Restylane® Injectable Gel
Lip Augmentation Indication

General and Plastic Surgery Devices
Panel Meeting
April 27, 2011
Restylane Overview

Presenter:

Mitchell S. Wortzman, Ph.D.
Executive Vice President, Chief Scientific Officer
Medicis Pharmaceutical Corporation
Introduction/Background

- *Restylane* is the trade name of the hyaluronic-derived dermal filler produced by Q-Med AB ("Q-Med"), a Swedish company based in Uppsala, Sweden

- Medicis Pharmaceutical Corporation ("Medicis" or "the company"), a U.S. corporation based in Scottsdale, Arizona, acquired the development and distribution rights to *Restylane* in 2003
Restylane Regulatory Chronology

- *Restylane* was first approved for marketing and sale in September 1996 in the European Union, Iceland, Liechtenstein and Norway (“EES”)

- The product has since been marketed worldwide in over 70 countries

- *Restylane* was approved in the US on December 12, 2003, and is currently indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds

- Duplicate PMA 040024 was approved on March 25, 2005 for same indication
Restylane Injectable Gel Indication

- Medicis is seeking approval for an expanded indication
  
  - *Restylane* is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation.
Clinical Practice

Presenter:

Robert Weiss, M.D.
Board Certified Dermatologist
Principal Investigator
Clinical Practice

**Physician Experience:**

- Hyaluronic Acid (HA) filler is frequently sought and commonly used in clinical practice for lip augmentation.

- In 2010 there were over 1.2 million HA procedures performed in the US.\(^1\)

- Tens of millions of dermal filler treatments performed worldwide.

- More than 85% are with HA.\(^2\)

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Clinical Practice

Demographics of patients seeking soft tissue filler procedure

- Predominantly female (95%)

- Over the age of 40 (83%)
  - 30 – 39 years old = 12%
  - 20 – 29 years old = 5%
  - 13 – 19 years old = 1%

Clinical Practice

- Ethnicity breakdown for cosmetic procedures
  - Caucasian = 70%
  - Hispanic = 11%
  - African-American = 8%
  - Asian-American = 6%
  - Other = 4%

Clinical Practice

- Publications Regarding Lip Augmentation

  - Scientific literature replete with references to lip augmentation
    - 344 PubMed entries under “lip augmentation”

  - Publication of lip augmentation using collagen as early as 1986

  - Extensive European use of hyaluronic acid for lips published in 1998

Clinical Practice

- Publication of US practice review shows 51% of HA dermal filler users received lip augmentation
- Recent ASAPS survey showed significant percentage of use of HA fillers in US is for lip augmentation

2. Aesthetic Surgery Education & Research Foundation Report April 2009 BOTOX® Cosmetic and Hyaluronic Acid Dermal Filler User Survey
Clinical Practice

Recommendations of Facial Soft Tissue Fillers conference proceedings

- Encourage industry to fund prospective studies on new and expanded indications
- Standardized validated methods for assessing outcomes
- Involve appropriate representative patient types

Clinical Practice

Summary:

- There is a need for data on the effectiveness and safety from well controlled prospective studies to provide guidance for physicians and patients.

- Medicis’ pivotal US lip study serves this purpose.
Program Development & Background

Presenter:

Xiaoming Lin
Vice President
Clinical Research and Development
Medicis Pharmaceutical Corporation
Program Development & Background

- Program Chronology:
  - MA-1300-13K
    - US Pilot Study
  - Medicis Lip Fullness Scale Development and Validation
  - MA-1300-14
    - Canadian Pilot Study
  - MA-1300-15
    - Pivotal US Study
MA-1300-13K US Pilot Study
Pilot Study MA-1300-13K

- A 20 subject prospective, open label, single center, blinded evaluator, pilot study of the safety and efficacy of *Restylane* in the restoration of soft tissue volume of the lips
Pilot Study MA-1300-13K

- **Effectiveness Summary:**
  - **Subjects’ Global Aesthetic Improvement Scale (GAIS):**
    - 100% assessed improvement through Week 12
    - 74% assessed improvement through Week 24
  - **Treating physician’s Global Aesthetic Improvement Scale (GAIS):**
    - 100% improvement through Week 12
    - 84% improvement through Week 24
Pilot Study MA-1300-13K

- Mass formation was reported in 90% of subject diaries as a result of a miscommunication with the subjects
  - Product palpability was reported as mass formation
  - None reported as AE

- Pivotal study included mass formation assessments
  - Assessed at all post treatment visits by a medical professional
  - One subject reported mass formation at one time point
Safety Summary:

Treatment Emergent Adverse Events:
- 6 treatment emergent adverse events (TEAEs) were experienced by 3 (15%) subjects
  - 2 of these events (both mild bruising) were considered related to treatment
- A single treatment with *Restylane* for lip augmentation was well tolerated
Medicis Lip Fullness Scale Development & Validation
Medicis Lip Fullness Scale (MLFS)

- Background of MLFS Scale Development:
  - Worked with board certified dermatologists and plastic surgeons to develop the lip scales
    - Physicians could use the scale to communicate the treatment goal with subjects in the study
    - Measure the treatment effect of the lip augmentation
Medicis Lip Fullness Scale (MLFS)

- **Background of MLFS Scale Development:**
  - Medicis worked closely with FDA during the scale development and validation process.
  - Results were presented and discussed with FDA at the pre-IDE meeting on September 4, 2008 and included in the approved IDE.
  - The scales were accepted by FDA as validated tools for effectiveness measurement for lip augmentation.
Medicis Lip Fullness Scale (MLFS)

- 5-point MLFS photoguide (upper and lower lips)

1 – Very Thin
2 – Thin
3 – Medium
4 – Full
5 – Very Full
MLFS Photoguide
Upper Lip
MLFS Photographs - Upper Lip

Very Thin (1)
MLFS Photographs - Upper Lip

Thin (2)

Photo 2
MLFS Photographs - Upper Lip

Medium (3)
MLFS Photographs – Upper Lip

Very Full (5)

Photo 1
MLFS Photoguide
Lower Lip
MLFS Photographs - Lower Lip

Very Thin (1)

Photo 1
MLFS Photographs - Lower Lip

Thin (2)

Photo 2
MLFS Photographs - Lower Lip

Medium (3)

Photo 2
MLFS Photographs - Lower Lip

Full (4)

Photo 3
MLFS Photographs - Lower Lip

Very Full (5)
MLFS Validation

- Validation of the Medicis Lip Fullness Scale included 2 different series of validation:
  
  1. Photographic assessment validation
  2. Live versus photographic assessment validation
MLFS Validation

- Weighted Kappa coefficients were interpreted as follows:

<table>
<thead>
<tr>
<th>Literature</th>
<th>Weighted Kappa Coefficient</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landis and Koch¹</td>
<td>&lt; 0.20</td>
<td>Poor agreement</td>
</tr>
<tr>
<td></td>
<td>0.20 – 0.39</td>
<td>Fair agreement</td>
</tr>
<tr>
<td></td>
<td>0.40 – 0.59</td>
<td>Moderate agreement</td>
</tr>
<tr>
<td></td>
<td>0.60 – 0.79</td>
<td>Substantial agreement</td>
</tr>
<tr>
<td></td>
<td>0.80 – 1.0</td>
<td>Almost Perfect agreement</td>
</tr>
</tbody>
</table>

MLFS Validation

- Photographic validation included:
  - 5 evaluators
  - 85 upper lip and 85 lower lip photographs
  - 2 evaluations at least two weeks apart
  - Photos represent:
    - Full range of lip ratings from very thin (1) to very full (5)
    - Different ages and genders
    - Different Fitzpatrick skin types
  - Each photograph for validation had a unique identification number
  - Photographs were randomly arranged for each round of assessment
MLFS Validation Results

Photographic Within Rater Reliability:

- Agreement was ‘substantial’ to ‘almost perfect’

- Upper Lip
  - Weighted kappa values varied between 0.70 and 0.87
  - Overall average weighted kappa was 0.81

- Lower Lip
  - Weighted kappa values varied between 0.63 and 0.90
  - Overall average weighted kappa was 0.81
MLFS Validation Results

- Photographic Between Rater Reliability:
  - Agreement was ‘substantial’
  - Upper Lip
    - Weighted kappa values varied between 0.60 and 0.83
    - Overall average weighted kappa was 0.72
  - Lower Lip
    - Weighted kappa values varied between 0.59 and 0.81
    - Overall average weighted kappa was 0.69
MLFS Validation

- Live vs. Photographic validation included:
  - 3 evaluators
  - 39 subjects for upper lip and 39 subjects for lower lips
  - Subjects represented:
    - Full range of lip ratings from very thin (1) to very full (5)
    - Different ages and genders
    - Different Fitzpatrick skin types
  - 1st Evaluation = live assessment
  - 2nd Evaluations = photo assessment of same subjects
    - 2 weeks later
    - In different sequence
MLFS Validation Results

- **Live vs. Photographic Within Rater**

  **Reliability:**
  
  - Agreement was ‘substantial’
  
  - **Upper Lip**
    - Weighted kappa values varied between 0.62 and 0.68
    - Overall average weighted kappa value was 0.65
  
  - **Lower Lip**
    - Weighted kappa values varied between 0.61 and 0.68
    - Overall average weighted kappa value was 0.64
MLFS Validation Results

Summary:

- Validation results demonstrated that the MLFS can be used by:
  - Different evaluators
  - Same evaluator at different time points

- Also demonstrated that MLFS can be used for:
  - Live evaluation
  - Photo evaluation

- Conclusion: 5-point MLFS is suitable for use in clinical studies for effectiveness measurement
MA-1300-14 Canadian Pilot Study
A 21 subject open label, pilot study in Canada to assess the effectiveness and safety of *Restylane* in the restoration of soft tissue fullness of the lips.
Pilot Study MA-1300-14

Effectiveness Summary:

- MLFS at Week 8
  - Blinded Evaluator
    - 89% of subjects had at least a one grade improvement in both upper and lower lips
  - Treating Investigator
    - 89% of subjects had at least a one grade improvement in both upper and lower lips

- Effectiveness results maintained throughout the 12 weeks of the study
At Week 8, percentages of subjects with a GAIS rating of “improved” or better:
- 100% by blinded evaluators
- 100% by treating investigator
- 94% by subjects

At all other time points (Weeks 2, 4, and 12), percentages of subjects with a GAIS rating of “improved” or better:
- 95% to 100% by blinded evaluators
- 95% to 100% by treating investigators
- 80% to 100% by subjects
Pilot Study MA-1300-14

- Very high agreement in response rate between MLFS assessment and GAIS assessment
  - At Week 8, the upper lip Blinded Evaluator MLFS and GAIS agreed in 100% of subjects (18/18)
  - At Week 8, the lower lip Blinded Evaluator MLFS and GAIS agreed in 89% of subjects (16/18)
Pilot Study MA-1300-14

- **Safety Summary:**
  - 8 AEs reported by 6 subjects
  - No SAEs were reported
  - Treatment with Restylane administered for lip augmentation was well tolerated
Conclusion of Pilot Studies

- *Restylane* for lip augmentation:
  - Is effective
  - Has an acceptable safety profile

- Confirmed the clinical utility of the MLFS
  - 1 grade improvement in MLFS represents a clinically meaningful result
MA-1300-15 Pivotal Study Design
MA-1300-15 Study Design

- 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
MA-1300-15 Study Design

- 180 subjects at 12 US centers
- At least 30 subjects with Fitzpatrick skin types IV, V, or VI
- 3:1 ratio Restylane treatment to no treatment
**MA-1300-15 Study Design**

- **Fitzpatrick Skin Type Scale:**

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Extremely fair, always burns, never tans</td>
</tr>
<tr>
<td>II</td>
<td>White, always burns, sometimes tans</td>
</tr>
<tr>
<td>III</td>
<td>White, sometimes burns, always tans</td>
</tr>
<tr>
<td>IV</td>
<td>Olive or light brown, rarely burns, always tans</td>
</tr>
<tr>
<td>V</td>
<td>Brown, never burns</td>
</tr>
<tr>
<td>VI</td>
<td>Heavily pigmented or black, never burns</td>
</tr>
</tbody>
</table>
MA-1300-15 Study Design

- Subjects randomized to *Restylane* treatment at baseline received a 2\textsuperscript{nd} treatment at 6 months.

- Subjects randomized to no treatment at baseline received their 1\textsuperscript{st} treatment at 6 months.

- The safety of all subjects was monitored throughout the study.
General Inclusion Criteria:

- 18 to 65 years of age
- Males and non pregnant females
- No confounding facial plastic surgery or cosmetic procedures for the duration of the study
- Fitzpatrick skin types I, II, or III
  - MLFS of very thin (1) or thin (2) on BOTH upper and lower
- Fitzpatrick skin types IV, V, or VI
  - MLFS of very thin (1) or thin (2) on EITHER upper or lower lip, or both lips
MA-1300-15 Study Design

- **Recommended Dose:**
  - 1.5 mL per lip per treatment session
  - Treat to optimal correction
    - Optimal correction agreed upon by treating physician and subject
Primary Endpoint:

To identify whether Restylane was more effective than no treatment in lip augmentation at 8 weeks

- Determined by the live blinded evaluator using MLFS
- Compared to the baseline MLFS assessment performed by the treating investigator
- Evaluated in the upper and lower lips separately
- Treatment success was defined as at least a one grade improvement on the MLFS in BOTH the upper and lower lips (co-primary endpoints)
MA-1300-15 Study Design

- Secondary Effectiveness Endpoints using the MLFS
  - Blinded evaluator assessment at Week 12 through study end
  - Treating investigator assessment at all study time points except 72-hour safety visit
  - Independent Photographic Reviewer (IPR) assessment at post study completion
    - Photos taken at baseline, Weeks 4, 8, 12, 16, 20, and 24
Clarification of Photo Naming Conventions

- Subject photos were named generically to ensure blinding

<table>
<thead>
<tr>
<th>Current Subject Photograph Label:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 10 – 24 Week Follow-up/Treatment</td>
</tr>
<tr>
<td>Visit 11 – 72 hours Post Treatment</td>
</tr>
<tr>
<td>Visit 12 – 2 Week Post Treatment</td>
</tr>
<tr>
<td>Visit 13 – 4 Week Post Treatment</td>
</tr>
</tbody>
</table>
MA-1300-15 Study Design

- Secondary Effectiveness Endpoints using the GAIS
  - Evaluated by the treating investigator and subject, using baseline photos for reference
  - All post baseline time points except 72-hour safety visit
  - Response defined as a GAIS rating of “improved” or better in the upper or lower lips
MA-1300-15 Study Design

- Safety Endpoints
  - Adverse Events
  - Subject Diary Data
  - Lip Safety Evaluations
MA-1300-15 Summary of Effectiveness

Presenter:

Ira Lawrence, M.D.
Chief Medical Officer, Senior Vice President
Research and Development
Medicis Pharmaceutical Corporation
MA-1300-15 Demographic Information

- 180 subjects enrolled
  - 135 received *Restylane* treatment at baseline
  - 45 received no treatment at baseline
- Mean age = 47.6 years
- Most subjects were female (99%) and Caucasian (94%)
- 139 subjects (77%) of Fitzpatrick skin types I, II, or III
- 41 subjects (23%) of Fitzpatrick skin types IV and V
MA-1300-15 Summary of Volume Utilized

- **Restylane** treatment group (at baseline)
  - Initial treatment mean volume
    - Upper and lower lips combined = 2.3 mL
  - Touch up treatment mean volume
    - Upper and lower lips combined = 0.8 mL
  - Initial treatment and touch up total mean volume
    - Upper and lower lips combined = 2.9 mL
MA-1300-15 Summary of Volume Utilized

- *Restylane* treatment group (at 6 month re-treatment)
  - Re-treatment at 6 months mean volume
    - Upper and lower lips combined = 1.5 mL
  - Touch up re-treatment mean volume
    - Upper and lower lips combined = 0.7 mL
  - Re-treatment at 6 months and touch up total mean volume
    - Upper and lower lips combined = 1.8 mL
MA-1300-15 Effectiveness Tools

- Medicis Lip Fullness Scale (MLFS)
  - Used in both live and photo assessment
  - Static assessment (not a change from baseline)

- Global Aesthetic Improvement Scale (GAIS)
  - Live assessment by subjects and treating investigator
  - Improvement from baseline
### MA-1300-15 Effectiveness Tools

#### Subjects and Treating Investigators GAIS

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Very Much Improved</td>
</tr>
<tr>
<td>2</td>
<td>Much Improved</td>
</tr>
<tr>
<td>1</td>
<td>Improved</td>
</tr>
<tr>
<td>0</td>
<td>No Change</td>
</tr>
<tr>
<td>-1</td>
<td>Worse</td>
</tr>
<tr>
<td>-2</td>
<td>Much Worse</td>
</tr>
<tr>
<td>-3</td>
<td>Very Much Worse</td>
</tr>
</tbody>
</table>
MA-1300-15 Summary of Effectiveness

- Primary endpoint: Week 8 blinded evaluator MLFS assessment
  
  - *Restylane* treatment group:
    
    - 94.8% were upper lip MLFS responders from baseline
    
    - 94.3% were lower lip MLFS responders from baseline
    
    - 92.6% were upper and lower lips combined MLFS responders from baseline
MA-1300-15 Summary of Effectiveness

- Primary endpoint: Week 8 blinded evaluator MLFS assessment

- No treatment group:
  - 36.4% were upper lip MLFS responders from baseline
  - 38.5% were lower lip MLFS responders from baseline
  - 28.9% were upper and lower lips combined MLFS responders from baseline
MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined

**Proportion (%) of Responders, Blinded Evaluator MLFS**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Restylane Treatment</th>
<th>No Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint Week 8</td>
<td>92.6</td>
<td>28.9</td>
</tr>
<tr>
<td>Week 12</td>
<td>90.1</td>
<td>36.8</td>
</tr>
<tr>
<td>Week 16</td>
<td>84.2</td>
<td>35.9</td>
</tr>
<tr>
<td>Week 20</td>
<td>75.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Week 24</td>
<td>69.6</td>
<td>36.8</td>
</tr>
</tbody>
</table>

**P-Value < 0.001 at all time points**

MLFS Responder = at least 1 grade increase from baseline on the MLFS
MA-1300-15 Summary of Effectiveness

- The difference in the proportion of MLFS responders from baseline between the Restylane and no treatment groups is highly statistically significant.
  - p-value <0.001 for upper and lower lips, separately and combined.
- The primary effectiveness endpoint was met which demonstrates that Restylane is highly effective for lip augmentation.
Secondary Endpoints:

- The differences between the Restylane and no treatment groups are highly statistically significant in favor of Restylane at all time points through Week 24 by MLFS assessment

  - Includes blinded evaluator, treating investigator, and IPR assessments
  - p-values are statistically significant at all time points
MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined

Proportion (%) of Responders, Independent Photographic Reviewer MLFS

- Week 4: Restylane Treatment - 75.8%, No Treatment - 5.3%
- Week 8: Restylane Treatment - 58.3%, No Treatment - 1.0%
- Week 12: Restylane Treatment - 47.9%, No Treatment - 7.9%
- Week 16: Restylane Treatment - 42.5%, No Treatment - 5.1%
- Week 20: Restylane Treatment - 39.3%, No Treatment - 7.7%
- Week 24: Restylane Treatment - 36.6%, No Treatment - 7.7%

P-Value < 0.001 at all time points

MLFS Responder = at least 1 grade increase from baseline on the MLFS
MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined

Proportion (%) of Responders, Treating Investigator MLFS

<table>
<thead>
<tr>
<th>Time point</th>
<th>Restylane Treatment</th>
<th>No Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>99.2</td>
<td>0</td>
</tr>
<tr>
<td>Week 8</td>
<td>89.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Week 12</td>
<td>88.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Week 16</td>
<td>75.2</td>
<td>5.1</td>
</tr>
<tr>
<td>Week 20</td>
<td>67.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Week 24</td>
<td>47.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

P-Value < 0.001 at all time points

MLFS Responder = at least 1 grade increase from baseline on the MLFS
GAIS Assessment of Improvement

- GAIS improvement is statistically significant between the *Restylane* treatment group and the no treatment group at each time point post baseline
  - Assessed by both subjects and treating investigator using baseline photos for reference
MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Proportion (%) of GAIS Responders Measured by the Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>99.2</td>
</tr>
<tr>
<td>Week 8</td>
<td>96.7</td>
</tr>
<tr>
<td>Week 12</td>
<td>91.7</td>
</tr>
<tr>
<td>Week 16</td>
<td>85.0</td>
</tr>
<tr>
<td>Week 20</td>
<td>76.1</td>
</tr>
<tr>
<td>Week 24</td>
<td>74.1</td>
</tr>
</tbody>
</table>

**P-Value < 0.001 at all time points**

GAIS Responder = score of ≥ 1 on GAIS

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MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined

Proportion (%) of GAIS Responders Measured by the Treating Investigator

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Restylane Treatment</th>
<th>No Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>100.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Week 8</td>
<td>97.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Week 12</td>
<td>90.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Week 16</td>
<td>78.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Week 20</td>
<td>70.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Week 24</td>
<td>60.9</td>
<td>0.0</td>
</tr>
</tbody>
</table>

P-Value < 0.001 at all time points

GAIS Responder = score of ≥ 1 on GAIS
MA-1300-15 Evaluator Agreement

- Concurrence of Effectiveness Measures
  - Using MLFS, each evaluator (blinded evaluator, treating investigator, and IPR) came to the same conclusion independently:
    - Restylane for lip augmentation is highly effective
  - Subjects and treating investigators confirmed aesthetic improvement using the GAIS
MA-1300-15 Evaluator Agreement

- Differences between the evaluators has been seen in other dermal filler programs
  - As identified in the 2003 FDA open public panel
  - As seen in published data

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Blinded live evaluator’s assessment is reliable and accurate:
- Used validated MLFS
- Able to examine the subject’s lips fully
- Blinded to:
  - baseline lip fullness
  - treatment assignment
  - volume used
- Predefined primary endpoint
MA-1300-15 Evaluator Agreement

- All effectiveness endpoints are consistent and highly statistically significant
  - By all evaluators
  - Regardless of tools utilized (MLFS or GAIS)
  - Throughout 24 weeks
MA-1300-15 Summary of Effectiveness

Baseline

Subject 01-013

Week 8
MA-1300-15 Summary of Effectiveness

Baseline

Subject 05-005

Week 8
MA-1300-15 Summary of Effectiveness

Baseline

Subject 05-005

Week 24
MA-1300-15 Summary of Effectiveness

- Effectiveness Summary:
  
  - *Restylane* is highly effective for lip augmentation and provides clinically meaningful visible aesthetic results for at least 6 months

  - These results are demonstrated by the blinded evaluator and confirmed by the treating investigator and IPR using the MLFS

  - These results are also confirmed by the treating investigator and subject GAIS
MA-1300-15 Summary of Safety

Presenter:

Stacy Smith, M.D.
Board Certified Dermatologist
Principal Investigator
MA-1300-15 Summary of Safety

- Extensive safety information collected throughout the study
  - Incidence of all adverse events throughout the study
  - 14 day subject diary data
  - Assessment of lip texture, firmness, symmetry, product palpability, mass formation, lip movement, function, and sensation
MA-1300-15 Summary of Safety

- **Treatment Emergent Adverse Events (TEAE)**
  - **1st Restylane Treatment Subjects**
    - 87% (149/172) experienced a TEAE
  - **2nd Restylane Treatment Subjects**
    - 65% (60/93) experienced a TEAE
  - **Untreated Control Subjects**
    - 38% (17/45) experienced a TEAE
MA-1300-15 Summary of Safety

- Lip Area TEAEs
  - Pain
  - Swelling
  - Tenderness
  - Contusion
  - Erythema
  - Skin Exfoliation

- The proportion of subjects with common lip area TEAEs decreased from the first treatment to the second treatment with *Restylane*
MA-1300-15 Summary of Safety

Common (>5%) Lip Area TEAEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>1st Treatment</th>
<th>2nd Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Swelling</td>
<td>68%</td>
<td>56%</td>
</tr>
<tr>
<td>Tenderness</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Contusion</td>
<td>45%</td>
<td>27%</td>
</tr>
<tr>
<td>Erythema</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Skin Exfoliation</td>
<td>8%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Percent of Subjects
MA-1300-15 Summary of Safety

- TEAEs by Severity
  - Overall, 1088 TEAEs reported during the study:
    - 88% were mild
    - 11% were moderate
    - 1% were severe
MA-1300-15 Summary of Safety

Severity of TEAEs

- Any TEAE: 88% (958/1088) - Mild 11%, Moderate 1%, Severe 1%
- Untreated Control Subjects: 85% (222/250) - Mild 15%, Moderate 0%, Severe 0%
- 1st Restyline Treatment: 85% (672/795) - Mild 14%, Moderate 1%, Severe 0%
- 2nd Restyline Treatment: 99% (264/267) - Mild 1%, Moderate 0%, Severe 0%

CONFIDENTIAL AND PROPRIETARY INFORMATION
MA-1300-15 Summary of Safety

- Severe TEAEs (8 subjects, 10 events)
  - Lip Area – treatment related – 3 subjects
    - Pain (4 events)
    - Swelling (1 event)
    - Onset = 1 to 2 days post treatment
    - Duration = 2 - 5 days
    - Acetaminophen only
  - Other events – not treatment related - 5 subjects
    - Diverticulitis, Uterine Leiomyoma, Influenza, Gastroenteritis, Pneumonia
    - Onset = >34 days post treatment
    - Duration = 1 - 8 days
Summary of Safety

Volume Used versus Adverse Events:

- Post hoc analysis at the request of FDA
- Trend towards more moderate adverse events and higher dose volume at initial treatment, not including touch-up (>3.0 mL of Restylane)
- The number of severe adverse events is so low that trending could not be determined
MA-1300-15 Summary of Safety

Incidence of TEAEs by Severity and Volume of Initial Injection (Not including Touch Up)

Includes AEs after initial treatment until touch-up treatment (or through 14 day after initial treatment for those subjects who did not receive a touch-up)
MA-1300-15 Summary of Safety

- Duration of Common TEAEs
  - Mean duration of less than 15 days
  - Trend toward shorter duration with 2\textsuperscript{nd} vs. 1\textsuperscript{st} treatment
## AE Duration (days)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>First Treatment</th>
<th>Second Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>mean 10.8 range 2-40</td>
<td>mean 7.3 range 2-21</td>
</tr>
<tr>
<td>Pain</td>
<td>mean 4.6 range 1-17</td>
<td>mean 3.4 range 1-11</td>
</tr>
<tr>
<td>Contusion</td>
<td>mean 8.6 range 2-36</td>
<td>mean 6.6 range 2-12</td>
</tr>
<tr>
<td>Tenderness</td>
<td>mean 9.2 range 1-26</td>
<td>mean 10.4 range 2-34</td>
</tr>
<tr>
<td>Skin Exfoliation</td>
<td>mean 5.2 range 1-16</td>
<td>mean 11.0 range 3-19</td>
</tr>
</tbody>
</table>
MA-1300-15 Summary of Safety

- **Serious Adverse Events**
  - 5 serious adverse events:
    1. Diverticulitis
    2. Pneumonia Pneumococcal
    3. Lumbar Spinal Stenosis
    4. Transient Ischaemic Attack
    5. Pregnancy
  - None were related to procedure or device
  - There were no deaths reported during the study and no subject discontinued due to an adverse event
MA-1300-15 Safety Tools

- **Subject Diary**
  - 14 days post baseline
  - 14 days post 6 months
- **Severity grades purposely not defined**
- **Open to subject interpretation**
MA-1300-15 Summary of Diary Data

Percent of *Subjects* Reporting Diary Symptoms (Maximum Severity)

**1st Treatment**
- Tolerable: 36%
- Affects Daily Activities: 10%
- Disabling: 3%
- Missing: 51%

**2nd Treatment**
- Tolerable: 27%
- Affects Daily Activities: 4%
- Disabling: 4%
- Missing: 63%

CONFIDENTIAL AND PROPRIETARY INFORMATION
MA-1300-15 Summary of Diary Data

Percentage of Diary *Entries*

**First Treatment**
- None: 71.03%
- Tolerable: 25.96%
- Affects Daily Activities: 2.78%
- Disabling: 0.24%

**Second Treatment**
- None: 78.69%
- Tolerable: 19.40%
- Affects Daily Activities: 1.74%
- Disabling: 0.16%
MA-1300-15 Summary of Diary Data

Mean Diary Symptom Duration Per Event

Days

<table>
<thead>
<tr>
<th>Diary Symptom</th>
<th>Affects daily activity</th>
<th>Disabling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Treatment</td>
<td>2.21</td>
<td>1.38</td>
</tr>
<tr>
<td>2nd Treatment</td>
<td>1.89</td>
<td>1.05</td>
</tr>
</tbody>
</table>

(Min, Max)
MA-1300-15 Summary of Diary Data

- “Affecting Daily Activities” and “Disabling”
  - Parameters not defined
  - Started directly after treatment
  - Short duration
  - 97% of subjects had at least “improved” GAIS at wk 2 visit
  - 78% chose to receive retreatment at 6 months
Baseline 72 Hours

Subject 04-004

72 Hours
MA-1300-15 Summary of Safety

Subject 04-004

72 Hours 2 Weeks
MA-1300-15 Summary of Safety

Baseline 72 Hours
Subject 10-011
MA-1300-15 Summary of Safety

72 Hours

Subject 10-011

2 Weeks
MA-1300-15 Summary of Safety

9 Lip Safety Assessments

- Lip Texture
- Lip Firmness
- Lip Symmetry
- Device Palpability
- Lip Movement
- Lip Function
- Lip Sensation
- Mass Formation
- Repeat Injection Ease
### Lip Texture (upper and lower lips assessed separately)

<table>
<thead>
<tr>
<th>NORMAL</th>
<th>ABNORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Mild</strong></td>
</tr>
<tr>
<td>Texture of the lip was even without visible undulations or excessive coarseness beyond that expected for stated age.</td>
<td>The lip showed a single area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that could be visualized only with close inspection.</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>The lip showed one area of textural irregularity (less than ¼ of the lip area) at conversational distance.</td>
</tr>
</tbody>
</table>
### Lip Firmness (upper and lower lips assessed separately)

<table>
<thead>
<tr>
<th>NORMAL</th>
<th>ABNORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip was supple when compressed laterally and surface distorted readily with minimal pressure. Pressure with a narrow diameter instrument (cotton-tipped applicator, toothpick etc) caused a focal depression in the surface of the lip. Upon palpation, lip was absent of abnormal structures such as scars or lumps; normal product feel without being visible.</td>
<td>Mild: Lip was slightly firm with lateral compression or required slightly greater than normal pressure to distort the surface. Moderate: Lip was firm with lateral compression or required distinctly greater than normal pressure to distort the surface or pressure with a narrow diameter instrument (cotton-tipped applicator or toothpick) caused a broader depression in the surface of the lip. Severe: Lip was 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 was felt and was visually distracting.</td>
</tr>
</tbody>
</table>
MA-1300-15 Summary of Safety

Lip Firmness

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>270</td>
<td>0</td>
</tr>
<tr>
<td>72 Hours</td>
<td>207</td>
<td>61</td>
</tr>
<tr>
<td>Touch Up</td>
<td>142</td>
<td>22</td>
</tr>
<tr>
<td>Week 2</td>
<td>214</td>
<td>44</td>
</tr>
<tr>
<td>Week 4</td>
<td>224</td>
<td>28</td>
</tr>
<tr>
<td>Week 8</td>
<td>228</td>
<td>16</td>
</tr>
<tr>
<td>Week 12</td>
<td>227</td>
<td>15</td>
</tr>
<tr>
<td>Week 16</td>
<td>229</td>
<td>13</td>
</tr>
<tr>
<td>Week 20</td>
<td>225</td>
<td>9</td>
</tr>
<tr>
<td>Week 24</td>
<td>230</td>
<td>2</td>
</tr>
</tbody>
</table>
### Lip Symmetry (upper and lower lips assessed separately)

<table>
<thead>
<tr>
<th>NORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>One side of the lip balanced or mirrored the other side.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABNORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>One side of the lip showed a 1 mm or less difference in height or a 1 mm or less difference in the length of the vermilion at repose.</td>
</tr>
</tbody>
</table>

| Moderate |
| One side of the lip showed 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. |

| Severe |
| One side of the lip showed a greater than 2 mm difference in height or a greater than 2 mm difference in the length of the vermilion at repose. |
MA-1300-15 Summary of Safety

Lip Symmetry

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>72 Hours</th>
<th>Touch Up</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>10</td>
<td>44</td>
<td>28</td>
<td>27</td>
<td>19</td>
<td>13</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Normal</td>
<td>260</td>
<td>224</td>
<td>136</td>
<td>231</td>
<td>233</td>
<td>231</td>
<td>225</td>
<td>227</td>
<td>221</td>
<td>220</td>
</tr>
</tbody>
</table>

CONFIDENTIAL AND PROPRIETARY INFORMATION
### MA-1300-15 Summary of Safety

- **Lip Movement**

<table>
<thead>
<tr>
<th>Member</th>
<th>Simmering</th>
<th>Drab</th>
<th>Babble</th>
<th>Spear</th>
<th>Peep</th>
<th>Fire</th>
<th>Staff</th>
<th>Verse</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

Can the subject effectively pronounce the following words?

This table shows whether the subject can pronounce each word. The columns represent different words, and the rows indicate whether the subject can pronounce them (YES) or not (NO).
MA-1300-15 Summary of Safety

Lip Movement - Did Subject Effectively Pronounce The Word?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>0</td>
<td>135</td>
</tr>
<tr>
<td>72 Hours</td>
<td>0</td>
<td>134</td>
</tr>
<tr>
<td>Touch Up</td>
<td>0</td>
<td>82</td>
</tr>
<tr>
<td>Week 2</td>
<td>0</td>
<td>129</td>
</tr>
<tr>
<td>Week 4</td>
<td>0</td>
<td>126</td>
</tr>
<tr>
<td>Week 8</td>
<td>0</td>
<td>122</td>
</tr>
<tr>
<td>Week 12</td>
<td>1</td>
<td>121</td>
</tr>
<tr>
<td>Week 16</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>Week 20</td>
<td>0</td>
<td>117</td>
</tr>
<tr>
<td>Week 24</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td>2 Weeks Post 6 Month</td>
<td>0</td>
<td>104</td>
</tr>
<tr>
<td>4 Weeks Post 6 Month</td>
<td>1</td>
<td>119</td>
</tr>
</tbody>
</table>

CONFIDENTIAL AND PROPRIETARY INFORMATION
MA-1300-15 Summary of Safety

Lip Function - Can Subject Drink/Suck Through A Straw Effectively?

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>134</td>
<td>133</td>
<td>82</td>
<td>128</td>
<td>126</td>
<td>122</td>
<td>119</td>
<td>120</td>
<td>117</td>
<td>115</td>
</tr>
</tbody>
</table>
Lip Sensation

- Monofilament Test
- Cotton Wisp Test

3 different points on the upper and lower lips were randomly tested. Subjects were blindfolded and asked to acknowledge sensation at each point.
MA-1300-15 Summary of Safety

Lip Sensation - Did Subject Feel the Monofilament?

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>72 Hours</th>
<th>Touch Up</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>135</td>
<td>134</td>
<td>82</td>
<td>129</td>
<td>126</td>
<td>122</td>
<td>120</td>
<td>120</td>
<td>117</td>
<td>116</td>
</tr>
</tbody>
</table>

Number of Assessments (Upper and Lower Lip Combined)
MA-1300-15 Summary of Safety

Lip Sensation - Did Subject Feel the Cotton Wisp?

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>72 Hours</th>
<th>Touch Up</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td>135</td>
<td>134</td>
<td>82</td>
<td>129</td>
<td>126</td>
<td>122</td>
<td>121</td>
<td>121</td>
<td>117</td>
<td>116</td>
</tr>
</tbody>
</table>
## MA-1300-15 Summary of Safety

### Device Palpability

#### UPPER LIP – Is the device palpable?

<table>
<thead>
<tr>
<th>NO</th>
<th>Expected Feel (Normal)</th>
<th>YES</th>
<th>Unexpected Feel (Abnormal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device is not palpable</td>
<td>Structure, upon palpation, has the feel of uniform density, without unexpected lumpiness</td>
<td></td>
<td>Structure, upon palpation, has the feel of non-uniform density or has unexpected lumpiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If abnormal, record as an Adverse Event</td>
</tr>
</tbody>
</table>

#### LOWER LIP – Is the device palpable?

<table>
<thead>
<tr>
<th>NO</th>
<th>Expected Feel (Normal)</th>
<th>YES</th>
<th>Unexpected Feel (Abnormal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device is not palpable</td>
<td>Structure, upon palpation, has the feel of uniform density, without unexpected lumpiness</td>
<td></td>
<td>Structure, upon palpation, has the feel of non-uniform density or has unexpected lumpiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If abnormal, record as an Adverse Event</td>
</tr>
</tbody>
</table>
MA-1300-15 Summary of Safety

Device Palpability

<table>
<thead>
<tr>
<th>Time</th>
<th>Palpable Expected Feel</th>
<th>Palpable Unexpected Feel</th>
<th>Not palpable</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 Hours</td>
<td>254</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Touch Up</td>
<td>161</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Week 2</td>
<td>246</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Week 4</td>
<td>239</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Week 8</td>
<td>220</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Week 12</td>
<td>210</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Week 16</td>
<td>197</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>Week 20</td>
<td>164</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>Week 24</td>
<td>143</td>
<td>0</td>
<td>89</td>
</tr>
</tbody>
</table>
MA-1300-15 Summary of Safety

- Reinjection Difficulty

If this is a re-treatment, was this treatment more difficult to administer than the first treatment?
- Yes
- No
- N/A (This is the initial treatment for the subject)

If yes, please note the reason why:
- Scar Tissue
- Presence of previous dermal filler creates more resistance
- Other: ____________________________
MA-1300-15 Summary of Safety

Repeat Treatment - Was Second Treatment More Difficult?

- No: 91
- Yes: 2

CONFIDENTIAL AND PROPRIETARY INFORMATION
MA-1300-15 Summary of Safety

- Lip Safety Assessment Summary
  - Texture and Firmness - Almost all mild, less than 4 weeks
  - Symmetry – 16 severe, resolved in 4 weeks, all with favorable GAIS scores
  - Palpability – few unexpected, resolved with massage
  - Movement, Function, Sensation, Mass Formation, Reinjection Ease
    - All unremarkable
Risk Benefit Profile

- TEAEs of moderate to severe
  - GAIS improved or better – 97%
  - Retreatment – 71%

- Diary entries of ADA or disabling
  - GAIS improved or better – 97%
  - Retreatment – 78%

- Any abnormality of Lip Safety assessments
  - GAIS improved or better – 99%
  - Retreatment – 77%
MA-1300-15 Summary of Safety

- Acceptable Risk-Benefit Profile:
  - TEAEs: mild and transient
  - Diary Data: subject based, comprehensive, generally short lived and well tolerated
  - Lip specific safety assessment: extensive and stringent, minimal abnormalities none long lasting
  - Repeat treatment does not pose additional safety concerns
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

Presenter:
Julius Few, M.D.
Board Certified Plastic Surgeon
Clinical Background

Clinical Background

- Significant experience treating patients with skin of color

- Fitzpatrick skin types IV to VI represent a very small number of patients seeking lip augmentation

- Aesthetic endpoint desires are different from general population
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

General Overview:

- There were a total of 41 (24%) subjects with Fitzpatrick skin type IV and V in the safety population
  - 31 randomized to Restylane treatment group
  - 10 randomized to no treatment group

- 39 (of 41) received at least a single treatment with Restylane
  - 31 at baseline
  - 8 at 6 months for first treatment

- 22 (of 31) received a second treatment at 6 months
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

- Effectiveness Results Week 8:
  - Proportion of MLFS and GAIS responders consistent with overall study population
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

Upper and Lower Lips Combined

Proportion (%) of Responders at Week 8,
Blinded Evaluator MLFS

<table>
<thead>
<tr>
<th>Population</th>
<th>Restylane Treatment Group</th>
<th>No Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzpatrick IV and V</td>
<td>93.5%</td>
<td>30%</td>
</tr>
<tr>
<td>Overall ITT</td>
<td>92.6%</td>
<td>28.9%</td>
</tr>
</tbody>
</table>

p-value < 0.001

MLFS Responder = at least 1 grade increase from baseline on the MLFS
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

Upper and Lower Lips Combined

Proportion (%) of GAIS Responders at Week 8, Subject GAIS

Study Population
- Fitzpatrick IV and V
- Overall Population

GAIS Responder = score of ≥ 1 on GAIS

P-Value < 0.001
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

Upper and Lower Lips Combined

Proportion (%) of GAIS Responders at Week 8, Investigator GAIS

- Fitzpatrick IV and V: 100%
- Overall Population: 57.5%

P-Value < 0.001

GAIS Responder = score of ≥ 1 on GAIS
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

Effectiveness Summary at Week 8:

- The difference in the proportion of MLFS responders between the Restylane and no treatment subjects in the Fitzpatrick skin type IV and V subgroup at Week 8 was statistically significant for the upper and lower lips combined.
  - p-value <0.001
- Similar to ITT population
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

- Treatment Emergent Adverse Events (TEAEs)
  - The incidence of subjects with TEAEs in the first and second treatment with Restylane were very similar
  - In the no treatment group there were 3 subjects with a TEAE
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

- Treatment Emergent Adverse Events (TEAEs)
- The commonly reported TEAEs are same as in the overall population
  - Pain
  - Swelling
  - Tenderness
  - Contusion
  - Erythema
  - Skin Exfoliation
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

TEAE Comparison - 1st Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/39 Pain</td>
<td>13%</td>
</tr>
<tr>
<td>36/172</td>
<td>21%</td>
</tr>
<tr>
<td>26/39 Swelling</td>
<td>67%</td>
</tr>
<tr>
<td>99/172</td>
<td>58%</td>
</tr>
<tr>
<td>8/39 Tenderness</td>
<td>21%</td>
</tr>
<tr>
<td>38/172</td>
<td>22%</td>
</tr>
<tr>
<td>17/39 Contusion</td>
<td>44%</td>
</tr>
<tr>
<td>75/172</td>
<td>44%</td>
</tr>
<tr>
<td>8/39 Erythema</td>
<td>21%</td>
</tr>
<tr>
<td>29/172</td>
<td>17%</td>
</tr>
<tr>
<td>4/39 Skin Exfoliation</td>
<td>10%</td>
</tr>
<tr>
<td>14/172</td>
<td>8%</td>
</tr>
</tbody>
</table>

Fitzpatrick Skin Types IV and V
Overall Population
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

TEAE Comparison - 2nd Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Fitzpatrick Skin Types IV and V</th>
<th>Overall Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Swelling</td>
<td>77%</td>
<td>55%</td>
</tr>
<tr>
<td>Tenderness</td>
<td>23%</td>
<td>17%</td>
</tr>
<tr>
<td>Contusion</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>Erythema</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Skin Exfoliation</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>
MA-1300-15 Subgroup Analysis
Fitzpatrick Skin Types IV and V

- Safety Summary:
  - There were no reports of keloids, scars or dyspigmentation events
  - Subjects with Fitzpatrick skin type IV or V appear to have a similar adverse event profile compared to the total study population
  - These data are consistent with a 150 subject study evaluating effectiveness and safety in Fitzpatrick skin types IV, V and VI in NLFs (MA-1400-01)
Overall Summary:

- *Restylane* is also effective in darker Fitzpatrick skin types for submucosal implantation for lip augmentation.

- The safety profile for this subgroup is acceptable, and consistent with the overall study population.
MA-1300-15 Overall Summary

Presenter:

Ira Lawrence, M.D.
Chief Medical Officer, Senior Vice President
Research and Development
Medicis Pharmaceutical Corporation
Points for Consideration Regarding PAS

- Expanded indication of already approved product
  - Lengthy worldwide experience
  - Extensively studied dermal filler
  - Non permanent implant
MA-1300-15 Overall Summary

- Robust Effectiveness data:
  - Highly statistically significant:
    - At all time points
    - By all evaluators
    - In all effectiveness measures
  - Aesthetically meaningful results in vast majority of patients at all time points
  - High level of patient satisfaction
MA-1300-15 Overall Summary

- Comprehensive Safety Profile:
  - Generally mild and transient AEs
  - Most patients chose re-treatment
  - No evidence of functional impairment
  - Repeat treatment does not pose additional risks
MA-1300-15 Overall Summary

- Favorable Risk-Benefit Assessment
  - Highly effective (MLFS)
  - High level of aesthetic satisfaction (GAIS)
  - 80% of eligible subjects chose to receive re-treatment
    - 78% patients who experienced an AE that Affected Daily Activities or was Disabling chose to receive re-treatment
Overall Summary

- Addition of the expanded indication to the IFU
  - Provides important safety and effectiveness information to patients and physicians
  - Will permit the training of healthcare providers
Based upon the data presented, Medicis believes that there is a reasonable assurance that Restylane is safe and effective for the expanded indication of submucosal implantation for lip augmentation.

The benefits of Restylane for submucosal implantation for lip augmentation outweigh the risks.
Thank You