



Restylane[®] Injectable Gel Lip Augmentation Indication

General and Plastic Surgery Devices
Panel Meeting
April 27, 2011

Restylane Overview

Presenter:

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Executive Vice President, Chief Scientific Officer
Medicis Pharmaceutical Corporation

Presentation Agenda

Topic:

Restylane Overview

Clinical Practice

Program Development & Background

Summary of Effectiveness

Summary of Safety

Subgroup Analysis

Conclusions

Presented By:

Dr. Mitchell Wortzman

Dr. Robert Weiss

Xiaoming Lin

Dr. Ira Lawrence

Dr. Stacy Smith

Dr. Julius Few

Dr. Ira Lawrence

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

¹ American Society of Plastic Surgeons Report of the 2010 Plastic Surgery Statistics

² Beasley KL, Weiss MA, Weiss RA. Hyaluronic acid fillers: a comprehensive review. *Facial Plast Surg.* 2009 25(2): 86-94.

Clinical Practice

- Demographics of patients seeking soft tissue filler procedure ¹
 - Predominantly female (95%)
 - Over the age of 40 (83%)
 - 30 – 39 years old = 12%
 - 20 – 29 years old = 5%
 - 13 – 19 years old = 1%

1. American Society of Plastic Surgeons Report of the 2010 Plastic Surgery Statistics

Clinical Practice

- Ethnicity breakdown for cosmetic procedures ¹
 - Caucasian = 70%
 - Hispanic = 11%
 - African-American = 8%
 - Asian-American = 6%
 - Other = 4%

1. American Society of Plastic Surgeons Report of the 2010 Plastic Surgery Statistics

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 ¹
 - Extensive European use of hyaluronic acid for lips published in 1998 ²

¹ Kesselring UK Rejuvenation of the lips *Ann Plast Surg.* 1986 Jun;16(6):480-6.

² Olenius M, The first clinical study using a new biodegradable implant for the treatment of lips, wrinkles, and folds. *Aesth. Plast. Surg.* 22:97–101, 1998

Clinical Practice

- Publication of US practice review shows 51% of HA dermal filler users received lip augmentation ¹
- Recent ASAPS survey showed significant percentage of use of HA fillers in US is for lip augmentation ²

1 OIMorris CL, Stinnett SS, Woodward JA. Patient-preferred sites of restylane injection in periocular and facial soft-tissue augmentation. *Ophthal Plast Reconstr Surg*. 2008 Mar-Apr;24(2):117-21

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 ¹

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

¹. Hanke CW, Rohrich RJ, Busso M, Carruthers A, Carruthers J, Fagien S, Fitzgerald R, Glogau R, Greenberger PE, Lorenc ZP, Marmur ES, Monheit GD, Pusic A, Rubin MG, Rzany B, Sclafani A, Taylor S, Weinkle S, McGuire MF, Pariser DM, Casas LA, Collishaw KJ, Dailey RA, Duffy SC, Edgar EJ, Greenan BL, Haenlein K, Henrichs RA, Hume KM, Lum F, Nielsen DR, Poulsen L, Shoaf L, Seward W, Begolka WS, Stanton RG, Svedman KJ, Thomas JR, Sykes JM, Wargo C, Weiss RA. Facial Soft-Tissue Fillers conference: Assessing the State of the Science. *J Am Acad Dermatol.* 2011 Apr;64(4 Suppl):S66-85, S85.e1-136.

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

Pilot Study MA-1300-13K

■ 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)



Photo 1



MLFS Photographs - Upper Lip

Thin (2)



MLFS Photographs - Upper Lip

Medium (3)



Photo 1



MLFS Photographs - Upper Lip

Full (4)



MLFS Photographs – Upper Lip

Very Full (5)



MLFS Photoguide

Lower Lip

MLFS Photographs - Lower Lip

Very Thin (1)



MLFS Photographs - Lower Lip

Thin (2)



Photo 2



MLFS Photographs - Lower Lip

Medium (3)

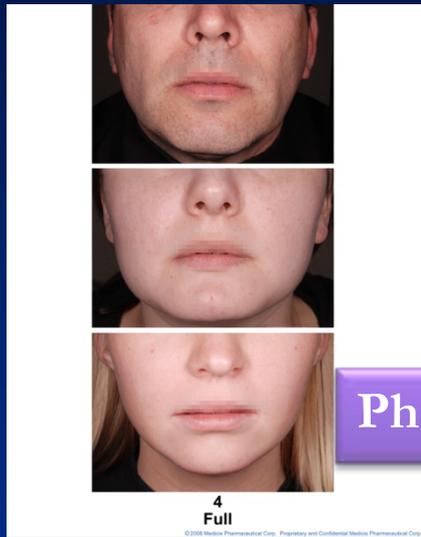


Photo 2



MLFS Photographs - Lower Lip

Full (4)



MLFS Photographs - Lower Lip

Very Full (5)

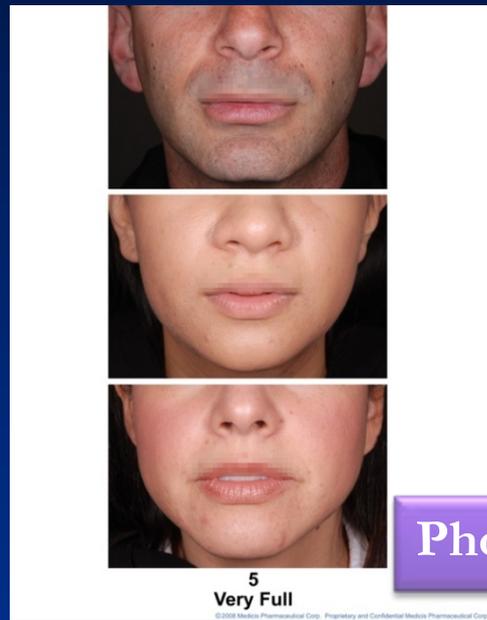


Photo 3



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:

| Literature | Weighted Kappa Coefficient | Interpretation |
|------------------------------|----------------------------|--------------------------|
| Landis and Koch ¹ | < 0.20 | 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 |

¹ Landis, J.R.; & Koch, G.G. (1977). The Measurement of Observer Agreement for Categorical Data. *Biometrics* 33 (1): 159–174. doi: 10.2307/2529310. PMID 843571

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

Pilot Study MA-1300-14

- 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

Pilot Study MA-1300-14

- 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:

| 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 |

MA-1300-15 Study Design

- Subjects randomized to *Restylane* treatment at baseline received a 2nd treatment at 6 months
- Subjects randomized to no treatment at baseline received their 1st treatment at 6 months
- The safety of all subjects was monitored throughout the study

MA-1300-15 Study Design

- 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

MA-1300-15 Study Design

- 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

| |
|--|
| Current Subject Photograph Label: |
| Visit 10 – 24 Week Follow-up/Treatment |
| Visit 11 – 72 hours Post Treatment |
| Visit 12 – 2 Week Post Treatment |
| Visit 13 – 4 Week Post Treatment |

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

| | |
|----|--------------------|
| 3 | Very Much Improved |
| 2 | Much Improved |
| 1 | Improved |
| 0 | No Change |
| -1 | Worse |
| -2 | Much Worse |
| -3 | Very Much Worse |

MA-1300-15 Summary of Effectiveness

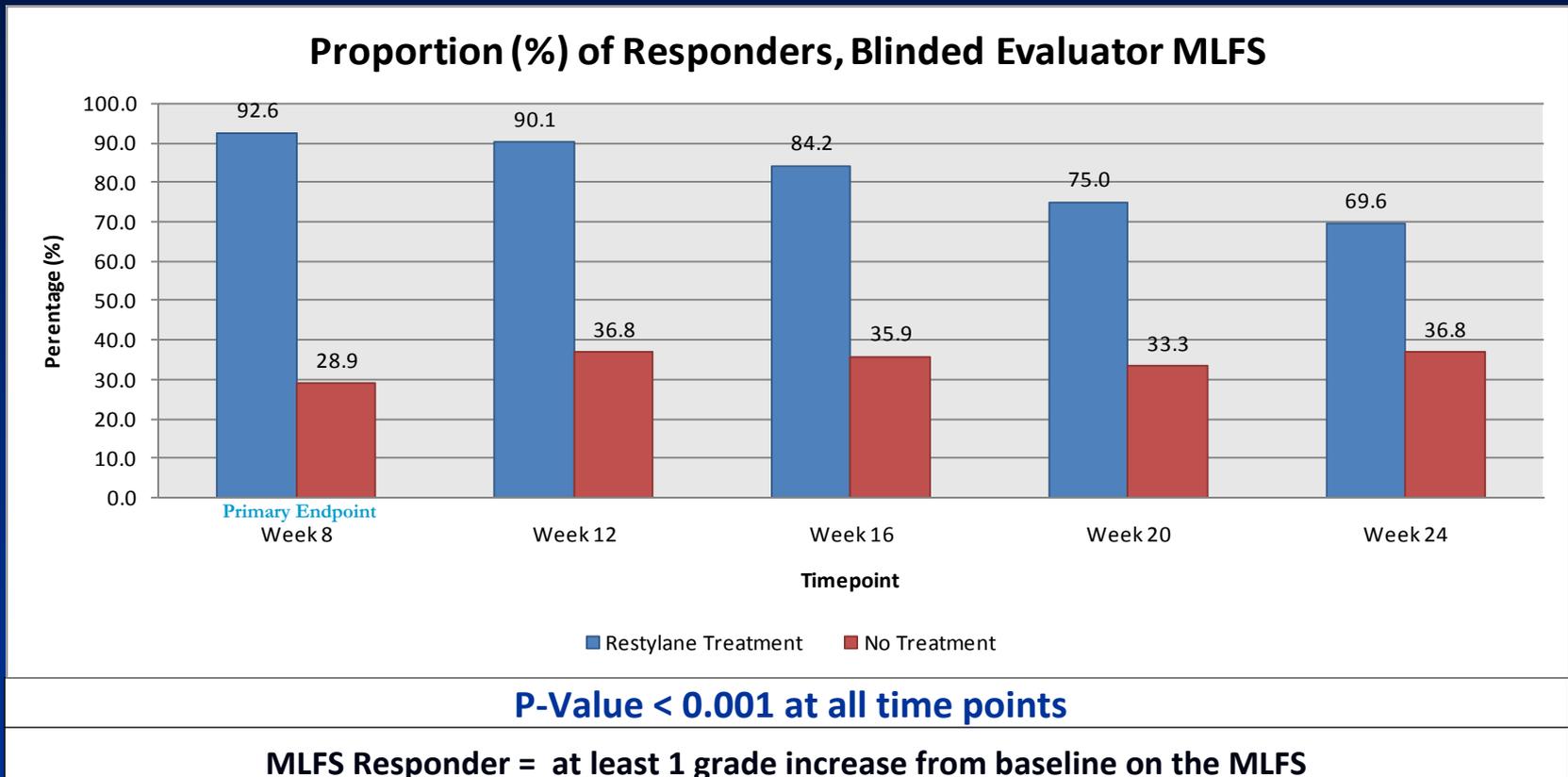
- Primary endpoint: Week 8 blinded evaluator MLFS assessment
 - *Restylane* treatment group:
 - 94.8% were upper lip MLFS responders from baseline
 - 94.3% were lower lip MLFS responders from baseline
 - 92.6% were upper and lower lips combined MLFS responders from baseline

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



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

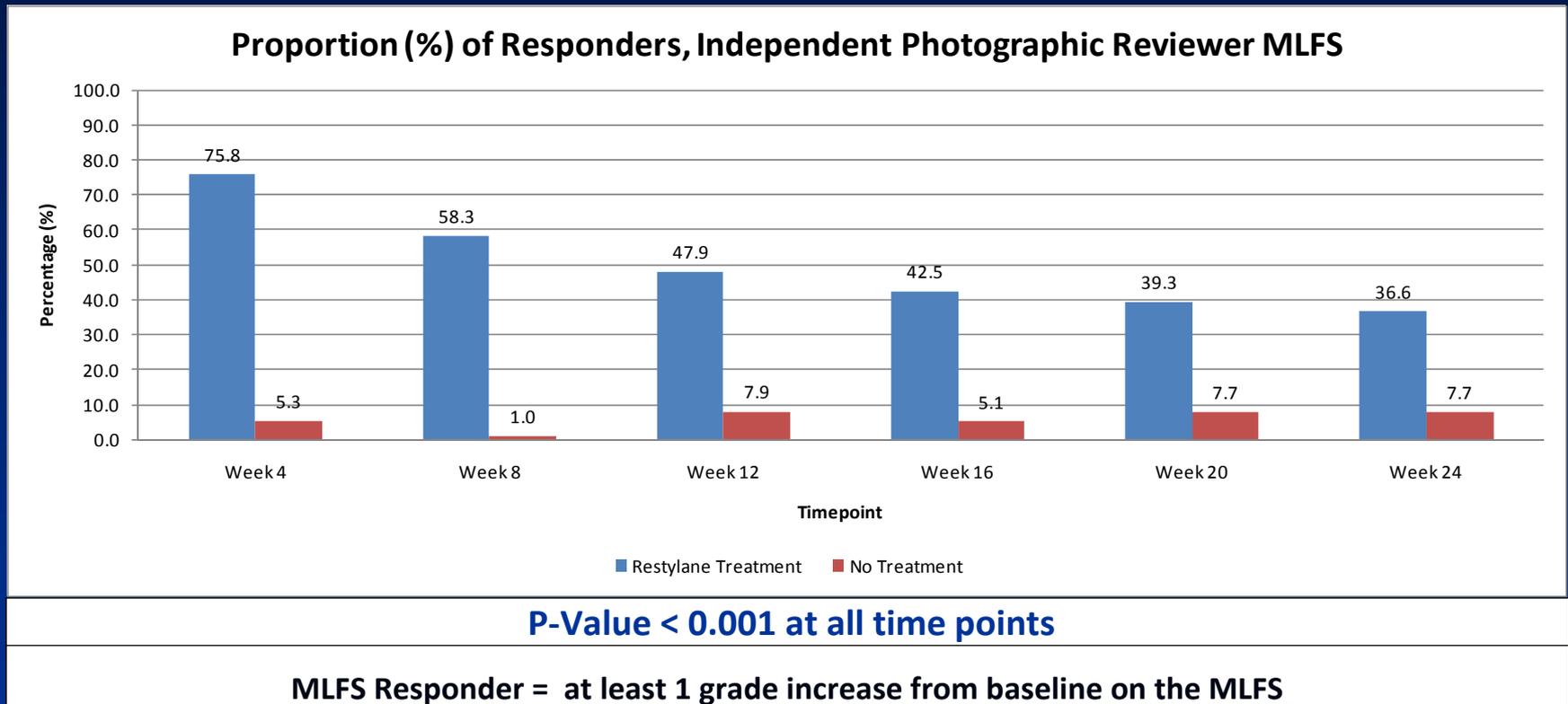
MA-1300-15 Summary of Effectiveness

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

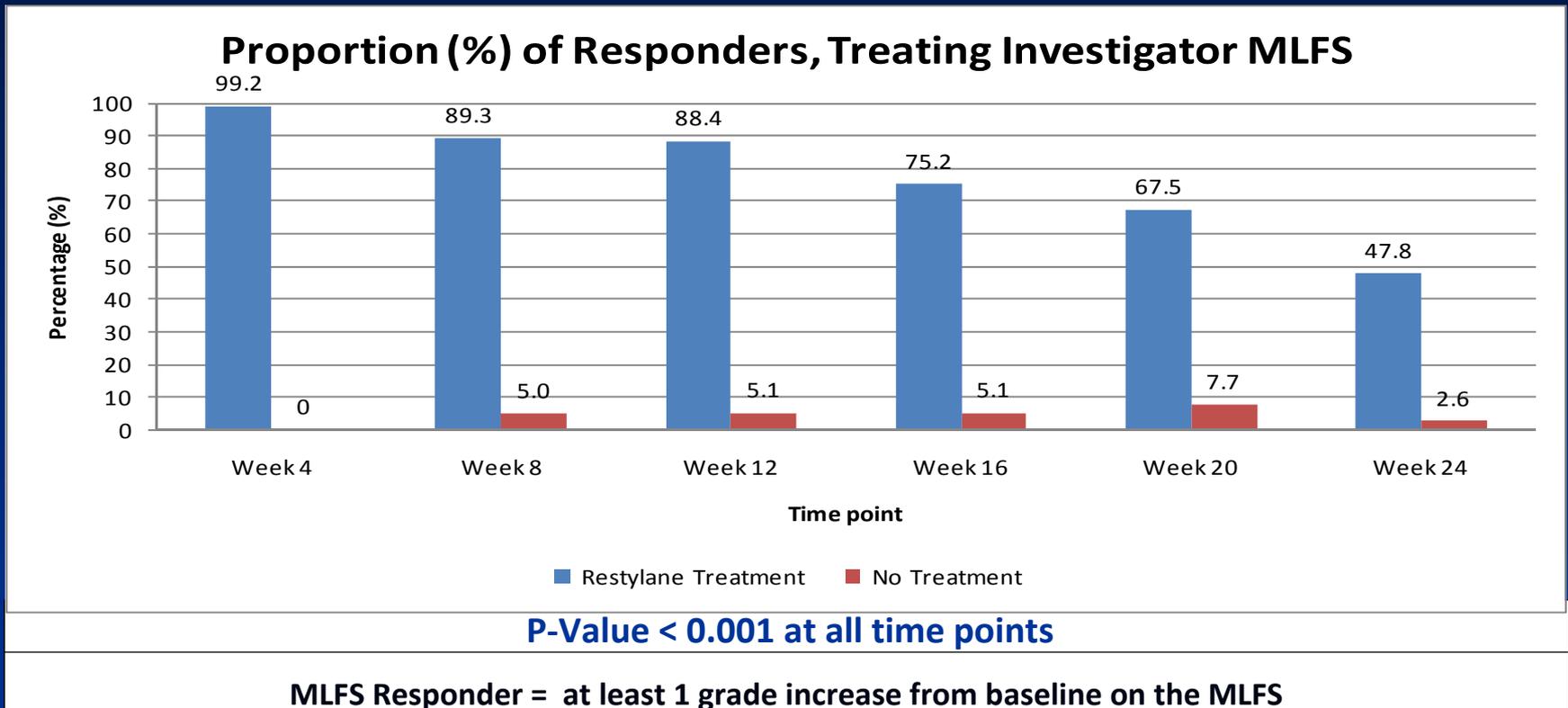
MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined



MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined



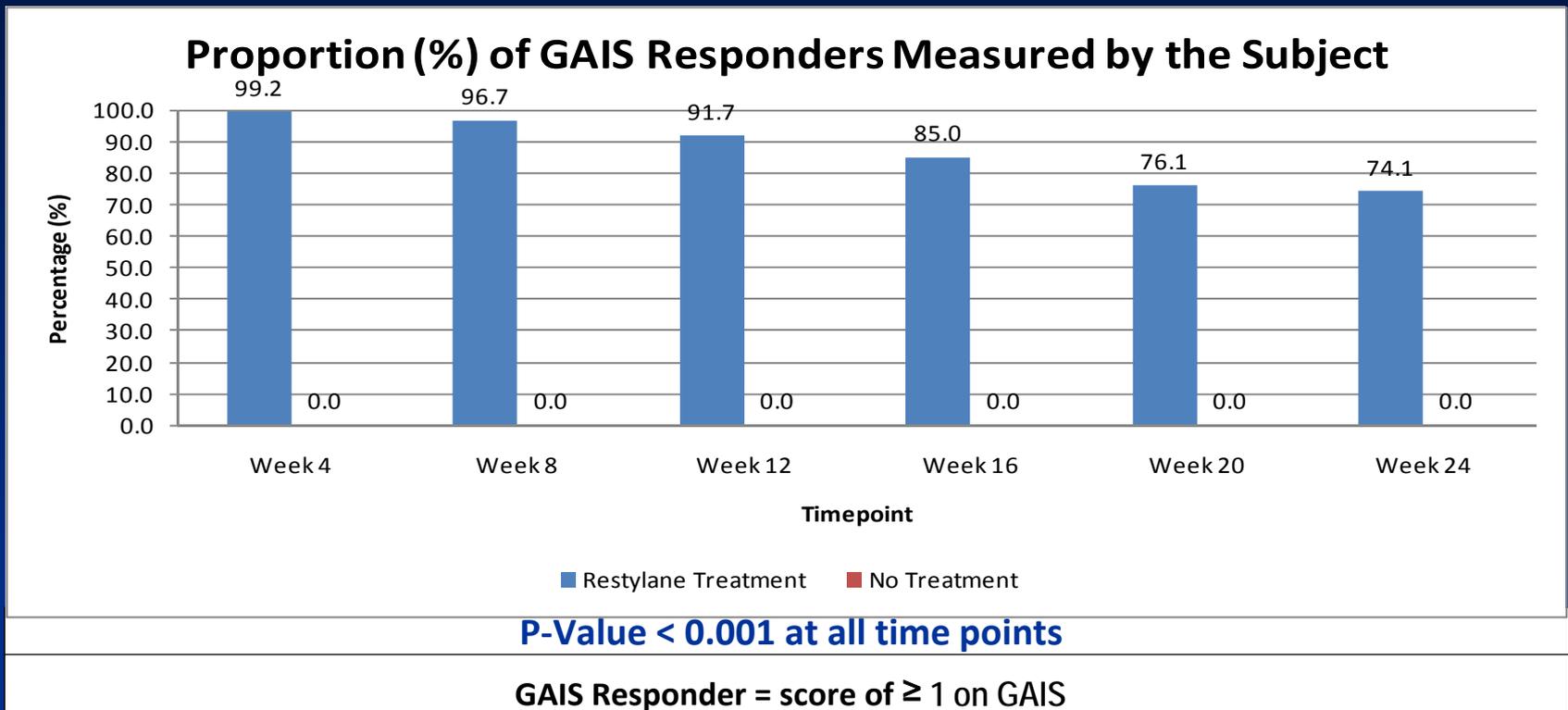
MA-1300-15 Summary of Effectiveness

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

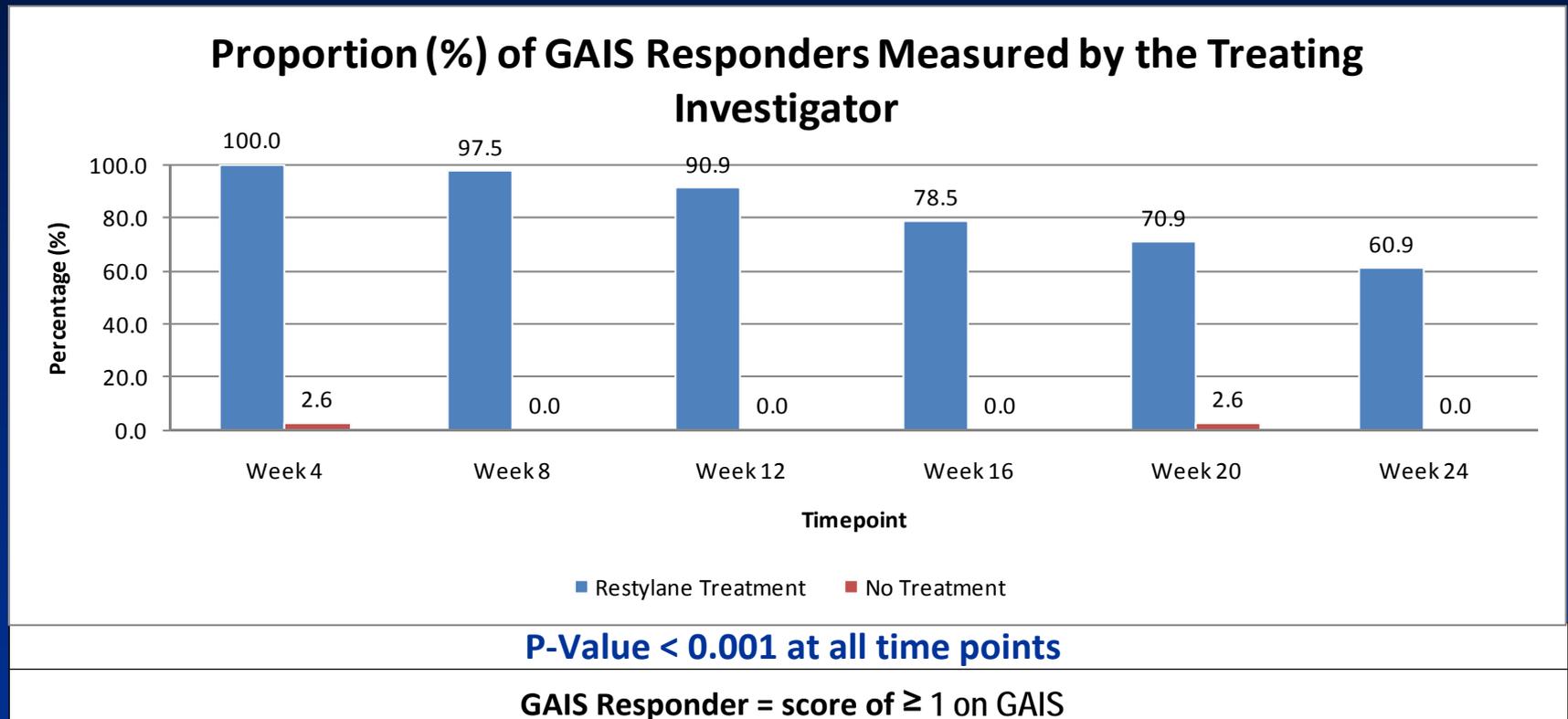
MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined



MA-1300-15 Summary of Effectiveness

Upper and Lower Lips Combined



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 data¹

¹ Cohen, S., Holmes, R. Artecoll: A Long-Lasting Injectable Wrinkle Filler Material: Report of Controlled, Randomized, Multicenter Clinical Trial of 251 Subjects. *Plast. Reconstr. Surg.* 114: 964, 2004

MA-1300-15 Evaluator Agreement

- 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



Week 8

Subject 01-013

MA-1300-15 Summary of Effectiveness



Baseline



Week 24

Subject 01-013

MA-1300-15 Summary of Effectiveness



Baseline



Week 8

Subject 05-005

MA-1300-15 Summary of Effectiveness



Baseline



Week 24

Subject 05-005

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

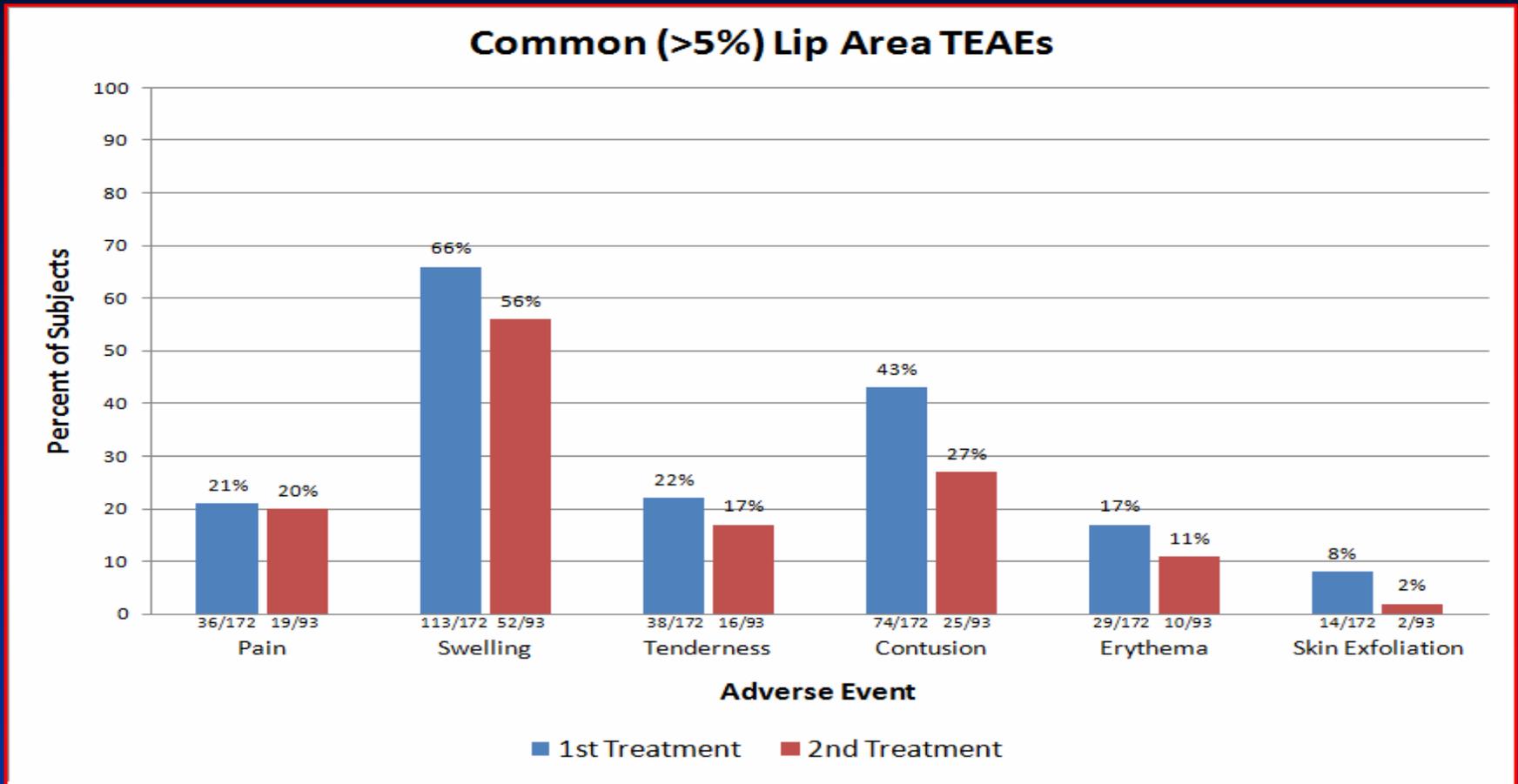
MA-1300-15 Summary of Safety

- 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

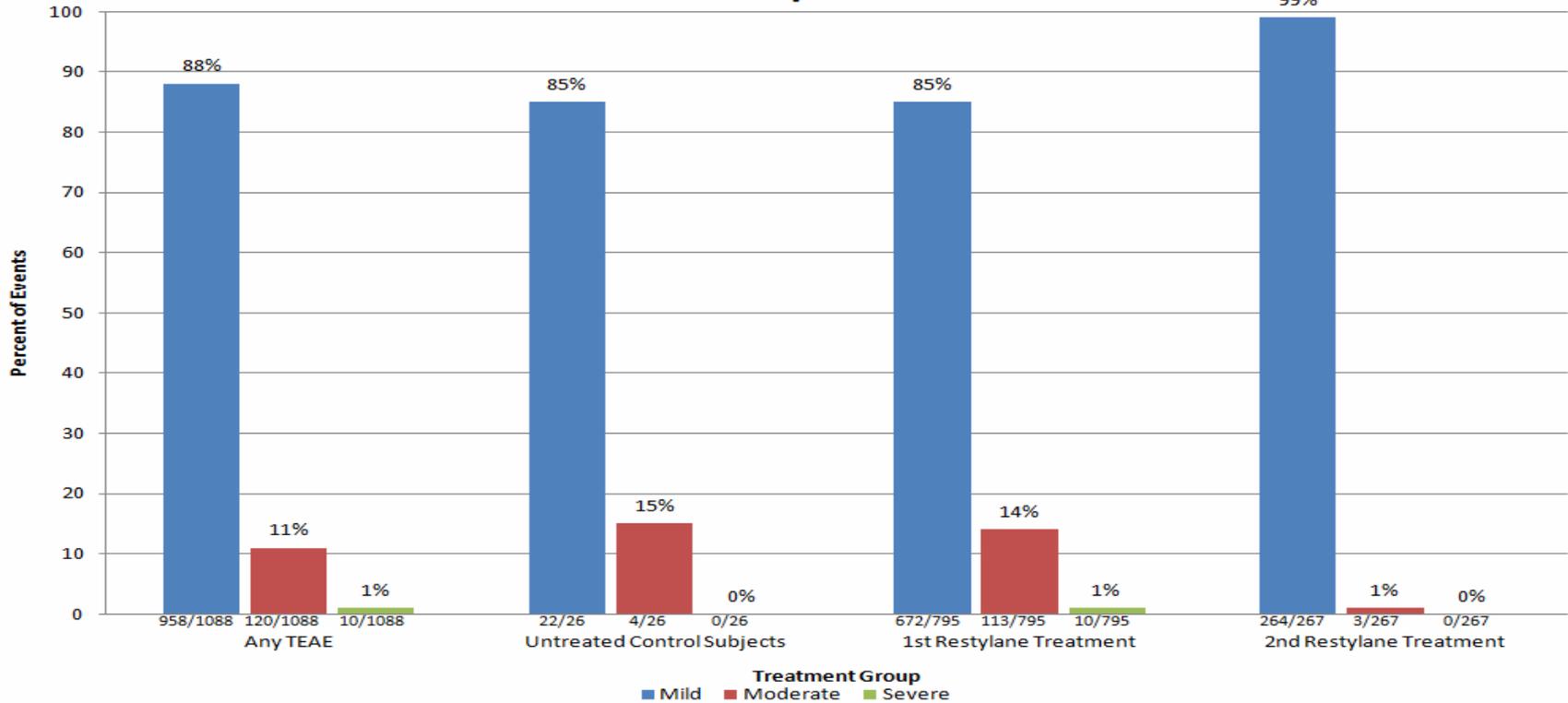


MA-1300-15 Summary of Safety

- 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



MA-1300-15 Summary of Safety

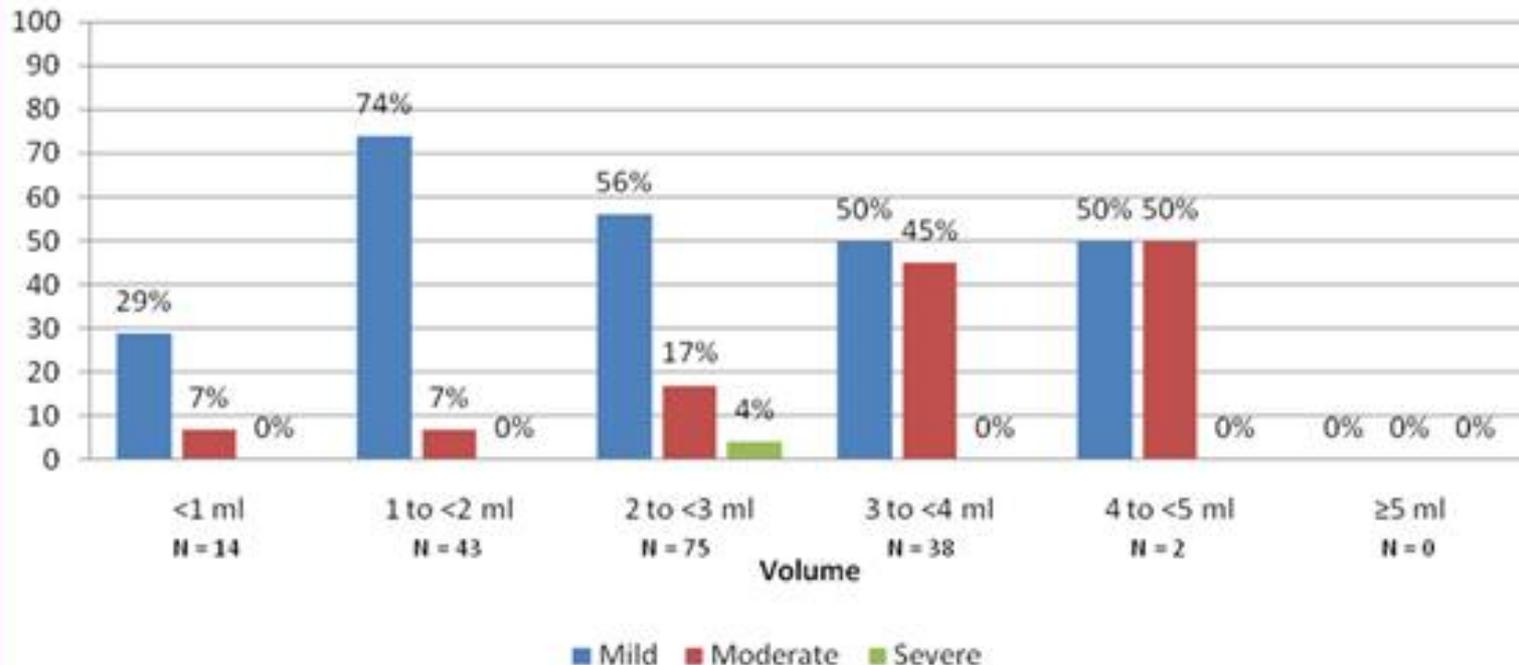
- Severe TEAEs (8 subjects, 10 events)
 - Lip Area – treatment related – 3 subjects
 - Pain (4 events)
 - Swelling (1 event)
 - Onset = 1 to 2 days post treatment
 - Duration = 2 - 5 days
 - Acetaminophen only
 - Other events – not treatment related - 5 subjects
 - Diverticulitis, Uterine Leiomyoma,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

MA-1300-15 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 2nd vs. 1st treatment

AE Duration (days)

| TEAE | First Treatment | Second Treatment |
|------------------|-------------------------|-------------------------|
| Swelling | mean 10.8 range 2-40 | mean 7.3 range 2-21 |
| Pain | mean 4.6 range 1-17 | mean 3.4 range 1-11 |
| Contusion | mean 8.6 range 2-36 | mean 6.6 range 2-12 |
| Tenderness | mean 9.2 range 1-26 | mean 10.4 range 2-34 |
| Skin Exfoliation | mean 5.2 range 1-16 | mean 11.0 range 3-19 |

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

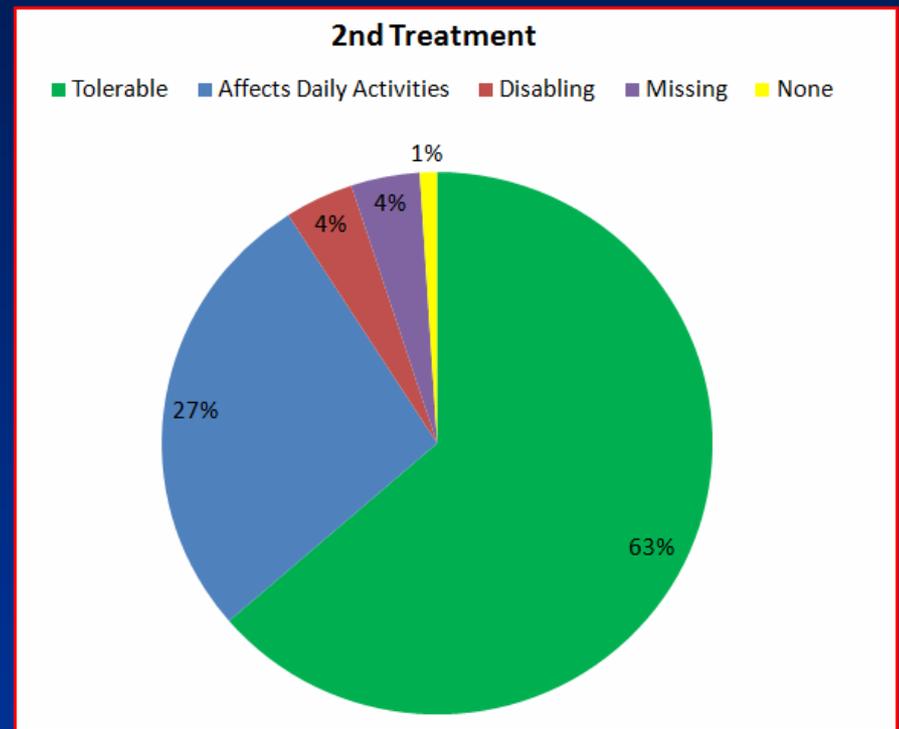
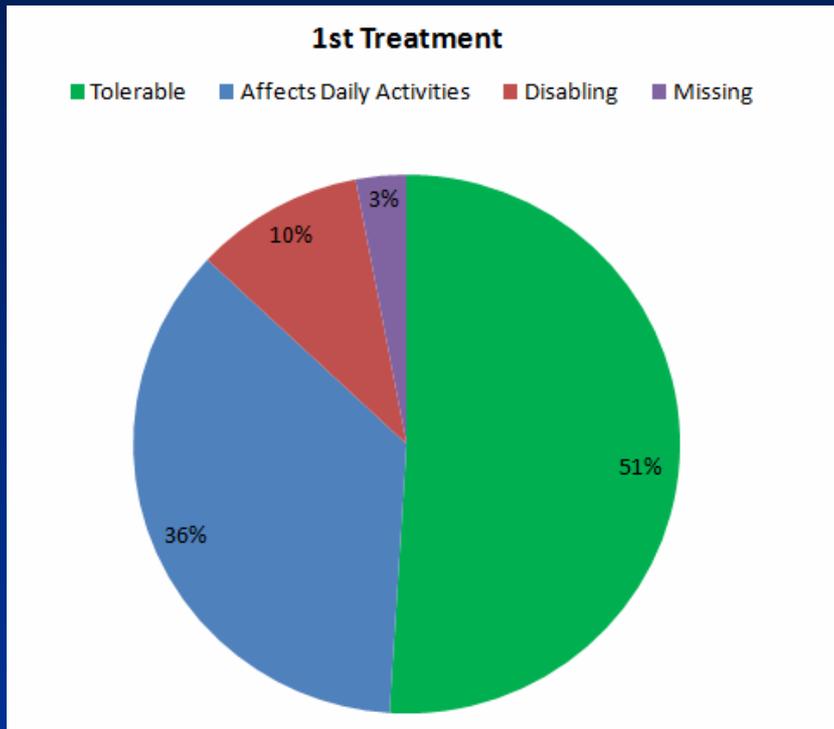
Treatment Day 1: _____ / _____ / _____
Site Number Subject Number Subject Initials

Date: ____ / ____ / ____
Month Day Year

| | Upper Lip | Lower Lip |
|---|--|--|
| Bruising | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling |
| Redness | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling |
| Swelling | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling |
| Pain <small>(including burning)</small> | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling |
| Tenderness | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling |
| Itching | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling | <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Tolerable <input type="checkbox"/> ² Affects daily activities <input type="checkbox"/> ³ Disabling |
| Other <small>(describe)</small> | _____ _____ _____ | |

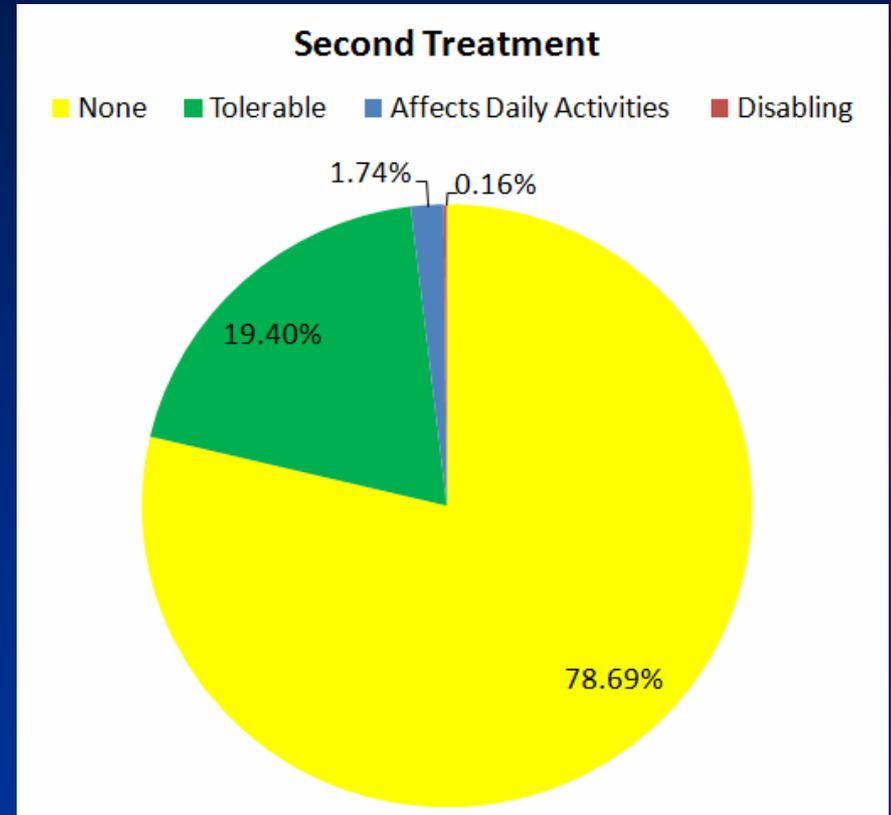
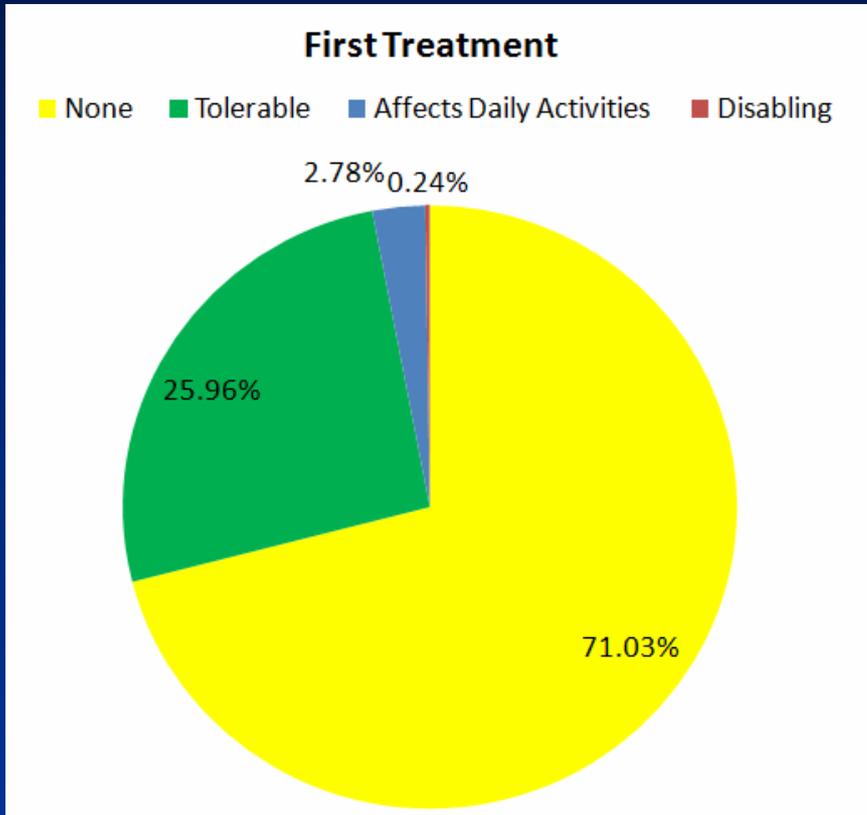
MA-1300-15 Summary of Diary Data

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

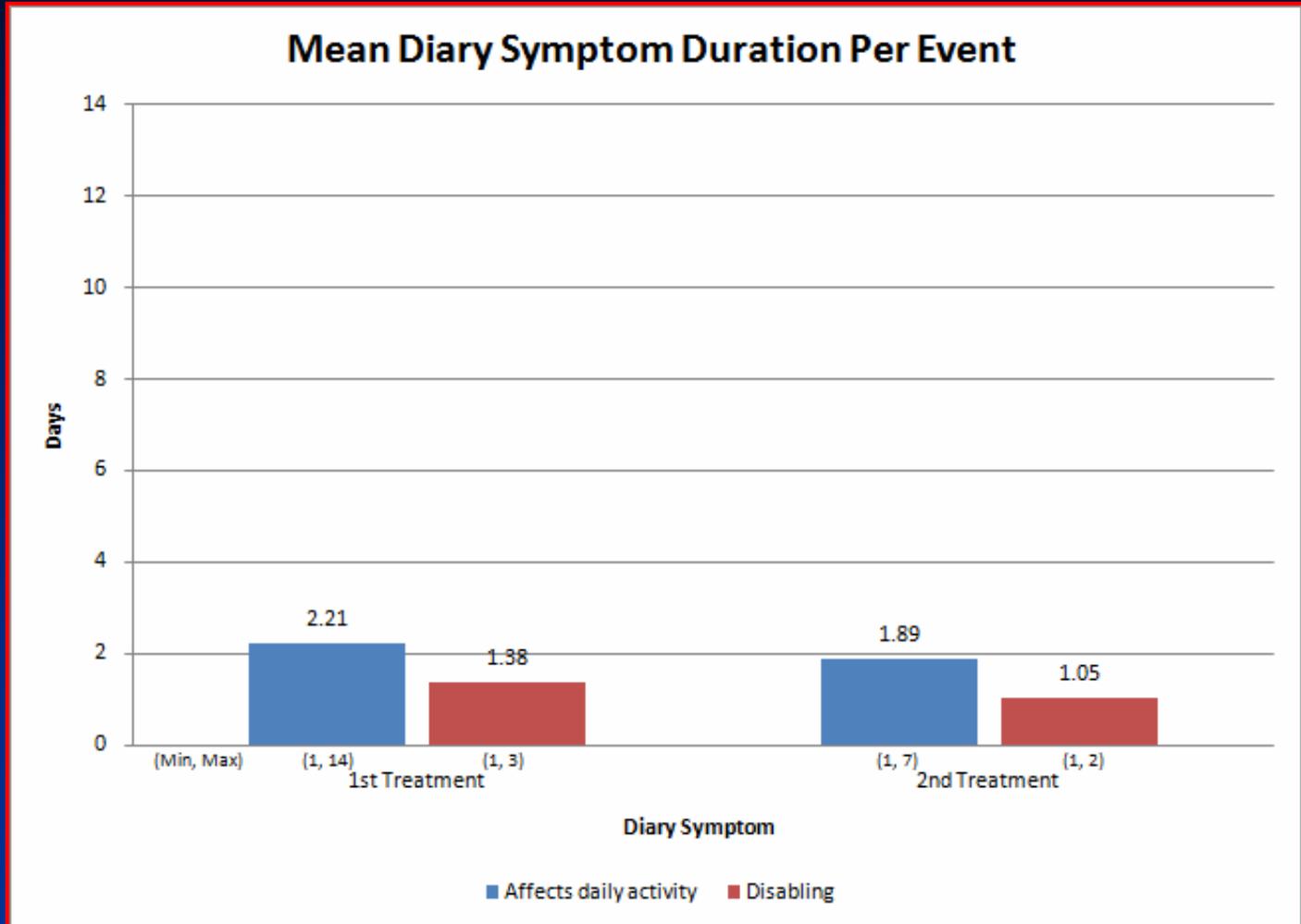


MA-1300-15 Summary of Diary Data

Percentage of Diary *Entries*



MA-1300-15 Summary of Diary Data



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

MA-1300-15 Summary of Safety



Baseline



72 Hours

Subject 04-004

MA-1300-15 Summary of Safety



72 Hours



2 Weeks

Subject 04-004

MA-1300-15 Summary of Safety



Baseline



72 Hours

Subject 10-011

MA-1300-15 Summary of Safety



72 Hours



2 Weeks

Subject 10-011

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

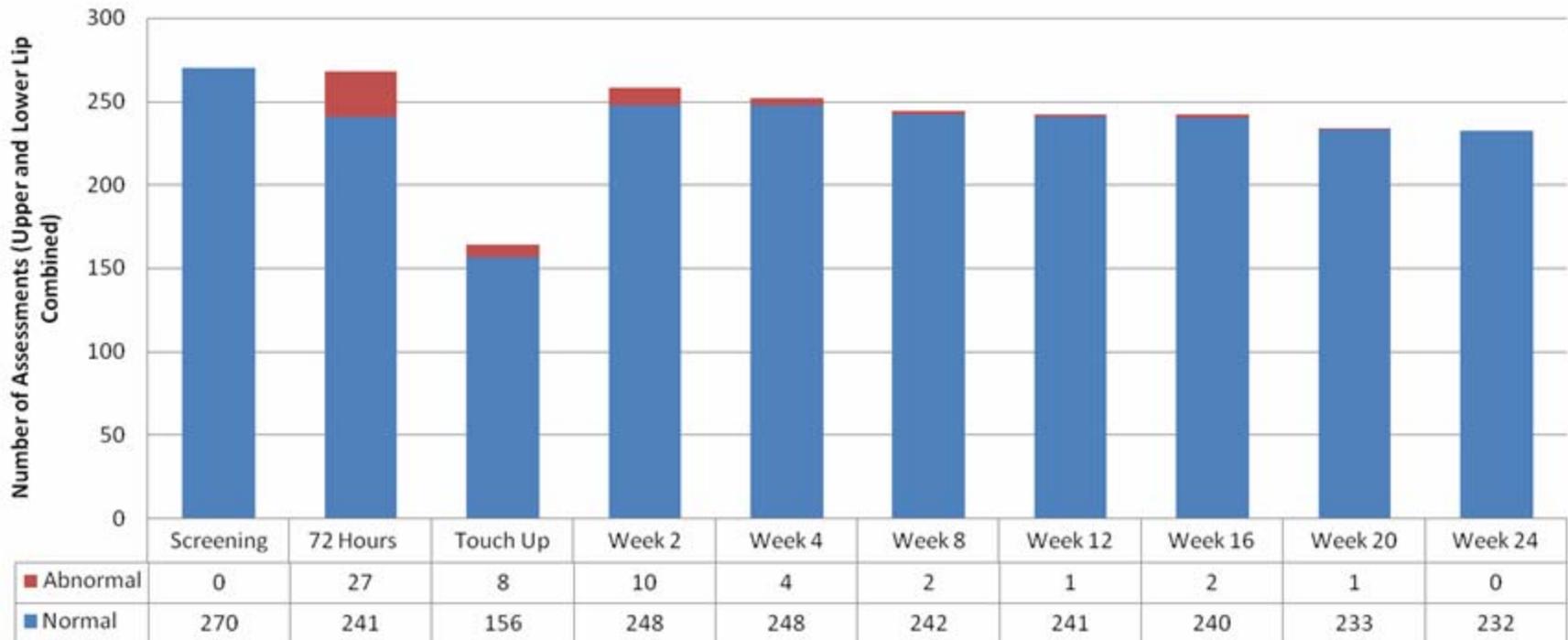
MA-1300-15 Summary of Safety

■ Lip Texture (upper and lower lips assessed separately)

| NORMAL | ABNORMAL | | |
|--|--|---|--|
| | Mild | Moderate | Severe |
| Texture of the lip was even without visible undulations or excessive coarseness beyond that expected for stated age. | 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. | <p>The lip showed more than one area of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that could be visualized only with close inspection.</p> <p>or</p> <p>The lip showed one area of textural irregularity (less than $\frac{1}{4}$ of the lip area) at conversational distance.</p> | <p>The lip showed two or more areas of textural irregularity (a small papule, area of excess smoothness, focal absence of perpendicular lines) that could be visualized at a conversational distance.</p> <p>or</p> <p>The lip showed one area of textural irregularity (more than $\frac{1}{4}$ of the lip area) at conversational distance.</p> |

MA-1300-15 Summary of Safety

Lip Texture



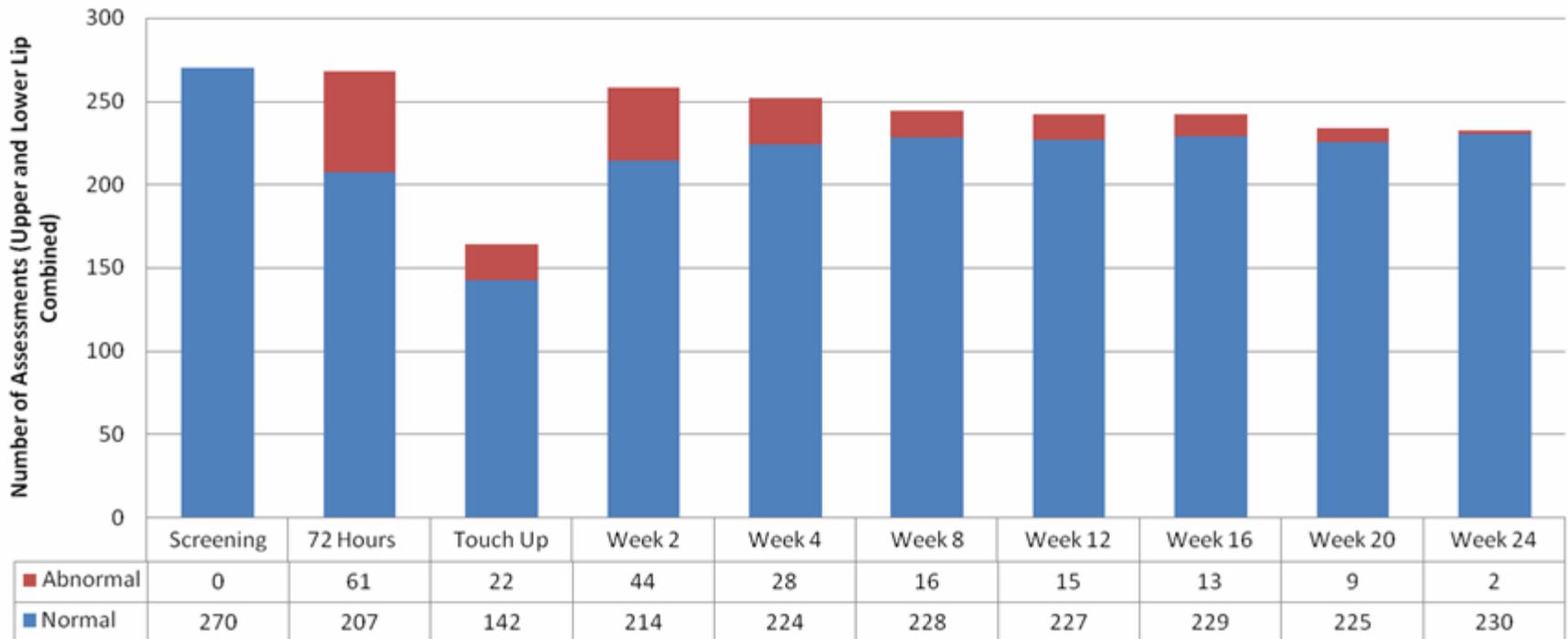
MA-1300-15 Summary of Safety

■ Lip Firmness (upper and lower lips assessed separately)

| NORMAL | ABNORMAL | | |
|--|--|--|---|
| | Mild | Moderate | Severe |
| 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. | Lip was slightly firm with lateral compression or required slightly greater than normal pressure to distort the surface. Upon palpation, an abnormal structure such as a scar or lump was felt, but was not visible. | 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. Upon palpation, an abnormal structure such as a scar or lump was felt and was visible. | 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. |

MA-1300-15 Summary of Safety

Lip Firmness



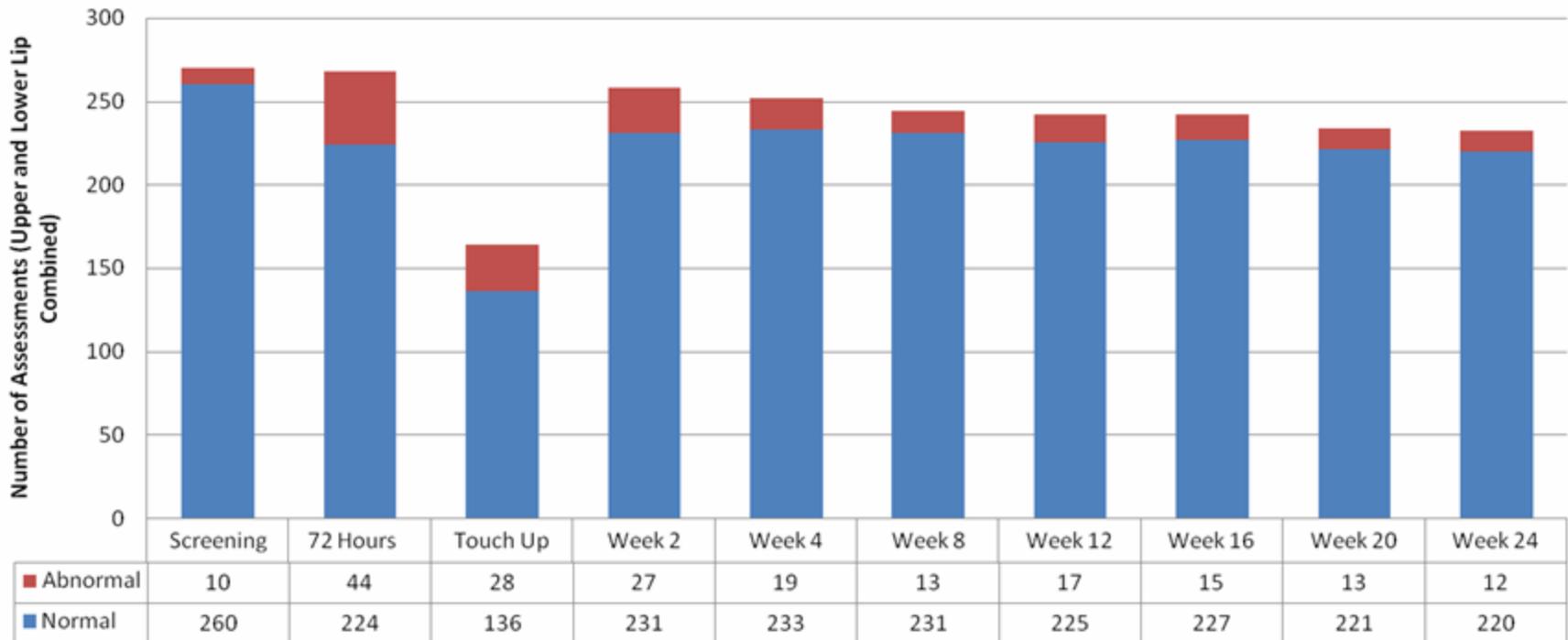
MA-1300-15 Summary of Safety

■ Lip Symmetry (upper and lower lips assessed separately)

| NORMAL | ABNORMAL | | |
|--|---|--|---|
| | Mild | Moderate | Severe |
| One side of the lip balanced or mirrored the other side. | 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. | 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. | 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



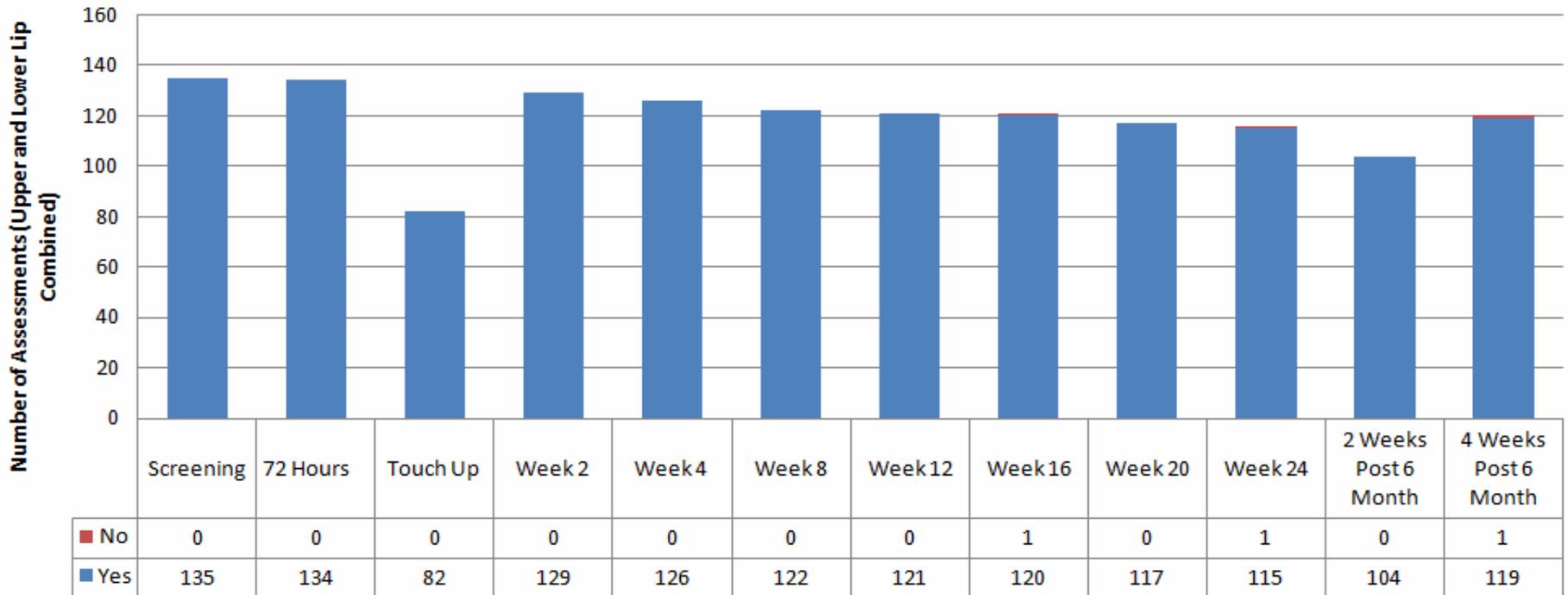
MA-1300-15 Summary of Safety

■ Lip Movement

| 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"/> |

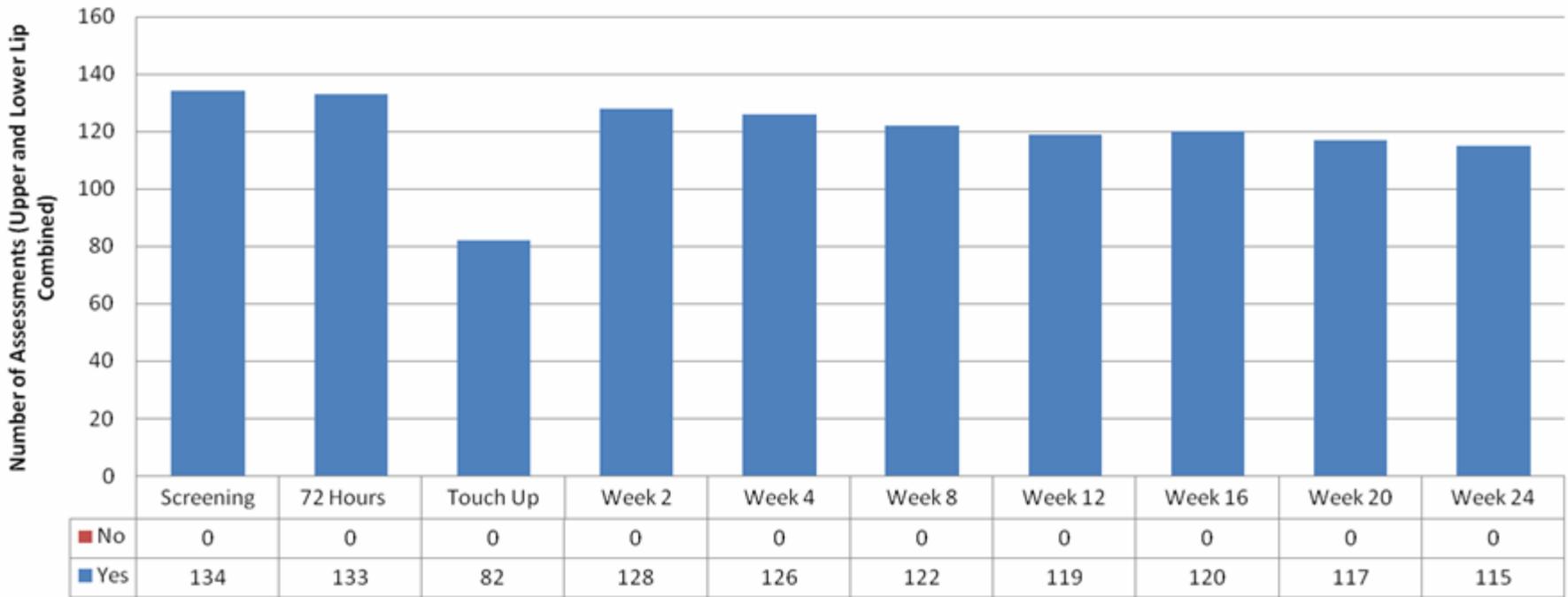
MA-1300-15 Summary of Safety

Lip Movement - Did Subject Effectively Pronounce The Word?



MA-1300-15 Summary of Safety

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



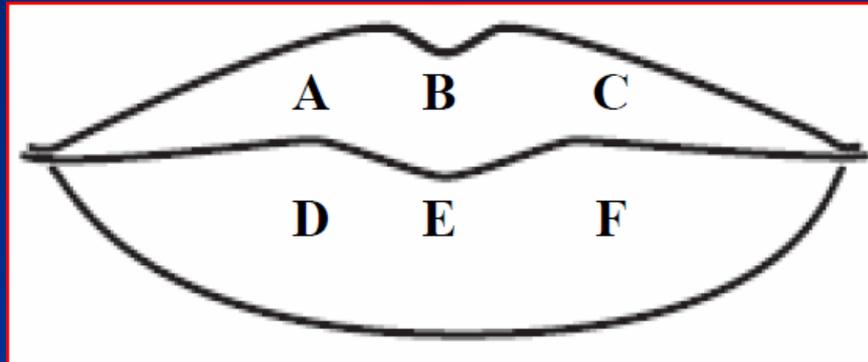
MA-1300-15 Summary of Safety

■ Lip Sensation

■ Monofilament Test

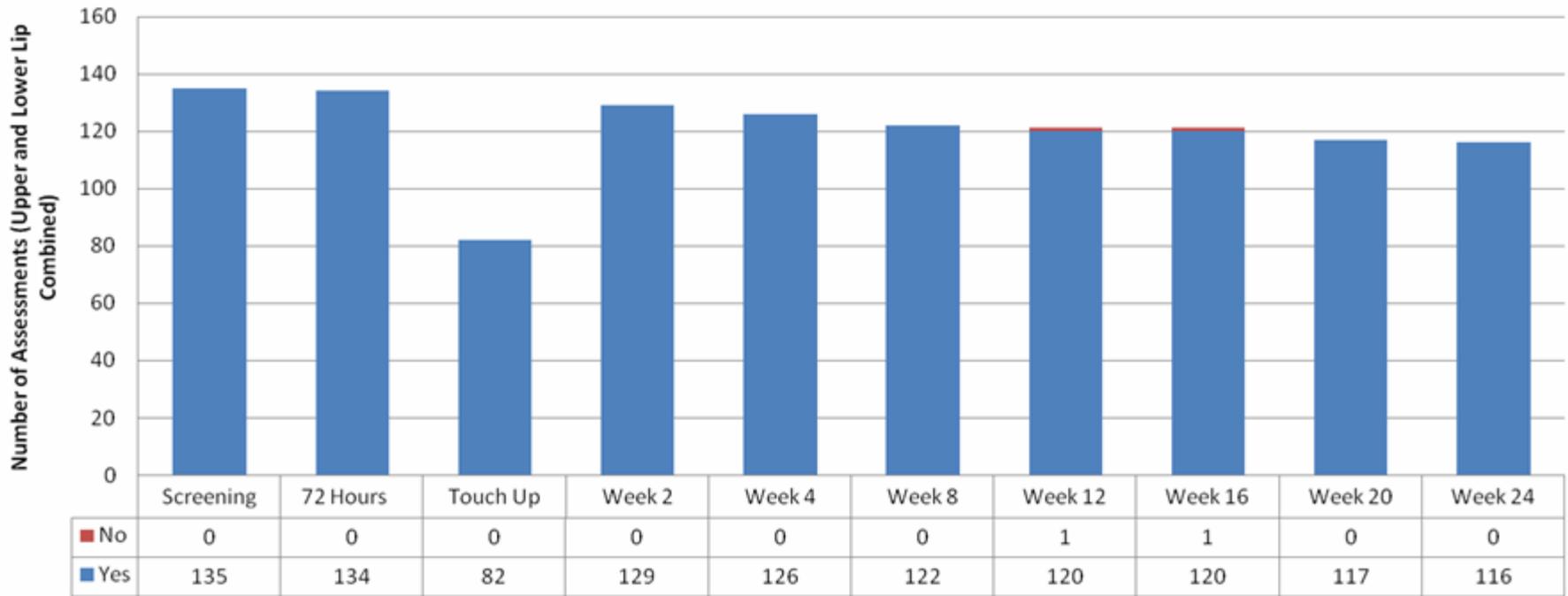
■ Cotton Wisp Test

- 3 different points on the upper and lower lips were randomly tested. Subjects were blindfolded and asked to acknowledge sensation at each point



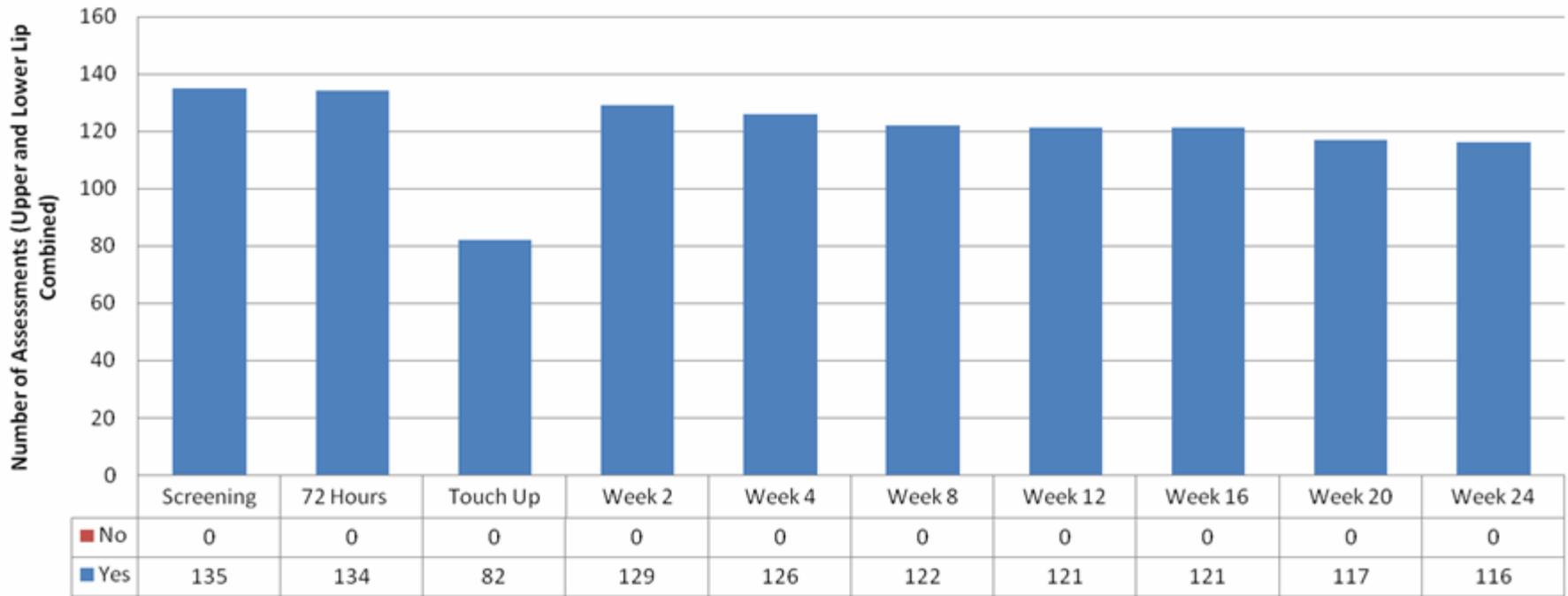
MA-1300-15 Summary of Safety

Lip Sensation - Did Subject Feel the Monofilament?



MA-1300-15 Summary of Safety

Lip Sensation - Did Subject Feel the Cotton Wisp?



MA-1300-15 Summary of Safety

■ Device Palpability

| 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 |

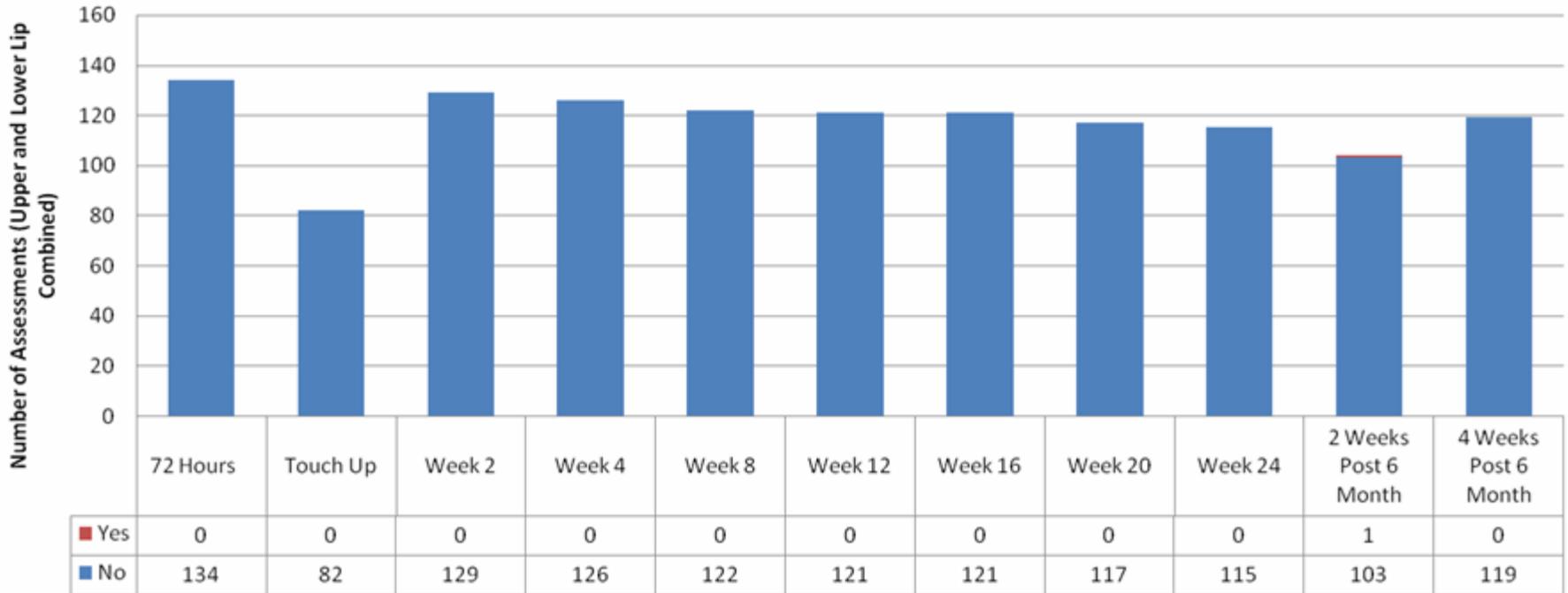
MA-1300-15 Summary of Safety

Device Palpability



MA-1300-15 Summary of Safety

Mass Formation - Did Subject Have Mass Formation?



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)

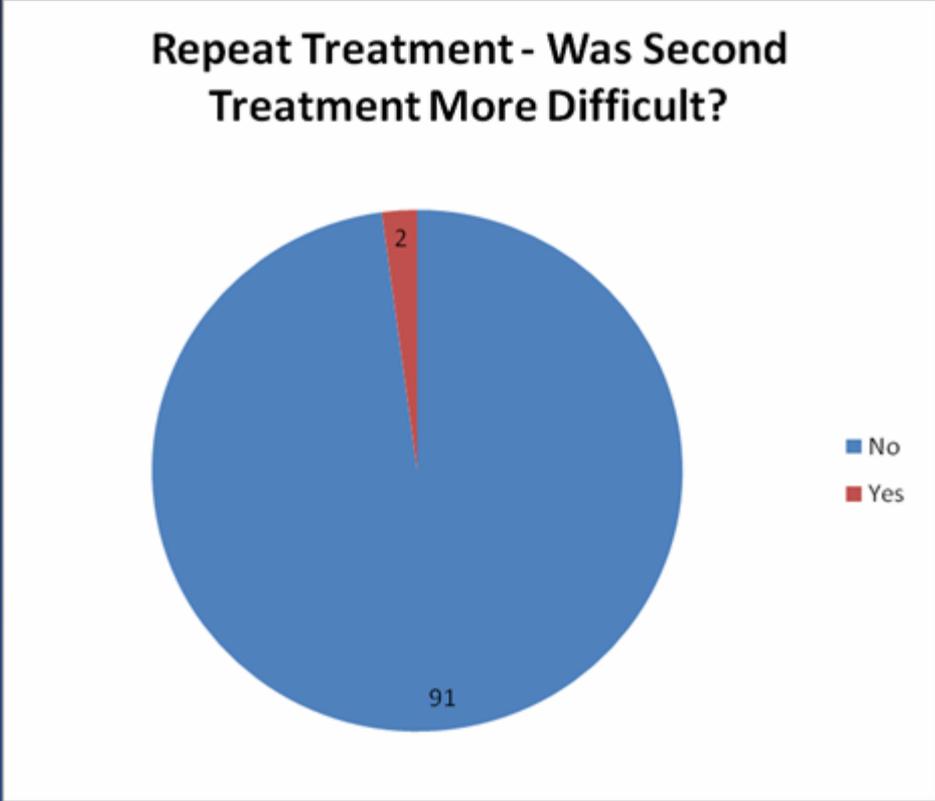
If yes, please note the reason why:

Scar Tissue

Presence of previous dermal filler creates more resistance

Other: _____

MA-1300-15 Summary of Safety



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

COSMETIC

Restylane and People of Color

Millicent Odunze, M.D.,
M.P.H.
Alvin Cohn, M.D.
Julius W. Few, M.D.
Chicago, Ill.

Background: Ethnic skin presents a unique paradox. Its melanin content provides protection from the sun, but the same skin can react to the slightest of injuries. The safety of Restylane in patients with increased susceptibility to keloid formation, hypertrophic scarring, hypersensitivity, and hyperpigmentation has not been studied. A retrospective review was used to determine whether Fitzpatrick skin types IV to VI are associated with an increased incidence of adverse outcomes related to Restylane use.

Methods: Sixty consecutive patients were injected with Restylane by a single surgeon (J.W.F.). Forty patients were categorized as Fitzpatrick skin types I to III and 20 as types IV to VI. Patient charts were reviewed for transient and permanent adverse outcomes related to Restylane injections, such as hypersensitivity, scar formation, altered pigmentation, and contour irregularities. All patients were evaluated at 2 to 4 weeks and 6 to 9 months.

Results: The authors observed that 97.50 percent of the Fitzpatrick type I to III patients had no transient adverse outcomes related to Restylane injections. One patient experienced a 36-hour episode of exaggerated angioedema of the lips after injection, which resolved spontaneously. Another patient had an inclusion cyst that required incision and drainage and a 7-day course of antibiotics. None of the type I to III patients had permanent adverse outcomes related to Restylane. There were no transient or permanent adverse outcomes among the type IV to VI subjects.

Conclusions: This study demonstrates that with proper and meticulous injection techniques, patients with Fitzpatrick skin types IV to VI can experience the same benefits of Restylane therapy as their lighter-complected counterparts. (*Plast. Reconstr. Surg.* 120: 2011, 2007.)

People of color now represent nearly 40 percent of the U.S. population, with Hispanic and African American groups growing most rapidly.¹ Plastic surgeons recognize the need for safe, effective treatments for patients of all ethnic backgrounds.² The number of darker-complected Americans pursuing cosmetic plastic surgery is increasing dramatically. According to the American Society of Plastic Surgeons there has been a 444 percent increase from 1997 to 2005 in the total number of cosmetic procedures. Specifically, there has been a 726 percent increase in the number of nonsurgical procedures during this period. Hyaluronic acid (Hyalofirm, Restylane) injection is up 890 percent from 2003. Racial and ethnic minorities had 20

percent of all cosmetic procedures: Hispanics, 9.1 percent; African Americans, 5.9 percent; Asians, 3.9 percent; and other non-Caucasians, 1.3 percent.^{3,4}

Introduced in Europe in 1996, hyaluronic acid has rapidly become a leading product in plastic surgery offices worldwide. Restylane, which is cross-linked hyaluronic acid manufactured by Q-Med Aesthetics (Stockholm, Sweden) and distributed in the United States by Medicis Pharmaceutical Corporation (Scottsdale, Ariz.), is commonly used as a soft-tissue filler for cosmetic purposes in the face. Since inflammatory hypersensitivity reactions and granuloma formation are reportedly very rarely, routine pretreatment skin testing is not generally recommended. In a study of 709 patients treated with hyaluronic acid and followed up clinically for at least 1 year, three patients (0.42 percent) developed delayed skin reactions. Three other patients were referred for evaluation of their skin reactions from other practitioners. Five of these six patients agreed to skin testing of their forearms. In the five patients tested, challenge intradermal skin testing was positive in four patients; the reactions started approximately 8 weeks

From the Division of Plastic Surgery, Feinberg School of Medicine, Northwestern University, and the Section of Plastic and Reconstructive Surgery, Pritzker School of Medicine, University of Chicago.

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2011

1. Odunze M, Cohen A, Few J. Restylane and People of Color. American Society of Plastic Surgeons. 2006

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

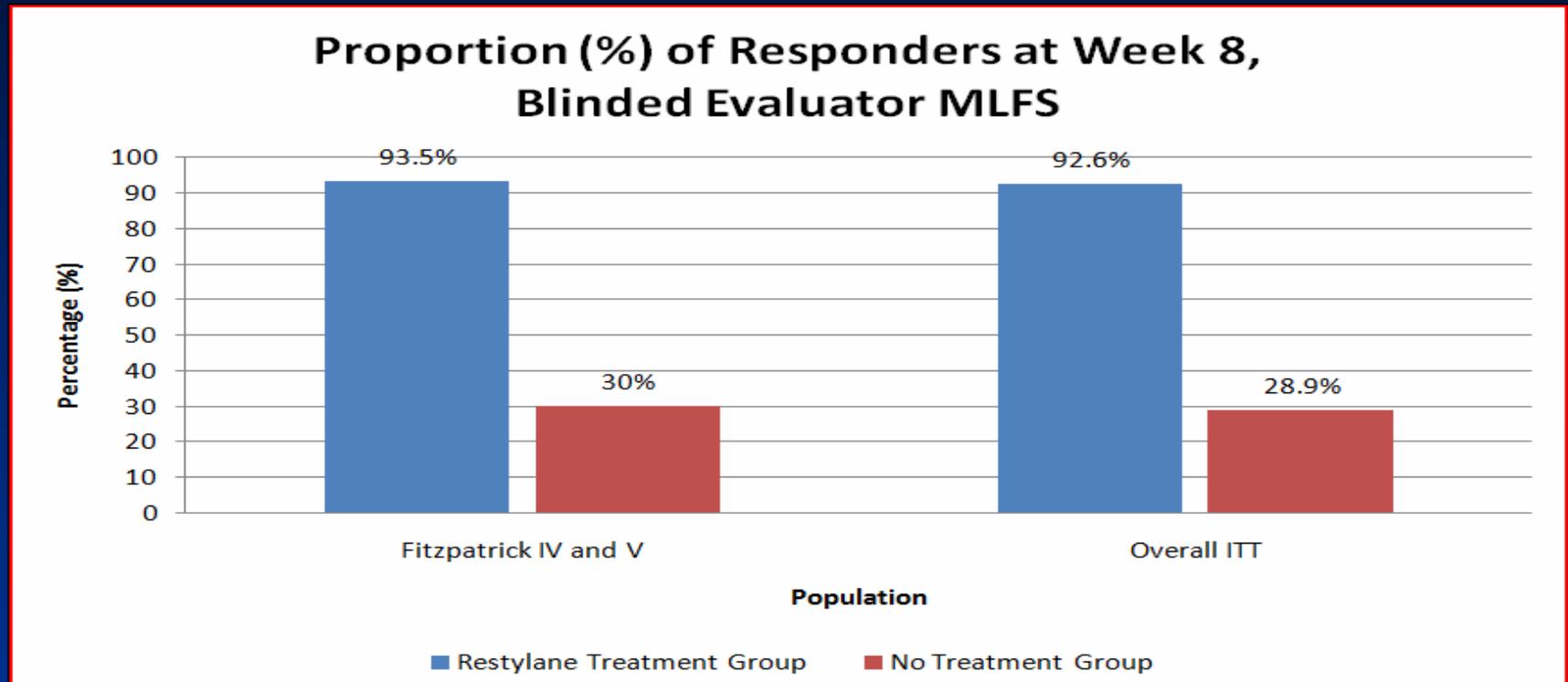
MA-1300-15 Subgroup Analysis

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

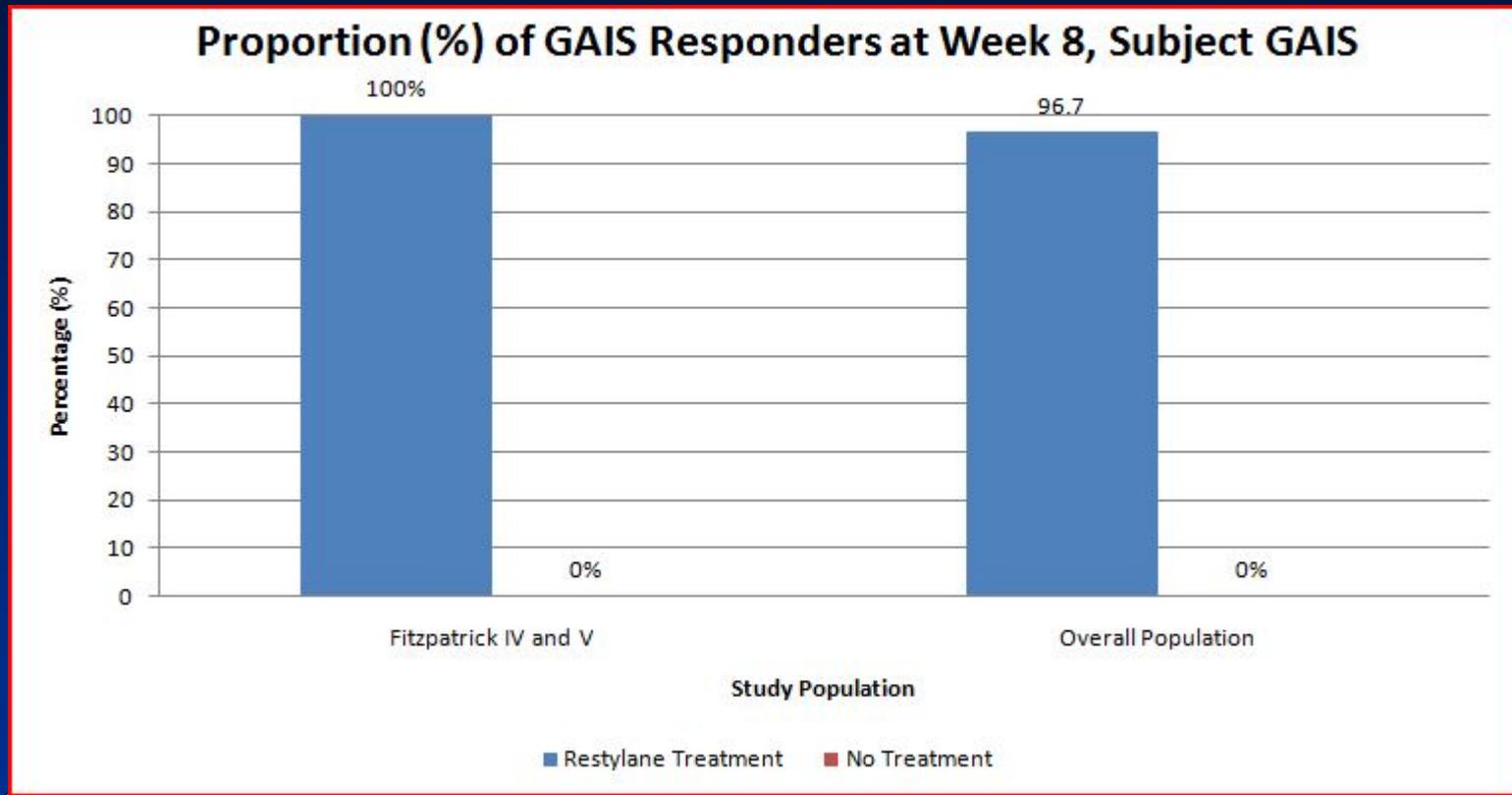


p-value < 0.001

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

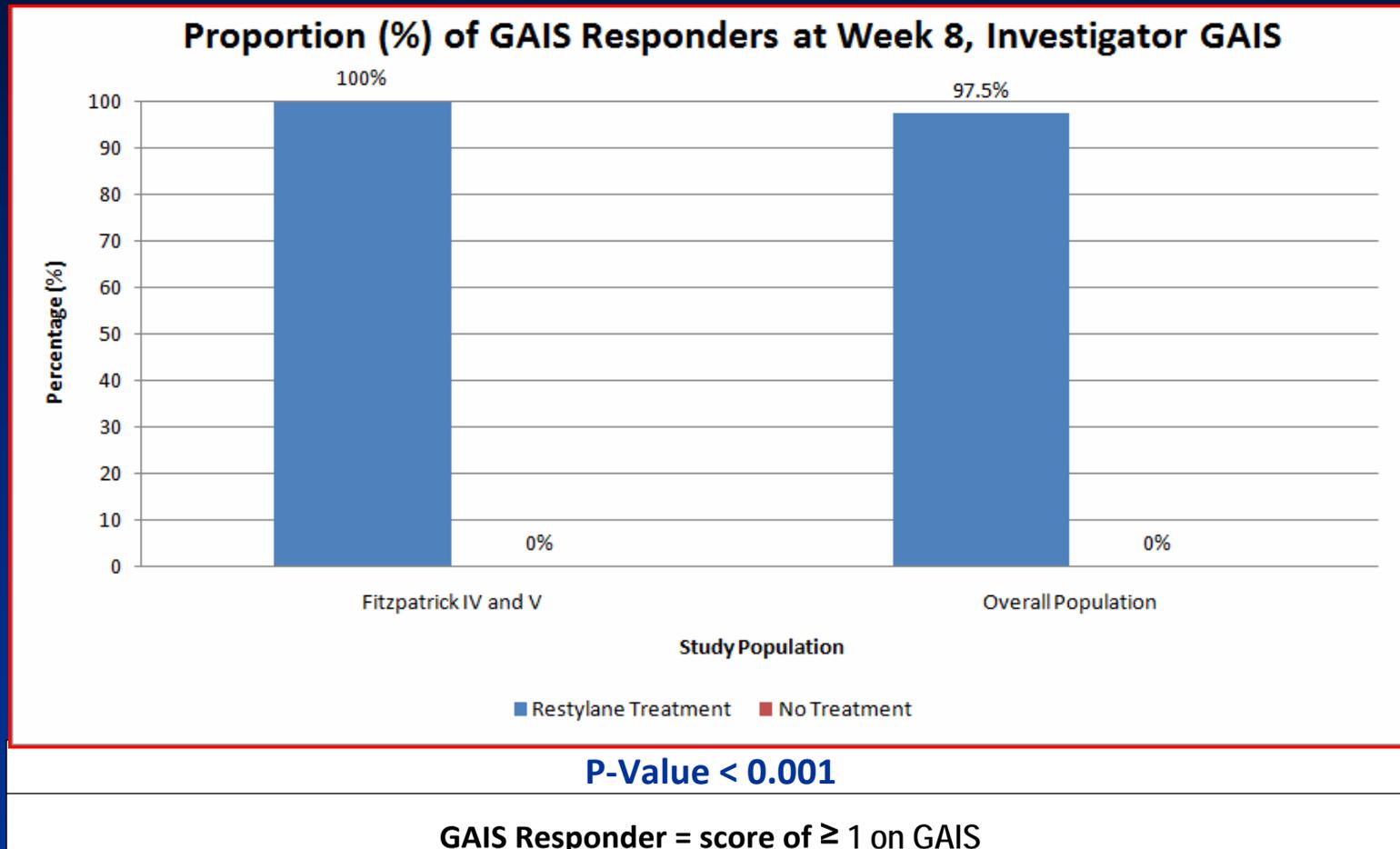


P-Value < 0.001

GAIS Responder = score of ≥ 1 on GAIS

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

Upper and Lower Lips Combined



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

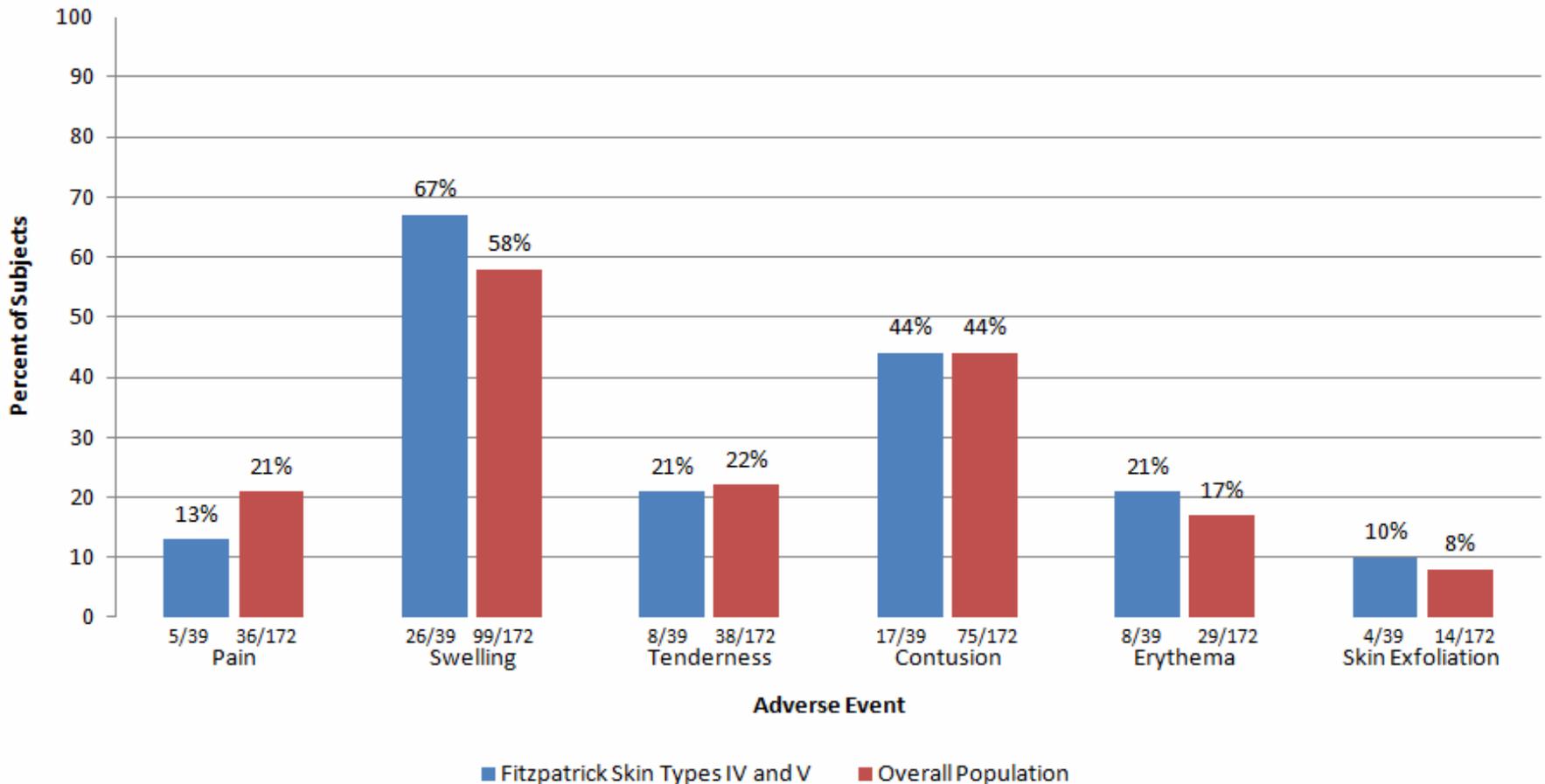
- Treatment Emergent Adverse Events (TEAEs)
 - The incidence of subjects with TEAEs in the first and second treatment with *Restylane* were very similar
 - In the no treatment group there were 3 subjects with a TEAE

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

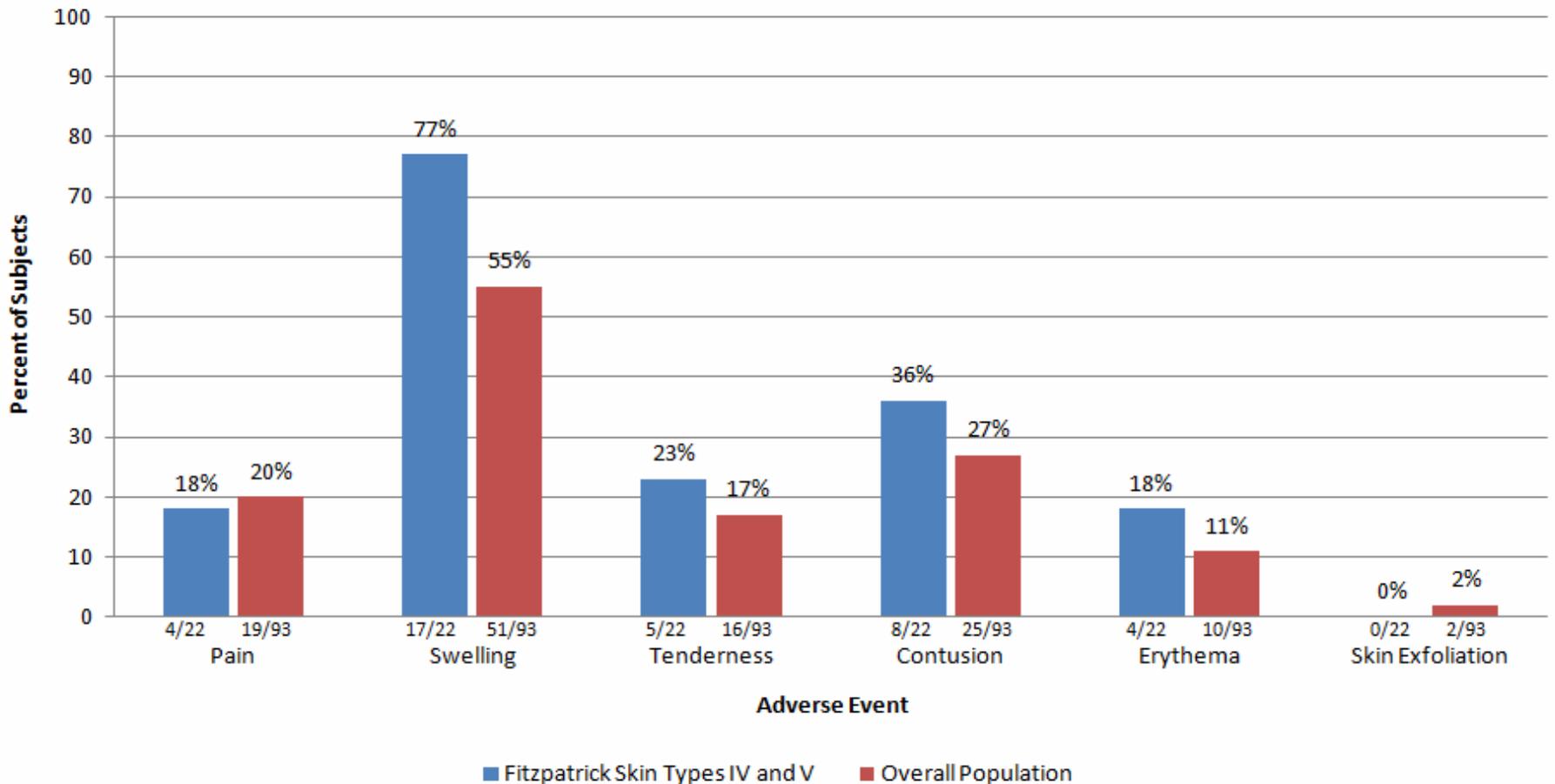
MA-1300-15 Subgroup Analysis Fitzpatrick Skin Types IV and V

TEAE Comparison - 1st Treatment



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

TEAE Comparison - 2nd Treatment



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)

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

- 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

Overall Summary

- 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