the subject, separately in the upper and lower lips, to assess the trend between the two scales.
- agreement among the proportion of responders between the MLFS (with response determined by at least a one grade increase) and the GAIS (with response determined by a score of 1 or greater), for the Treating Investigator separately in the upper and lower lips.

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- agreement among the MLFS between the Treating Investigator, Blinded Evaluator, and IPR assessments, separately in the upper and lower lips.

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12. SAFETY EVALUATIONS

12.1. SAFETY ASSESSMENTS

Safety evaluations for this study include an interview with the subject at each visit by the Investigator or coordinator to elicit information about any medical occurrence that meets the definition of Adverse Event. That information should be documented in the source and CRF without regard for cause or relation to device implantation. If in the process of the interview, additional information regarding medical history or pre-planned medical or surgical procedures is revealed, proper documentation for addition to the database is necessary.

In addition to the interview, subjects will fill out a Diary for 14 days after baseline (Visit 2) and for 14 days after 6-Month treatment (Visit 10). The Investigator or coordinator should review the Diary for completion. The adverse event data recorded in the Diary will be handled separately.

It is the responsibility of the Investigator to determine severity of the Adverse Event and relatedness of the experience to the device using the definitions below. The description of each Adverse Event will include questions relating to relationship to the injection procedure and separately, relationship to the device.

12.2. DOCUMENTATION OF SAFETY ASSESSMENTS

Documentation of each Adverse Event will be fully recorded in the source and transcribed to the CRF. Included in the description of the Adverse Event will be the following:

- Local or systemic
- Severity / intensity
- Contributed to or caused by the device or procedure
- Anticipated or unanticipated adverse device effect / event
- Serious Injury or not serious

12.3. DEFINITIONS

Adverse event – An adverse event (AE) is any untoward medical occurrence or an unintended sign, symptom, or disease temporally associated with the use of the device, whether or not considered related to the device. An AE is further defined as:

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- any diagnosis, sign, symptom, or abnormal laboratory value **not** present, detected, or complained of at the baseline assessment.
- any diagnosis, sign, symptom, or abnormal laboratory value **noted at baseline** that worsens in severity or intensity or increases in frequency during the study.

Frequency – the frequency of an adverse event will be described as single, continuous event, or recurrent/intermittent.

Local adverse event – an adverse event at a localized site that does not have a systemic component. Collection of local adverse events will be further defined in the CRF as to whether it is located in the area of the device injection.

Systemic adverse event – an adverse event occurring in an organ/system that is not limited to a local presentation.

Serious injury – an adverse event that:

- is life-threatening or,
- results in permanent impairment of a body function or,
- results in permanent damage to a body structure or,
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

An adverse event that meets the definition of Serious Injury will be documented on a separate Serious Injury Report in addition to the Adverse Event page in the CRF.

Unanticipated adverse device effect / event – any serious effect on health or safety or any life-threatening problem or death caused by, or associated with, this device, if that effect was not previously identified in nature, severity, or degree of incidence in the investigational plan or Investigator Brochure. Any other unanticipated serious problem associated with this device that relates to the rights, safety, or welfare of the subjects is also considered an unanticipated adverse device effect / event.

Severity (intensity) of Adverse Events - The Investigator is to classify the severity of an adverse event according to the following definitions:

- Mild: does not interfere with routine activities, can perform daily functions
- Moderate: interferes with routine activities, can perform daily functions, but with concerted effort

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- Severe: unable to perform routine activities

Study procedure caused or contributed to the event. The Investigator is to evaluate the adverse event as to whether it was contributed to or caused by the injection procedure according to the definitions outlined in the table below.

Study device caused or contributed to the event. The Investigator is to evaluate the adverse event as to whether it was contributed to or caused by the device according to the definitions outlined in the following table.

Association	Definition
Not related	The event can be readily explained by other factors, does not follow a known response pattern to the device and no temporal relationship exists with the device.
Unknown	The relation of the adverse event has some temporal relationship to the device, is not clearly due to another condition and the involvement of the study device is unknown. The event does not follow a known response pattern to the device.
Caused by or Contributed to	The adverse event follows a reasonable temporal sequence related to treatment by the device, follows a known or suspected response pattern and a plausible alternative etiology cannot be identified.

12.4. EXPEDITED REPORTING

12.4.1. EXPEDITED REPORTING (TO MEDICIS)

All Serious Injuries will be reported to Medicis within 24 hours of the Investigator or any site staff becoming aware of the event.

Ira D. Lawrence, M.D.
Medicis Global Services Corporation (MGSC)
Cellular phone: 1-773-551-2830
Phone: 480-291-5629
Fax number: 480-291-7511
e-mail: clinicalresearch@medicis.com.

12.5. CLINICAL LABORATORY SAFETY ASSESSMENTS

There are no clinical laboratory safety assessments.

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12.6. OTHER SAFETY ASSESSMENTS

12.6.1. EVALUATION OF LIP TEXTURE, FIRMNESS, AND SYMMETRY

At screening, 72 hours, and at Weeks 2, 4, 8, 12, 16, 20, 24, 72 hours post-treatment, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment a study staff member (other than the Treating Investigator and Blinded Evaluator) that is qualified by training and experience to perform safety assessments will score lip texture, firmness, and symmetry. These parameters will be rated as “Normal” or “Abnormal.” All abnormal ratings will be rated as mild, moderate, or severe.

The following scale will be used to assess lip texture for each lip separately. The most severe score will be recorded. Subjects with any abnormal rating of texture (mild, moderate, or severe) at screening will be excluded from the study.

TEXTURE:

NORMAL	ABNORMAL		
	Mild	Moderate	Severe
Texture of the lip is even without visible undulations or excessive coarseness beyond that expected for stated age.	The lip shows a single area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) can be visualized only with close inspection.	The lip shows more than one area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that can be visualized only with close inspection. or The lip shows one area of textural irregularity (less than ¼ of the lip area) at conversational distance.	The lip shows two or more areas of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that can be visualized at a conversational distance. or The lip shows one area of textural irregularity (more than ¼ of the lip area) at conversational distance.

The following scale will be used to assess lip firmness for each lip separately. The most severe score will be recorded. Subjects with any abnormal rating of firmness (mild, moderate, or severe) at screening will be excluded from the study.

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FIRMNESS:

NORMAL	ABNORMAL		
	Mild	Moderate	Severe
Lip is supple when compressed laterally and surface distorts readily with minimal pressure. Pressure with a narrow diameter instrument (cotton-tipped applicator, toothpick etc) causes a focal depression in the surface of the lip. Upon palpation, lip is absent of abnormal structures such as scars or lumps; normal product feel without being visible.	Lip is slightly firm with lateral compression or requires slightly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump is felt, but is not visible.	Lip is firm with lateral compression or requires distinctly greater than normal pressure to distort the surface or pressure with a narrow diameter instrument (cotton-tipped applicator or toothpick) causes a broader depression in the surface of the lip. Upon palpation, an abnormal structure such as a scar or lump is felt and is visible.	Lip is very firm with lateral compression or requires significantly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump is felt and is visually distracting.

The following scale will be used to assess lip symmetry for each lip separately. The most severe score will be recorded. Subjects with symmetry rating of moderate or severe at screening will be excluded from the study.

Lip symmetry –note that lip symmetry compares the left side to the right side of an upper or lower lip individually. Thus there will be a grade for asymmetry of the upper lip and a separate grade for asymmetry of the lower lip. The investigator will observe the subjects lips closely for any asymmetry. If any asymmetry is noted, measurements of the difference in either the vertical height of the vermilion or its lateral length will be conducted in order to classify the degree of asymmetry using the table below. Additionally, subjects who have no noticeable asymmetry will undergo measurement of the vertical height of their vermilion at the midpoint between the subject’s centerline and oral commissure on each side. Measurements differing by 1 mm or less will be considered “normal” while any greater difference in measurement will result in categorization of asymmetry according to the table below.

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SYMMETRY:

NORMAL	ABNORMAL		
	Mild	Moderate	Severe
One side of the lip balances or mirrors the other side.	One side of the lip shows a 1 mm or less difference in height or a 1 mm or less difference in the length of the vermillion at repose.	One side of the lip shows a 1.1 mm to 2 mm difference in height or a 1.1 to 2 mm difference in the length of the vermillion at repose.	One side of the lip shows a greater than 2 mm difference in height or a greater than 2 mm difference in the length of the vermillion at repose.

See [Appendix B – Clinical Scales](#).

12.6.2. EVALUATION OF LIP MOVEMENT, FUNCTION, AND SENSATION

At screening, 72 hours, and at Weeks 2, 4, 8, 12, 16, 20, 24, 72 hours post-treatment, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment, a study staff member (other than the Treating Investigator and Blinded Evaluator) that is qualified by training and experience to perform safety assessments, will assess each subject’s lip movement, function, and sensation. The following tests will be administered:

Lip Movement: The subject’s ability to effectively pronounce a series of 10 pre-selected words (Member, Simmering, Drab, Babble, Spear, Peep, Fire, Staff, Verse, Liver) will be assessed. Each word pronounced correctly will score one point. A score of 8 or more pronounced correctly will be considered a normal finding. Subjects unable to pronounce three or more pre-selected words to evaluate lip movement will be excluded from the study.

Lip Function: The subject’s ability to effectively suck water through a straw will be assessed. Inability to suck water through a straw will be considered abnormal.

Lip Sensation: Lip sensation will be tested using two methods: 1) Monofilament test - assessing the subject’s ability to feel the sensation of a Semmes-Weinstein 0.4G monofilament on 3 points on the upper lip and 3 points on the lower lip, and 2) Cotton Wisp test - assessing the subject’s ability to feel the sensation of a cotton wisp on 3 points on the upper lip and 3 points on the lower lip. Inability to feel the monofilament or cotton wisp at any point will be considered abnormal. The 3 different points on the upper and lower lips will be tested randomly. Subjects will be blindfolded and asked to acknowledge sensation or lack of sensation at each point.

See [Appendix B – Clinical Scales](#).

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12.6.3. ASSESSMENT OF PALPABILITY

Product palpability in the lips will be assessed by a study staff member (other than the Treating Investigator and Blinded Evaluator) that is qualified by training and experience to perform safety assessments at 72 hours and at Weeks 2, 4, 8, 12, 16, 20, 24, 72 hours post-treatment, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment. The evaluator will answer the following questions in the CRF after the assessment is complete: ‘Is the product palpable?’ If yes, ‘is this the expected feel or unexpected feel (non-uniform density or unexpected lumpiness) for the product?’ An assessment of unexpected feel (abnormal) is to be recorded as an adverse event. See [Appendix B – Clinical Scales](#).

12.6.4. ASSESSMENT OF MASS FORMATION

Mass formation in the lips will be assessed by a study staff member (other than the Treating Investigator and Blinded Evaluator) that will be qualified by training and experience to perform safety assessments at baseline, 72 hours and at Weeks 2, 4, 8, 12, 16, 20, 24, 72 hours post-treatment, Visit T 2, and 2 weeks and 4 weeks after 6-Month treatment. Mass formation will be defined as lumps or aggregation of coherent material. An assessment of mass formation is to be recorded as an adverse event. See Appendix B – Clinical Scales.

12.6.5. ASSESSMENT OF RE-INJECTION

At Week 24, after administering the re-treatment injection, Treating Investigators will be asked to assess subjects with prior randomized treatment for signs of difficulty upon repeat injection, such as difficulty during injection due to presence of scar tissue or previous filler.

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13. STUDY PROCEDURES BY VISIT DAY

13.1. BASELINE ASSESSMENTS (VISIT 1, SCREENING VISIT)

Screening Visit and Initial Treatment (Day 0) may be performed on the same day. The following screening assessments will be performed within 28 days of baseline:

- Obtain informed consent.
- Interview for medical history (including any prior dermatological procedures or implants).
- Interview for concomitant medications/procedures.
- Obtain height and weight.
- Obtain demographic data (including determination of Fitzpatrick Skin Type).
- MLFS assessment.

Subjects with Fitzpatrick skin types I, II, or III must have a score of 1 (Very Thin) or 2 (Thin) on BOTH upper and lower lip, as evaluated by the Treating Investigator to be eligible. The MLFS score for the upper lip and lower lip do not have to be equal at study entry as long as each lip score is 1 (Very Thin) or 2 (Thin). The group of subjects with Fitzpatrick skin types IV, V, or VI must have the required MLFS score for at least one lip (either upper or lower) as assessed at baseline by the Treating Investigator to be enrolled.

- Assess eligibility.
- Study staff member assesses lip texture, firmness, and symmetry.
- Subjects with mild, moderate, or severe abnormal rating for texture or firmness are to be excluded from the study.
- Subjects with moderate or severe abnormal rating for symmetry are to be excluded from the study.
- Study staff member assesses lip movement, function and sensation (Monofilament test and Cotton Wisp test). Subjects will be excluded if unable to pronounce three or more of the pre-selected words, unable to effectively suck water through a straw, or unable to feel a monofilament or cotton wisp at any one of the designated randomized points (3 on the upper lip and 3 on the lower lip).
- Mass formation assessment by study staff member. Exclude if mass formation is present.

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- Schedule treatment visit.

13.2. TREATMENT (VISIT 2, DAY 0)

- Obtain urine pregnancy test, for all females.
- Obtain pre-treatment photographs.
- Review for concomitant medications/procedures.
- Assess adverse events if treatment day differs from screening day.
- Potential study participants who meet all inclusion/exclusion criteria and who give written informed consent to participate in the study will be randomized in a 3:1 ratio (*Restylane*-treatment/no treatment) in accordance with the randomization procedures (Section 7.2):
 - Treatment with *Restylane* for lip augmentation
or
 - No treatment for lip augmentation – control
- Achieve an "optimal cosmetic result" of lip volume. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject.
- In cases where the enrolled subject has a Fitzpatrick Skin Type of IV, V or VI and only one of the lips meets MLFS eligibility for randomization and the subject is randomized to treatment, both lips may be treated to optimal correction to improve overall symmetry, at the discretion of the Investigator in consultation with the subject. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject.
- Evaluate the subject for post-treatment AEs.
- Dispense Subject Diary and instruct subject on Diary completion.
- Schedule the 72-hour visit.

13.3. FOLLOW-UP

13.3.1. 72 HOURS (VISIT 3) (DAY 3 [\pm 24 HOURS] SAFETY VISIT)

- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events.

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- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.

13.3.2. VISIT 4 (2 WEEKS ± 3 DAYS)

- Assess MLFS – Treating Investigator.
- Assess GAIS – Treating Investigator.
- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.
- For subjects randomized to treatment, the Treating Investigator and subject evaluate the need for Touch-Up by determining if optimal lip augmentation has been achieved. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved.
 - If TOUCH-UP **is not necessary** continue visit as Visit 4, 2-week follow- up;
- Review and Collect Subject Diary.
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events.

13.3.3. OPTIONAL VISIT T (2 WEEKS ± 3 DAYS)

- Assess MLFS – Treating Investigator.
- Assess GAIS – Treating Investigator.
- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.
- Evaluate need for Touch-Up. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved.
 - If TOUCH-UP **is necessary**, VISIT 4, 2-WEEK FOLLOW-UP will be deferred and OPTIONAL TOUCH-UP T Visit will take place with product assigned at randomization.
- Review and Collect Subject Diary.
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events.

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- Perform Touch-Up treatment.
- Schedule subject for VISIT 4, 2-WEEK FOLLOW-UP appointment.

13.3.4. VISIT 5 (WEEK 4 ± 5 DAYS)

- Assess MLFS – Treating Investigator.
- Assess GAIS – Treating Investigator.
- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events.

13.3.5. VISITS 6 - 9 (WEEK 8, 12, 16, AND 20 ± 5 DAYS)

- Assess MLFS – Treating Investigator.
- Assess MLFS – Blinded Evaluator.
- Assess GAIS – Treating Investigator.
- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events.

13.3.6. VISIT 10 (WEEK 24 ± 5 DAYS); 6-MONTH TREATMENT VISIT

- Assess MLFS – Treating Investigator.
- Assess MLFS – Blinded Evaluator.
- Assess GAIS – Treating Investigator.
- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain pre-treatment photographs.
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events.
- Obtain urine pregnancy test, for all females.

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- Treat all subjects for lip augmentation (second treatment for previously randomized treated subjects and first treatment for no treatment control subjects)
- Achieve an "optimal cosmetic result" of lip volume. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved.
- In cases where only one of the lips previously met MLFS eligibility for treatment, both lips may be treated to optimal correction to improve overall symmetry, at the discretion of the Investigator in consultation with the subject. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved.
- Evaluate the subject for post-treatment AEs.
- Evaluate for assessment of difficulty during repeat injection for subjects with prior randomized treatment.
- Dispense Subject Diary and instruct subject on Diary completion.
- Inform the subject about the visit at 72 hours.

13.3.7. VISIT 11 (3 DAYS \pm 24 HOURS AFTER 6-MONTH TREATMENT VISIT)

- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events. Any subject that experiences an adverse outcome after the repeat injection will be followed for 3 months or until resolution of the adverse outcome is observed, whichever time is shorter.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.

13.3.8. VISIT 12 (2 WEEKS \pm 3 DAYS AFTER 6-MONTH TREATMENT VISIT)

- Assess MLFS – Treating Investigator.
- Assess MLFS – Blinded Evaluator.
- Assess GAIS – Treating Investigator.
- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.

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- Review and collect Subject Diary.
- The Treating Investigator and subject evaluate the need for Touch-Up by determining if optimal lip augmentation has been achieved. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved.
 - If TOUCH-UP **is not necessary** continue visit as Visit 12, 2-WEEK FOLLOW-UP;
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events. Any subject that experiences an adverse outcome after the repeat injection will be followed for 3 months or until resolution of the adverse outcome is observed, whichever time is shorter.

13.3.9. OPTIONAL VISIT T 2 (2 WEEKS ± 3 DAYS AFTER 6-MONTH TREATMENT VISIT)

- Assess MLFS – Treating Investigator.
- Assess MLFS – Blinded Evaluator.
- Assess GAIS – Treating Investigator.
- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.
- Evaluate need for Touch-Up. Optimal lip augmentation is defined as the best possible aesthetic result that can be obtained for an individual study participant, as agreed upon by the physician and subject. Subjects will not be required to receive unnecessary additional injections if optimal correction has been achieved.
 - If TOUCH-UP **is necessary**, VISIT 12, 2-WEEK FOLLOW-UP will be deferred and OPTIONAL TOUCH-UP T Visit will take place.
- Review and Collect Subject Diary.
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events.
- Perform Touch-Up treatment.
- Schedule subject for VISIT 12, 2-WEEK FOLLOW-UP appointment.

13.3.10. VISIT 13 (4 WEEKS ± 5 DAYS AFTER 6-MONTH TREATMENT VISIT) OR EARLY WITHDRAWAL

- Assess MLFS – Treating Investigator.
- Assess MLFS – Blinded Evaluator.
- Assess GAIS – Treating Investigator.

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- Assess GAIS – Subject.
- Assess lip texture, firmness, symmetry – study staff member.
- Assess lip movement, function, sensation – study staff member.
- Assess palpability, mass formation – study staff member.
- Obtain photographs.
- Interview for Concomitant Medications and Treatments.
- Interview and assess for Adverse Events. Any subject that experiences an adverse outcome after the repeat injection will be followed for 3 months or until resolution of the adverse outcome is observed, whichever time is shorter.

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14. STATISTICAL METHODS

14.1. ANALYSIS POPULATIONS

Two analysis populations will be defined for this study:

The Intent-to-treat (ITT) population includes all subjects treated with *Restylane* or those randomized to receive no treatment. The primary efficacy and all safety analyses will be based on the ITT population.

The Per-Protocol (PP) population includes all subjects in the ITT population who have effectiveness evaluations at the co-primary endpoints and who have no major protocol deviations. The efficacy analyses will be repeated on the PP population if there is at least a 10% difference in the number of subjects in the PP and ITT populations.

14.2. ANALYSIS OF PRIMARY OBJECTIVES

The proportion of Responders (i.e., at least a one grade increase from the Treating Investigator's baseline assessment of the MLFS for the upper and lower lip) will be calculated for each treatment group at Week 8 for the Blinded Evaluator assessment. The statistical difference in the proportion of Responders between the *Restylane* and no-treatment subjects will be evaluated using Fisher's Exact Tests for the ITT population. The treatment will be deemed a success if the p-value for the treatment difference on the co-primary endpoints is less than 0.05 for the analysis of the upper lip AND for the analysis of the lower lip.

Subjects who did not have a Week 8 assessment will have their data imputed using a hot deck procedure. Additional sensitivity analyses will be conducted imputing missing data with the subject's baseline MLFS value as well as with their last observation carried forward.

Exploratory summaries of the co-primary efficacy endpoint will be conducted for the following parameters: study site, age (categorized as <50 or ≥50 years of age), gender, race (Caucasian, Non-Caucasian), need for touch-up (yes, no), method of injection (linear antegrade, linear retrograde, serial puncture, or other), depth of injection (sub-mucosal or other), and volume of injection. Logistic regression modeling will be used to determine the impact of these parameters on the co-primary efficacy endpoints.

14.3. ANALYSIS OF SECONDARY OBJECTIVES

The proportion of Responders on the MLFS will be calculated for each treatment group at Weeks 8, 12, 16, 20, and 24 for the Blinded Evaluator, as well as at Weeks 2, 4, 8, 12, 16,

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20, 24, as well as 2 and 4 weeks after the 6-Month treatment for the Treating Investigator and IPR assessments, separately for the upper and lower lips. The proportion of Responders on the GAIS will be calculated for each treatment group at Weeks 2, 4, 8, 12, 16, 20, 24, as well as 2 and 4 weeks after the 6-Month treatment for the Treating Investigator and subject assessments, separately for the upper and lower lips.

The statistical difference in the proportion of Responders (based on the MLFS or the GAIS) between the *Restylane* and no-treatment subjects will be evaluated using Fisher's exact tests. Missing data will not be imputed for the secondary objectives.

The correlation among the degree of response per the MLFS (1+, 2+, 3+, 4+ grade increase) and the GAIS scores for the Treating Investigator and subject assessments at each time point will be determined using Spearman's rank correlation coefficients, separately for the upper and lower lips.

Agreement among the proportion of responders between the MLFS (with response determined by at least a one grade increase) and the GAIS (with response determined by a score of 1 or greater) will be determined using weighted kappa statistics, for the Treating Investigator assessments, separately for the upper and lower lips.

Agreement among the MLFS values for the Treating Investigator, Blinded Evaluator, and IPR assessments will be determined using weighted kappa statistics, separately for the upper and lower lips.

The proportion of responders based on the MLFS and the GAIS assessments will also be summarized for the subset of subjects with Fitzpatrick skin types IV, V, or VI, separately for the upper and lower lips.

14.4. SAMPLE SIZE

For the primary efficacy assessment of the superiority of treatment with Restylane as compared to no treatment, a sample size of at least 120 treated subjects and 40 no treatment subjects for each lip (accounting for a 10% drop-out rate) will yield 99% power to detect a difference in response at Week 8 of 25% in the no treatment subjects versus 70% in the treated subjects (based on a one-sided Fisher's Exact test with $\alpha=0.05$).

With a total of at least 135 treated subjects, the distance from the estimated incidence of an adverse event to the upper limit of a one-sided 95% confidence interval will be at most 0.071. An adverse event that will occur in 1% of the population will have a 0.74 probability of being observed in at least one subject in the clinical study of 135 treated subjects (based on binomial probability). Within the subgroup of at least 22 treated subjects with Fitzpatrick skin type IV, V or VI, the distance from the estimated incidence

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of an adverse event to the upper limit of a one-sided 95% confidence interval will be at most 0.175. An adverse event that will occur in 5% of the population of people with Fitzpatrick skin types IV, V, or VI will have a 0.67 probability of being observed in at least one subject in the clinical study of 22 treated subjects with Fitzpatrick skin types IV, V, or VI (based on binomial probability).

14.5. INTERIM REPORT

There is no interim analysis planned for this study.

14.6. ANALYSIS OF SAFETY

Safety analyses will be performed on the ITT population. The frequency and percentage of patients with adverse events will be summarized by coded body system and preferred term for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA). At each level of summarization (global, system organ class, and preferred term), a patient will be counted once if he/she has reported one or more adverse events at that level. Tabular summaries will be presented for all adverse events, by severity, by relationship to treatment, and for serious adverse events. Duration and time to onset of treatment-emergent adverse events will be summarized by treatment group using descriptive statistics (mean, median, standard deviation, minimum and maximum value). Adverse events will also be summarized by the method of injection (linear antegrade, linear retrograde, serial puncture, or other) and depth of injection (sub-mucosal or other), as well as separately for subjects with Fitzpatrick skin type of IV, V or VI. No statistical testing will be performed.

The frequency and percentage of Diary recordings of the presence or not, as well as the extent (tolerable, affects daily activities, disabling), of bruising, redness, swelling, pain, tenderness, or itching around the lips will be summarized after the initial and 6-Month treatments.

The frequency and percentage of subjects with abnormal lip texture, lip firmness, and lip symmetry, as assessed by the study staff member will be summarized for baseline, 72 hours, Weeks 2, 4, 8, 12, 16, 20, and 24, as well as 72 hours and Weeks 2 and 4 after the 6-Month treatment. The frequency of and percentage of subjects in which the product was palpable will be summarized for 72 hours, Weeks 2, 4, 8, 12, 16, 20, and 24, as well as 72 hours, Weeks 2 and 4 after the 6-Month treatment. The frequency and percentage of subjects with abnormal lip movement, lip function, and lip sensation (Monofilament test and Cotton Wisp test), as assessed by the study staff member, will be summarized for baseline, 72 hours, Weeks 2, 4, 8, 12, 16, 20, and 24, as well as 72 hours and Weeks 2 and 4 after the 6-Month treatment. The frequency and percentage of subjects with mass

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formation, as assessed by the study staff member, will be summarized for baseline, 72 hours, and Weeks 2, 4, 8, 12, 16, 20, and 24, as well as 72 hours and Weeks 2 and 4 after the 6-Month treatment.

After the 6-Month treatment, the frequency and percentage of subjects with signs of difficulty during the repeat injection will be summarized.

14.7. DATA HANDLING

Standards for data handling will be established as part of the statistical analysis plan, including how data are transferred from case report forms to perform analyses, data verification, and the mechanism for resolution of discrepancies. When the database is declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made with written documentation explaining the reason for changes and any subsequent analyses or data presentation must identify the database version used.

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15. MANAGEMENT/COMPLIANCE/QUALITY ASSURANCE

15.1. STUDY TERMINATION

The Protocol may be terminated by Medicis immediately upon notice to the Investigator, if any of the following conditions occur:

- If the authorization and approval to perform the Protocol is withdrawn by any authorized regulatory agency or Institutional Review Board or the study is placed on clinical hold.
- If new animal, human and/or toxicological test results from this or other studies support termination of the Protocol.
- If the emergence of any adverse reaction or side effect with the study product in the study or elsewhere is of such magnitude or incidence in the opinion of Medicis to support termination.
- Medicis may also terminate the study for any internal business reasons at Medicis' sole discretion.
- If Medicis fails to secure compliance with requirements of the protocol and Good Clinical Practice at a specific site the study must be terminated at that site.

In the event of a termination, Medicis will provide information on the handling of currently enrolled subjects who have not completed the protocol.

15.2. MONITORING

Monitoring visits provide Medicis with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, assure that all protocol requirements, applicable FDA regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records. Monitoring is required by federal regulations. The Investigator will allow Medicis representatives to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and corresponding portions of office, hospital, and laboratory records (source documents) of each study participant. CRFs must be up-to-date and available for each monitoring visit. The Investigator or appropriate personnel must be available during the monitoring visits.

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15.3. MEDICIS AUDITS/QUALITY ASSURANCE

Medicis may require a site audit for cause or as a means to prepare the site for inspection by outside regulatory authorities. The Investigator or appropriate personnel must be available during audits.

Quality assurance includes verification of data by data management in the event of inconsistency, missing data, or apparent discrepancies. During data management, queries to resolve such issues will be sent to the site. The study cannot be closed until all queries are addressed. Prompt response to queries is required.

15.4. INSPECTION BY REGULATORY AGENCY

The Investigator shall permit access to the records of the investigation to an authorized Investigator of the US Food and Drug Administration or other national regulatory body who properly presents credentials. U.S. governmental authorities must be permitted prompt access, at reasonable times and in a reasonable manner, to all study information, including confidential information, when relating to a clinical investigation of a drug study conducted under an IND exemption under 21 CFR Part 312 (*see* 21 CFR § 312.58) or, for an investigation of a medical device study conducted under an Investigational Device Exemption, under 21 CFR § 812.145. However, an FDA Investigator of a device study is NOT permitted to see subject identifier information unless FDA has reason to suspect that adequate informed consent was not obtained or that reports required to be submitted to Medicis or IRB have not been submitted or are incomplete, inaccurate, false, or misleading. The study informed consent should advise the enrolled subject of such legally required access to confidential information.

15.5. CASE REPORT FORMS / SOURCE DOCUMENTS

Case report forms will be used for transcribing all data from source documents for each subject. Source documents are the point of first entry for all data collected. The Investigator will ensure that the case report forms are properly and completely filled in. Case report forms must be completed for all subjects who have given informed consent and have been admitted to the study. CRFs must be monitored against source documents. If data in the CRF is not duplicated in a source document, a source document should be created and maintained by the site to capture that information. Source documentation for subjects include but are not limited to the physician's subject records or the hospital's computer database, diaries, photographs, x-rays and electrocardiograms. All source documents will be maintained at the study site. In rare cases, source data may be recorded directly onto the case report forms and if so, a copy of the CRF page must be maintained among source documents by the Investigator.

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All recordings on the CRFs are to be done in black ink. Military time should be used for all time entries. Dates should be entered in dd/mmm/yyyy format. Changes and/or additions to data entered on original case report forms must be made in the following manner: The original entry will be lined out with a single line through the error (neither erasures nor correction fluid should be used) so as to leave it legible. The correction will be entered, initialed, and dated by the person making the correction. The Principal Investigator or delegate may enter corrections on the original case report forms. The CRFs themselves contain more comprehensive information and instructions on completion and handling.

Whenever possible, an original recording of an observation should be retained as source document.

15.6. STUDY RECORDS/SOURCE DOCUMENTS MAINTENANCE

All records pertaining to the conduct of the clinical study, including signed CRFs, informed consent forms, drug accountability records, source documents, and other study documentation must be retained until:

- In the case of a drug, two years after the United States Food and Drug Administration (FDA) approves a relevant application (e.g., Biological License Application or BLA; New Drug Application or NDA);
- In the case of a medical device, two years after the investigation is completed or terminated or upon approval of a Premarket Application (PMA), as applicable;
- Two years following termination or withdrawal of the Investigational New Drug application (IND); or,
- For the length of time requested by Medicis, if longer.

In any case, the Investigator must not destroy any records associated with the study without contacting Medicis and receiving approval. The Investigator must notify Medicis in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, he/she must contact Medicis to arrange alternative record storage options. Study documentation includes all case report forms, data correction forms, source documents, monitoring logs, Medicis-Investigator correspondence, protocols and amendments, clinical supplies receipt, dispensing and final disposition records, IRB correspondence and approvals, signed consent forms, and Statement of Investigator forms.

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15.7. PROTOCOL COMPLIANCE

The Investigator must comply with all terms of the protocol. All protocol deviations must be described clearly on the case report form. The subject is also expected to comply with the protocol as set forth in the informed consent and implicit in subject participation. During the recruitment phase, it is imperative that the subjects understand that they are expected to return for the designated follow-up treatment and evaluations, and the importance of doing so. The informed consent provides for medical record, telephonic or other electronic follow-up if necessary. If the subject is not willing to participate in the follow-up, he/she must be excluded from participation.

15.8. PROTOCOL AMENDMENTS

All protocol amendments and exceptions, with the exception of those which remove an emergency or immediate health risk to the subject, must be approved in writing by the IRB and Medicis before implementation. The provisions for emergency amendment are set forth in federal regulations and require, if feasible, prior contact with Medicis, the IRB and federal regulatory agencies. If contact is not feasible before the change, Medicis, the IRB, and federal regulatory agency must be contacted as time permits. All changes to the final study protocol must be documented in a written protocol amendment either before implementation or, in the event of an immediate health hazard, within 5 working days.

15.9. DEVIATION FROM THE PROTOCOL

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and remove the participant from immediate hazard as discussed above.

Deviations from the protocol may nevertheless occur (*e.g.*, subject failure to attend scheduled visit during a visit window, accidental omission of notations from the CRF, misunderstanding with regard to visit procedures, etc.). Any deviation from the protocol must be fully recorded in the source documents to permit analysis of the effect of the deviation on the data collected, subject safety, or data analysis.

Deviations from the protocol must be reported to the IRB according to their policies.

15.10. CONFIDENTIALITY/STUDY SUBJECT IDENTIFICATION

All information not previously published concerning the test product and Medicis' research, including patent applications, manufacturing processes, basic scientific data, information in the Investigator Brochure, this protocol, or other information provided by

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Medicis/Q-Med, is considered confidential and should remain the sole property of Medicis/Q-Med, pursuant to the written contractual agreement between these parties which governs the handling of Proprietary and Confidential Commercial Information. The Investigator agrees to use the information only in connection with this study and will not use it for other purposes without written permission from Medicis/Q-Med. The terms of the Investigator Agreement govern the definition and handling of confidential information.

It is understood by the Investigator that data from the study may be used by Medicis/Q-Med in connection with the development of the study product. Data and information may therefore be disclosed as required to other Investigators and to Regulatory Authorities or be placed in the product label or other information disseminated by Medicis. By signing this protocol, the Investigator affirms that study subject data, and especially study subject identifier information, will be maintained in confidence as set forth in the protocol and any written contractual agreement. Confidential information will be divulged to the Institutional Review Board, Ethical Review Committees, or similar expert committee; affiliated institutions; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and ethical considerations, Medicis or representatives of Medicis or Q-Med, or applicable regulatory agency may review study documents, including study subject identifying and other confidential information, in order to verify CRF data and in accordance with federal regulations. The Investigator understands that clinical studies conducted under an investigational provision (IDE or IND) are exempt from the study subject identifier confidentiality provisions of the Health Insurance Portability and Access Act of 1996 (HIPAA), as provided at 45 CFR § 512(b)(iii), and the study subject should be made aware of this exception in the informed consent. Medicis/Q-Med shall, to the extent feasible, protect study subject identifier information.

U.S. governmental authorities are permitted to copy confidential information relating to personal identification only when relating to a clinical investigation of a drug study conducted under an IND exemption under 21 CFR Part 312 (*see* 21 CFR § 312.58(a)) or, for an investigation of a medical device study conducted under an Investigational Device Exemption, only when the agency has reason to suspect that adequate informed consent was not obtained or that reports required to be submitted by the Investigator to Medicis/Q-Med or IRB have not been submitted or are incomplete, inaccurate, false or misleading. *See* 21 CFR § 812.145(c).

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15.11. COMPLIANCE WITH LAW

By signing this protocol, the Investigator agrees to conduct the study in an efficient and diligent manner and in conformance with the protocol, generally accepted standards of good clinical practice, conditions of protocol approval imposed by the Institutional Review Board, and all applicable federal, state and local laws, rules and regulations. The Investigator shall prepare and maintain complete and accurate documents relating to the investigation in compliance with the protocol, good clinical practice standards and applicable federal, state and local laws, rules and regulations including all correspondence with another Investigator, an IRB, Medicis or monitor, or FDA and each subject's case history and exposure to the investigational product as required on the case report forms and maintain all supporting data in subject records. For each study subject participating in the study, the Investigator will promptly submit all original CRFs to Medicis. Furthermore, the Investigator also agrees to submit other necessary documents as required by this protocol following completion or termination of the clinical evaluation or as otherwise required pursuant to any agreement with Medicis or Representative of Medicis. Study documents will be promptly and fully disclosed to Medicis by the Investigator upon request for inspection, copying, review and audit at reasonable times by representatives of Medicis or any regulatory agencies. The Investigator agrees to promptly take any reasonable steps, requested by Medicis or representative of Medicis, as a result of an audit, to cure deficiencies in the document or CRFs. The investigational product will be used only on subjects properly enrolled in the study. Upon completion or termination of the study or the Investigator's participation in the study, the Investigator will account for and/or return to Medicis any remaining supply of the investigational product as Medicis directs. The Investigator will maintain records of receipts, type and quantity, dates of receipt, batch numbers, and the names of all persons who may have received used or disposed of each investigational product and whether and how any such products were returned, repaired, or destroyed. The study product will be stored in a secure location. The Investigator shall record any deviations from protocol management of a subject. The Investigator will maintain a signed copy of the protocol.

The Investigator will maintain study records for at least two years after completion of the investigation or, if needed for purposes of supporting a pre-market approval application or new drug application, until two years after such process is completed, if longer, or until notified by Medicis, if longer. The Investigator assumes responsibility for record maintenance.

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15.12. FINANCIAL DISCLOSURE

The Investigator agrees to disclose any financial conflicts of interest that may occur between him- or herself, an immediate family member, the sub-investigators working for the Investigator, and their immediate families, and Medicis and its affiliates and related entities during the course of this investigation and for one year after conclusion of the study. Financial conflicts of interest include: a) any compensation affected by the outcome of the study; b) a significant equity interest, including options, exceeding \$50,000 in Medicis; or, c) a proprietary interest in the investigational product such as a royalty or patent ownership, or license fee. Medicis will provide a form at the conclusion of the study, developed by the U.S. Food and Drug Administration and potentially revised from time to time, that requires disclosure of such conflicts of interest, and the Investigator agrees to complete such form and disclose such information as it may then contemporaneously require. Medicis will provide a sample of such form at the start of the study to ensure that the Investigator is aware of this responsibility and may require completion of the form at study initiation or an update during or after the study as well to identify Investigators who may have conflicts.

15.13. INVESTIGATOR AND SITE QUALIFICATIONS; DEBARMENT

Persons debarred from conducting or working in clinical studies by any court or regulatory agency will not be allowed to conduct or work on the study. The Investigator will immediately disclose in writing if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened. To that end, the Investigator has not been personally and will not use as an assistant any person who is debarred from participation in clinical trials under the Generic Drug Enforcement Act of 1992 (21 USC § 301 et seq.) or any other provision of law (*e.g.*, 21 CFR § 312.70). If such a proceeding should commence, involving the Investigator or any assistant, the Investigator will promptly inform Medicis. Further, the Investigator has not and no person or entity affiliated with the Investigator or under the Investigator's supervision is excluded from participation in a Federal Health Care Program as defined in 42 U.S.C. § 1320a. The Investigator has never been convicted of a felony.

The Investigator will provide a signed, accurate, non-misleading, and current copy of his or her curriculum vitae to Medicis that demonstrates his or her qualifications to conduct this study and, if requested, will provide a list of sub-investigators or health professionals who are assisting in the conduct of this study and documentation of their qualifications.

The facilities where this study will be conducted have the necessary subject population and personnel to properly conduct the study.

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16. PUBLICATION POLICY

A publication committee will be formed by Medicis ("Publication Committee"). Investigators recognize that study data from a single center are not scientifically valid unless understood and combined together with data generated by other centers involved in the study or read in light of such combined data. The Publication Committee shall be provided a copy of the final study report as filed with the U.S. Food and Drug Administration and shall have the sole responsibility and authority for the preparation of manuscripts for submission. Accordingly, Investigators expressly acknowledge and agree that any publication arising from study data from an individual site will be submitted to, reviewed by, and approved by such Publication Committee before submission for publication. Individual site data may not be published until after expiration of a reasonable time period to permit publication of the combined results obtained from all the study sites.

16.1. RESERVATION OF RIGHTS

Notwithstanding the grant of publication rights provided in Section 16, Medicis reserves the right to review the contents of any publication of the study data at least sixty (60) days in advance before such publication is submitted for publication or presentation and to comment upon, but not make any editorial changes in, the data and conclusions set forth in the proposed publication, provided, however, the Investigators or Publication Committee, as applicable and in good faith, shall review and consider incorporating Medicis' comments into any such publication and that such publication is approved by the Publication Committee composed of peers of the Investigator in question in the event of a multicenter study. Notwithstanding the foregoing, in no event may any Proprietary or Confidential Commercial Information be published without Medicis' prior written consent and Medicis reserves the right to further delay or prevent the publication of any material containing such Information. Investigators agree that any publication will acknowledge the efforts and contributions of any Medicis personnel and the members of the Publication Committee involved in the study in accordance with customary scientific practice. Investigators hereby agree that Medicis may freely use, copy and disseminate any publication without further obligation to Investigator.

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17. REFERENCE LIST

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3. Gormley DE, Eremia S. Quantitative assessment of augmentation therapy. J Dermatol Surg Oncol 1990;16(12):1147-1151.
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5. Hayt E. "Kiss My Puffy Lips" New York Times, August 4, 2005.

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18. LIST OF APPENDICES

APPENDIX A: SCHEDULE OF STUDY PROCEDURES MA-1300-15

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APPENDIX A: SCHEDULE OF STUDY PROCEDURES: MA-1300-15

	Screening	Baseline and Tx	Day 3 (72 Hours)	Optional Touch-up ²	2 Week Follow-Up	4 Week Follow-Up	8, 12, 16, 20 Week Follow-Up	24 Week Follow-Up/ Treatment	72 hours Post-Treatment	Optional Touch-Up	2 Week Post-Treatment	4-Week Post-Treatment or Early Withdrawal
	Visit 1	Visit 2	Visit 3	Visit T	Visit 4	Visit 5	Visit 6-9	Visit 10	Visit 11	Visit T 2	Visit 12	Visit 13
	Day -28 to Day 0	Day 0	Day 3 (± 24 hours)	2 wks after initial treatment (± 3 days)	2 wks after randomization or touch-up (± 3 days)	4 wks after randomization or touch-up (±5 days)	8, 12, 16, 20 wks after randomization or touch-up (±5 days)	24 wks after treatment or touch-up (±1 wk)	72 hours after Week 24 treatment (±24 hours)	2 weeks after Week 24 treatment (±3 days)	2 weeks after Week 24 treatment or touch-up (±3 days)	4 weeks after Week 24 treatment or touch-up (±5 days)
Procedure												
Informed Consent	X											
Medical History	X											
Ht, wt, and demographics	X											
Assessment of eligibility	X											
Urine pregnancy test		X						X				
MLFS: Treating Investigator	X ¹			X	X	X	X	X		X	X	X
MLFS: Blinded Evaluator							X	X		X	X	X
GAIS: Treating Investigator, subject				X	X	X	X	X		X	X	X
Lip texture, firmness, symmetry:	X		X	X	X	X	X	X	X	X	X	X
Lip movement, function, sensation:	X		X	X	X	X	X	X	X	X	X	X
Palpability, mass formation:	X		X	X	X	X	X	X	X	X	X	X
Assess repeat injection								X				
Randomization		X										
Treatment		X		X ²				X		X ²	X	
Dispense Subject Diary		X						X				
Review of Subject Diary				X ³	X ³					X ³	X ³	
Collect Subject Diary				X ³	X ³					X ³	X ³	
Photography		X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs		X	X	X	X	X	X	X	X	X	X	X

¹ Subjects with Fitzpatrick skin types I, II, or III must have a score of 1 (Very Thin) or 2 (Thin) on either upper or lower lips on the MLFS as assessed at baseline by the Treating Investigator to be eligible. Subjects with Fitzpatrick skin types IV, V, or VI must have the required MLFS score for at least one lip (either upper or lower) as assessed at baseline by the Treating Investigator to be eligible.

² Touch-up with the products assigned by randomization will be provided at 2 weeks post-treatment (Visit T/Visit T 2), if appropriate for optimal correction. If touch-ups are given at the 2 Week Follow-Up Visit (Visit T/T 2), another 2 Week Follow-Up Visit must be scheduled 2 weeks after the touch-up treatment visit. All subsequent visits will then be calculated from the touch-up visit.

³ The Diary is to be reviewed and collected two weeks after treatment, either at Visit T/T2 if subject is receiving touch-up OR at Visit 4 or Visit 12 if subject is not receiving touch-up.

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APPENDIX B – CLINICAL SCALES

LIP TEXTURE ASSESSMENT

The following scale is to be used to assess lip texture for each lip separately: If lip texture is abnormal, indicate level of abnormality. The most severe score should be recorded.

UPPER LIP			
NORMAL	ABNORMAL		
	Mild	Moderate	Severe
Texture of the lip is even without visible undulations or excessive coarseness beyond that expected for stated age.	The lip shows a single area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) can be visualized only with close inspection.	The lip shows more than one area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that can be visualized only with close inspection. or The lip shows one area of textural irregularity (less than ¼ of the lip area) at conversational distance.	The lip shows two or more areas of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that can be visualized at a conversational distance. or The lip shows one area of textural irregularity (more than ¼ of the lip area) at conversational distance.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

LOWER LIP			
NORMAL	ABNORMAL		
	Mild	Moderate	Severe
Texture of the lip is even without visible undulations or excessive coarseness beyond that expected for stated age.	The lip shows a single area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) can be visualized only with close inspection.	The lip shows more than one area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that can be visualized only with close inspection. or The lip shows one area of textural irregularity (less than ¼ of the lip area) at conversational distance.	The lip shows two or more areas of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that can be visualized at a conversational distance. or The lip shows one area of textural irregularity (more than ¼ of the lip area) at conversational distance.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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LIP FIRMNESS ASSESSMENT

Touch the surface of each lip to determine if lip is supple with immediate resumption of fullness after application of pressure. If lip firmness is abnormal, indicate level of abnormality. The most severe score should be recorded.

UPPER LIP			
NORMAL	ABNORMAL		
	Mild	Moderate	Severe
Lip is supple when compressed laterally and surface distorts readily with minimal pressure. Pressure with a narrow diameter instrument (cotton-tipped applicator, toothpick etc) causes a focal depression in the surface of the lip. Upon palpation, lip is absent of abnormal structures such as scars or lumps; normal product feel without being visible.	Lip is slightly firm with lateral compression or requires slightly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump is felt, but is not visible.	Lip is firm with lateral compression or requires distinctly greater than normal pressure to distort the surface or pressure with a narrow diameter instrument (cotton-tipped applicator or toothpick) causes a broader depression in the surface of the lip. Upon palpation, an abnormal structure such as a scar or lump is felt and is visible	Lip is very firm with lateral compression or requires significantly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump is felt and is visually distracting.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

LOWER LIP			
NORMAL	ABNORMAL		
	Mild	Moderate	Severe
Lip is supple when compressed laterally and surface distorts readily with minimal pressure. Pressure with a narrow diameter instrument (cotton-tipped applicator, toothpick etc) causes a focal depression in the surface of the lip. Upon palpation, lip is absent of abnormal structures such as scars or lumps; normal product feel without being visible.	Lip is slightly firm with lateral compression or requires slightly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump is felt, but is not visible.	Lip is firm with lateral compression or requires distinctly greater than normal pressure to distort the surface or pressure with a narrow diameter instrument (cotton-tipped applicator or toothpick) causes a broader depression in the surface of the lip. Upon palpation, an abnormal structure such as a scar or lump is felt and is visible	Lip is very firm with lateral compression or requires significantly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump is felt and is visually distracting.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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LIP SYMMETRY ASSESSMENT

The following scale is to be used to assess lip symmetry for each lip separately. The most severe score is to be recorded.

Note that lip symmetry compares the left side to the right side of an upper or lower lip individually. Thus, there will be a grade for asymmetry of the upper lip and a separate grade for asymmetry of the lower lip. The investigator will observe the subjects lips closely for any asymmetry. If any asymmetry is noted, measurements of the difference in either the vertical height of the vermilion or its lateral length will be conducted in order to classify the degree of asymmetry using the table below. Additionally, subjects who have no noticeable asymmetry will undergo measurement of the vertical height of their vermilion at the midpoint between the subject’s centerline and oral commissure on each side. Measurements differing by 1 mm or less will be considered “normal” while any greater difference in measurement will result in categorization of asymmetry according to the table below.

UPPER LIP			
NORMAL	ABNORMAL		
	Mild	Moderate	Severe
One side of the lip balances or mirrors the other side.	One side of the lip shows a 1 mm or less difference in height or a 1 mm or less difference in the length of the vermilion at repose.	One side of the lip shows a 1.1 mm to 2 mm difference in height or a 1.1 to 2 mm difference in the length of the vermilion at repose.	One side of the lip shows a greater than 2 mm difference in height or a greater than 2 mm difference in the length of the vermilion at repose.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

LOWER LIP			
NORMAL	ABNORMAL		
	Mild	Moderate	Severe
One side of the lip balances or mirrors the other side.	One side of the lip shows a 1 mm or less difference in height or a 1 mm or less difference in the length of the vermilion at repose.	One side of the lip shows a 1.1 mm to 2 mm difference in height or a 1.1 to 2 mm difference in the length of the vermilion at repose.	One side of the lip shows a greater than 2 mm difference in height or a greater than 2 mm difference in the length of the vermilion at repose.
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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DEVICE PALPABILITY ASSESSMENT

Restylane® is generally “palpable” without being visible (meaning you should be able to feel the product under the skin). The only visible effect should be a general increase in fullness. Touch the surface of each lip to determine if the structure, upon palpation, has the feel of uniform density, without unexpected lumpiness.

UPPER LIP – Is the device palpable?		
NO	YES	
	Expected Feel (Normal)	Unexpected Feel (Abnormal)
Device is not palpable	Structure, upon palpation, has the feel of uniform density, without unexpected lumpiness	Structure, upon palpation, has the feel of non-uniform density or has unexpected lumpiness
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> If abnormal, record as an Adverse Event

LOWER LIP – Is the device palpable?		
NO	YES	
	Expected Feel (Normal)	Unexpected Feel (Abnormal)
Device is not palpable	Structure, upon palpation, has the feel of uniform density, without unexpected lumpiness	Structure, upon palpation, has the feel of non-uniform density or has unexpected lumpiness
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> If abnormal, record as an Adverse Event

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MASS FORMATION ASSESSMENT

Evaluate the lips for lumps or an aggregation of coherent material.

UPPER LIP – Is there mass formation?	
NO	YES
<input type="checkbox"/>	<input type="checkbox"/> If Mass Formation exists, record as an Adverse Event

LOWER LIP – Is there mass formation?	
NO	YES
<input type="checkbox"/>	<input type="checkbox"/> If Mass Formation exists, record as an Adverse Event

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LIP MOVEMENT ASSESSMENT

Evaluate the subject's ability to speak a series of words containing bilabial consonants.

1. Pronounce the following words distinctly
2. Instruct the subject to repeat each word
3. Asses the pronunciation of the bilabial (m, b, p) and dentolabial (f,v) consonants

Can the subject effectively pronounce the following words?									
Member		Simmering		Drab		Babble		Spear	
YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Peep		Fire		Staff		Verse		Liver	
YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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LIP FUNCTION ASSESSMENT

Evaluate the subject's ability to drink through a straw and control the direction of fluid flow.

Perform the test using the straw provided

- Prepare water, straw and 30-60 cc of water
- Instruct subject to sit up comfortable
- Instruct subject to drink the water using the straw
- Observe for adequate lip seal to prevent leakage of fluid
- Observe that fluid filled the straw and passed into the mouth with minimal effort

Does the subject display the ability to drink through a straw effectively?

YES

NO

If No, describe the problem and record as an Adverse Event:

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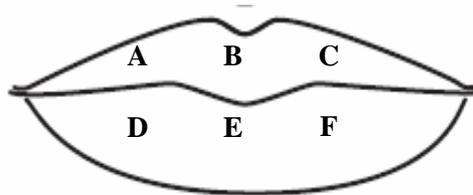
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LIP SENSATION ASSESSMENT – MONOFILAMENT TEST

The 3 different points on the upper and lower lips will be tested randomly. Subjects will be blindfolded and asked to acknowledge sensation or lack of sensation at each point.

ADMINISTERING THE MONOFILAMENT TEST

1. Explain to the subject that you will be testing sensation perception of their upper and lower lip.
2. Instruct them to indicate with a raised finger when a sensation is felt.
3. Show the monofilament to the subject.
4. Touch their arm with the filament to demonstrate how it will feel when placed on the lip.
5. Ask the subject to hold their mouth open as when saying Ahhh in the word “about”.
6. RANDOMLY apply the 0.4G monofilament to each area of the subject’s lips below (NOT IN ANY PARTICULAR ORDER). Hold each spot for 1-2 seconds.



- A = Subject’s right upper lip**
B = Subject’s middle upper lip
C = Subject’s left upper lip
D = Subject’s right lower lip
E = Subject’s middle lower lip
F = Subject’s left lower lip

7. Repeat testing one more time at each location if the subject failed to sense the touch the first time.

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DOCUMENTING THE RESULTS OF THE MONOFILAMENT TEST

Place an "X" in the box that corresponds with the subject's response.

subject's <u>right</u> upper lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>middle</u> upper lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>left</u> upper lip YES NO <input type="checkbox"/> <input type="checkbox"/>
subject's <u>right</u> lower lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>middle</u> lower lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>left</u> lower lip YES NO <input type="checkbox"/> <input type="checkbox"/>

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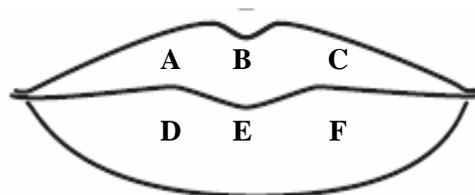
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LIP SENSATION ASSESSMENT – COTTON WISP TEST

The 3 different points on the upper and lower lips will be tested randomly. Subjects will be blindfolded and asked to acknowledge sensation or lack of sensation at each point.

ADMINISTERING THE COTTON WISP TEST

1. Explain to the subject that you will be testing sensation perception of their upper and lower lip.
2. Instruct them to indicate with a raised finger when a sensation is felt.
3. Show the wisp of cotton to the subject.
4. Touch their arm with the wisp of cotton to demonstrate how it will feel when placed on the lip.
5. Ask the subject to hold their mouth open as when saying Ahhh in the word “about”.
6. RANDOMLY brush wisp lightly across each area of the subject’s lips below (NOT IN ANY PARTICULAR ORDER)



- A = Subject’s right upper lip**
B = Subject’s middle upper lip
C = Subject’s left upper lip
D = Subject’s right lower lip
E = Subject’s middle lower lip
F = Subject’s left lower lip

7. Repeat testing one more time at each location if the subject failed to sense the touch the first time.

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DOCUMENTING THE RESULTS OF THE COTTON WISP TEST

Place an "X" in the box that corresponds with the subject's response.

subject's <u>right</u> upper lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>middle</u> upper lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>left</u> upper lip YES NO <input type="checkbox"/> <input type="checkbox"/>
subject's <u>right</u> lower lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>middle</u> lower lip YES NO <input type="checkbox"/> <input type="checkbox"/>	subject's <u>left</u> lower lip YES NO <input type="checkbox"/> <input type="checkbox"/>

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