

Panel Question 1

- The incidence and duration of adverse outcomes in patient diaries after the first Restylane injection were presented in Tables 17 and 18 of the Executive Summary. Most subjects (99%) reported adverse outcomes and 41.5% of these patients reported adverse outcomes that affected daily activity or were disabling. The most common adverse outcomes (i.e., bruising, redness, swelling, pain, tenderness, and itching) and most (85%) resolved within two weeks. 15% of the events (typically swelling and tenderness) lasted longer than two weeks.
- The incidence and duration of Treating Investigator-diagnosed treatment emergent adverse events (TEAE) reported by 5% or greater of the study population were presented in Tables 14 and 15 of the Executive Summary.

Panel Question 1

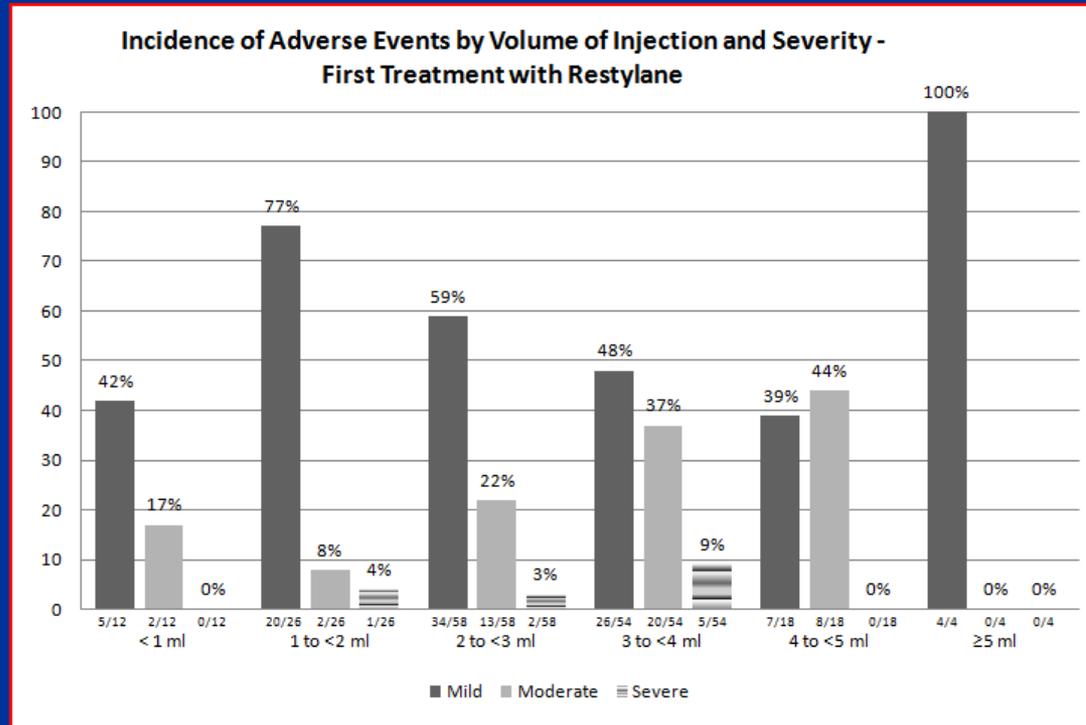
- Lip texture, firmness, and symmetry assessments were discussed on pages 35-39 of the Executive Summary.
- The results of the sponsor and FDA assessments of Medical Device Reports for use of Restylane off-label in lip augmentation were presented on pages 29-30 and 30-35 of the Addendum to the Executive Summary, respectively.

Panel Question 1

1. Based on the patient and physician reported adverse outcomes as well as the Postmarket reports of Restylane used in lip injection, please discuss the safety of Restylane injections for lip augmentation.

Panel Question 2

- Moderate or severe adverse events occurred in 21% (20/96) subjects that received less than 3.0 mL of Restylane and 43% (33/76) for subjects that received more than 3.0 mL of Restylane ($p=0.0014$). The relationship between Restylane dose and the incidence of moderate and severe adverse events was:



Panel Question 2

2. Based on these outcomes, please discuss the clinical implications of injecting different amounts of Restylane in the lip with a focus on:
 - a. the lack of correlation between injected dose and change in lip fullness;
 - b. the risk / benefit ratio of injecting doses greater than 3.0 ml in both lips; and
 - c. approaches for informing future physicians about appropriate injection doses (e.g., should the product label cite a maximum injectable dose)?

Panel Question 3

3. Please provide comment on the following patient populations that were under-represented in Study MA-1300-15.
 - a. The study enrolled four patients under the age of 22 years. Please discuss the appropriateness of Restylane lip augmentation in patients under the age of 22. For example, does this patient population (seeking lip augmentation rather than restoration of lip appearance related to aging), raise any safety or effectiveness concerns that warrant additional Pre-Market study?

Panel Question 3

- b. The study enrolled 38 persons with Fitzpatrick Type IV, 3 patients with Type V and no patients with Type VI skin. Product effectiveness assessments were based on 31 Restylane and 10 No Treatment patients.

Please comment on the safety and effectiveness of Restylane for lip augmentation in this patient population and whether any safety or effectiveness issues warrant additional Pre-Market study. Such considerations may include the data collected in: 1) the pivotal study and 2) a previous Study in which 150 subjects (with Fitzpatrick Types IV, V and VI skin) received Restylane and Perlane injections in the nasolabial folds.

Panel Question 3

c. The study enrolled 179 female and 1 male patients.

Please comment on whether lip augmentation in men raises any safety or effectiveness concerns that warrant additional Pre-Market study.

Panel Question 4

4. The percent of Treatment Responders as judged on the MLFS by Blinded Evaluators, Treating Investigators and Independent Photographic Reviewers are presented below.

Assessment Time Point	Treatment Group	Blinded Live Evaluator	Treating Investigator	IPR	All 3
Week 8	Restylane	0.93	0.89	0.58	0.53
	No Treatment	0.29	0.05	0.10	0
	Difference	0.64	0.84	0.48	0.53

The levels of agreement for these decisions are reflected in the reported Weighted Kappa statistics.

	Blinded vs. Treating		Blinded vs. IPR		IPR vs. Treating	
	Upper	Lower	Upper	Lower	Upper	Lower
Exact Agreement	51%	57%	41%	44%	39%	36%
Weighted Kappa	0.37	0.42	0.26	0.25	0.21	0.16

Panel Question 4

The absolute change in MLFS from Baseline for Upper and Lower Lips at Week 8 as determined by Blinded Evaluators were presented in Table 7 of the Executive Summary Addendum.

Panel Question 4

Based on these data and other information presented in the PMA supplement:

- a. Please comment on the effectiveness of Restylane in lip augmentation; and
- b. Please comment on the most appropriate method for describing product effectiveness in the product label.

Panel Question 5

5. The premarket device performance data from Study MA-1300-15, “Randomized, Evaluator-Blinded No Treatment Controlled Multicenter Study,” reflect single Restylane treatment sessions in 172 patients and repeat Restylane treatment sessions at Week 24 in 93 patients.

Please discuss whether a Post Approval Study is recommended to evaluate the safety and effectiveness of multiple Restylane treatments for lip augmentation.

Panel Question 5

If so, please comment on:

- a. the safety and effectiveness endpoints that should be assessed;
- b. the inclusion of specific patient populations;
- c. the duration of follow-up; and
- d. and the study design.

Panel Question 6

6. Regarding future studies of dermal fillers for lip augmentation, Attachment 1 to the sponsor's Executive Summary presents the 5-grade Lip Fullness Scales (MLFS) for upper and lower lips. As discussed above, a high level of agreement between the Blinded Evaluators, the Treating Investigators, and Independent Photographic Reviewers was not observed.

Based your clinical training and experience, please comment on approaches that future studies might employ to improve measurements of device safety and effectiveness in lip augmentation.

Panel Question 6

For example, please comment on:

- a. Which assessor (e.g., Blinded Evaluator, Treating Investigator, or Independent Photographic Reviewer) provides the most accurate evaluation of patient outcome?
- b. What role(s) should patient evaluations play in determining clinical safety and effectiveness (e.g., co-primary effectiveness endpoints)?
- c. What issues should a sponsor consider when developing a metric for evaluating the effectiveness in lip augmentation?
- d. How might a sponsor demonstrate the magnitude of a change on a lip appearance scale that correlates with a clinically significant result?

Panel Question 7

7. Is there a reasonable assurance that Restylane is safe 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?

Panel Question 8

8. Is there a reasonable assurance that Restylane is effective 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?

Panel Question 9

9. Do the benefits of Restylane 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 outweigh the risks of Restylane for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for lip augmentation, for purposes of approval?