Proposed Panel Questions

1. The incidence and duration of adverse outcomes reported in patient diaries after the first Restylane injection are presented below for all subjects. 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) were anticipated and most (85%) resolved within two weeks. 15% of the events (typically swelling and tenderness) lasted longer.

Adverse Outcomes Reported in Patient Diaries after the First Treatment
(reproduced from Table 17 (page 32) Executive Summary)

	1st Treatment Subjects Reporting Symptoms	**1st Treatment with *Restylane***			
		None	**Tolerable**	**Affects Daily Activity**	**Disabling**
Upper Lip	167/169 (99%)	2 (1%)	90 (53%)	62 (37%)	15 (9%)
Lower Lip	161/168 (96%)	7 (4%)	98 (58%)	51 (30%)	12 (7%)

Duration of Adverse Events at Implant Site after the First Treatment
(reproduced from Table 18 (page 33) Executive Summary)

Location/ Adverse Event	**First Treatment with *Restylane***				
	Number of Days				
	Any (%)	**1 (%)**	**2-7 (%)**	**8-13 (%)**	**14 (%)**
Upper Lip					
Bruising	130 (76%)	8 (6%)	88 (68%)	31 (24%)	3 (2%)
Redness	126 (73%)	20 (16%)	86 (68%)	19 (15%)	1 (<1%)
Swelling	166 (97%)	7 (4%)	95 (57%)	43 (26%)	21 (13%)
Pain (includes Burning)	143 (83%)	37 (26%)	94 (66%)	10 (7%)	2 (1%)
Tenderness	162 (94%)	15 (9%)	84 (52%)	45 (28%)	18 (11%)
Itching	49 (28%)	17 (35%)	27 (55%)	5 (10%)	0
Lower Lip					
Bruising	132 (77%)	11 (8%)	99 (75%)	19 (14%)	3 (2%)
Redness	120 (70%)	21 (18%)	84 (70%)	14 (12%)	1 (<1%)
Swelling	158 (92%)	7 (4%)	93 (59%)	34 (22%)	24 (15%)
Pain (includes Burning)	134 (78%)	35 (26%)	86 (64%)	12 (9%)	1 (<1%)
Tenderness	152 (88%)	10 (7%)	84 (55%)	39 (26%)	19 (13%)
Itching	48 (28%)	15 (31%)	29 (60%)	4 (8%)	0

The incidence and duration of treatment emergent adverse events (TEAE) reported by Treating Investigators are presented below for all subjects.

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Incidence of Treatment Emergent Adverse Events
Reported in 5% or Greater of the Study Population by Severity
(reproduced from Table 14 (page 29) Executive Summary)

System Organ Class	Severity	Treatment Group					
		No Treatment at Baseline n=45		**First Restylane Treatment n= 172**		**Second Restylane Treatment n= 93**	
		Events	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**
Any TEAE	Total	26	17 (38%)	795	149 (87%)	267	60 (65%)
	Mild	22	13 (29%)	672	96 (56%)	264	57 (61%)
	Moderate	4	4 (9%)	113	45 (26%)	3	3 (3%)
	Severe	0	0	10	8 (5%)	0	0
General Disorders and Administrative Site Conditions							
Pain	Total	1	1 (2%)	97	36 (21%)	51	19 (20%)
	Mild	1	1 (2%)	73	22 (13%)	50	18 (19%)
	Moderate	0	0	21	12 (7%)	1	1 (1%)
	Severe	0	0	3	2 (1%)	0	0
Swelling	Total	0	0	222	99 (58%)	101	51 (55%)
	Mild	0	0	186	78 (45%)	101	51 (55%)
	Moderate	0	0	36	21 (12%)	0	0
	Severe	0	0	0	0	0	0
Tenderness	Total	0	0	69	38 (22%)	29	16 (17%)
	Mild	0	0	60	31 (18%)	29	16 (17%)
	Moderate	0	0	9	7 (4%)	0	0
	Severe	0	0	0	0	0	0
Infections and Infestations							
Nasopharyngitis	Total	3	2 (4%)	9	9 (5%)	2	2 (2%)
	Mild	3	2 (4%)	8	8 (5%)	1	1 (1%)
	Moderate	0	0	1	1 (< 1%)	1	1 (1%)
	Severe	0	0	0	0	0	0
Injury, Poisoning and Procedural Complications							
Contusion	Total	0	0	130	75 (44%)	40	25 (27%)
	Mild	0	0	116	66 (38%)	40	25 (27%)
	Moderate	0	0	14	9 (5%)	0	0
	Severe	0	0	0	0	0	0
Nervous System Disorders							
Headache	Total	3	2 (4%)	17	12 (7%)	3	3 (3%)
	Mild	3	2 (4%)	17	12 (7%)	3	3 (3%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Skin and S.C. Tissue Disorders							
Erythema	Total	0	0	57	29 (17%)	19	10 (11%)
	Mild	0	0	57	29 (17%)	19	10 (11%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0
Skin Exfoliation	Total	0	0	21	14 (8%)	2	2 (2%)
	Mild	0	0	21	14 (8%)	2	2 (2%)
	Moderate	0	0	0	0	0	0
	Severe	0	0	0	0	0	0

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Subjects receiving their first Restylane series had a mean TEAE duration of 15.6 days, compared to 10.4 days after the second Restylane series and 12.4 days for the No Treatment group.

Assessments of lip texture, firmness, and symmetry in the pivotal study revealed:

- One patient with severely abnormal lip texture, (who reported an improved score on the GAIS scale at the same time); several patients who suffered moderately abnormal lip texture, who all resolved within 4 weeks, except for one subject whose final outcome was unknown, because the study ended 4 weeks after re-treatment.

- Approximately 10% of patients exhibited at least mild abnormal lip texture and approximately 23% of subjects exhibited mild abnormal lip firmness. One subject experienced moderate lip firmness which resolved in less than 2 weeks.

- Approximately 25% of subjects reported abnormal lip symmetry at some point in the study with 3% of subjects exhibited severe abnormal lip symmetry. All of these patients reported satisfaction with their treatment on the GAIS scale.

- At Week 8 approximately 90% and at Week 24, approximately 60% of the patients reported a palpable implant (with an expected feel). Five subjects reported eight events of lump/lumps assessed as an "unexpected feel" and one patient had a mass reported as a cyst which required drainage. All of these events resolved by the end of the study.

FDA review of the MAUDE database identified several Medical Device Reports *(*MDRs) that appear to be more serious then observed in the pivotal study (i.e., anaphylactic shock, lesions that later turned into necrosis, grape-sized lumps that were incised and drained (and were "gram positive cultures), severe angioedema, severe erythema and swelling in the lips and all over her face to the point that eyes were shut, numbness below the lower lip, and a lesion at the vermillion border which was hypertrophic scar tissue). FDA also notes that MDRs often indicate that patients received Restylane injections into lips as well as other areas of the face. Therefore no specific trend of adverse events can be detected for the lip augmentation per se. There were only 15 reports indicating lip injection as the single site of injection and the only adverse events in those reports reported more than once were allergic reaction and lesions referred to as "lumps and bumps". Please discuss the safety of Restylane injections for lip augmentation.

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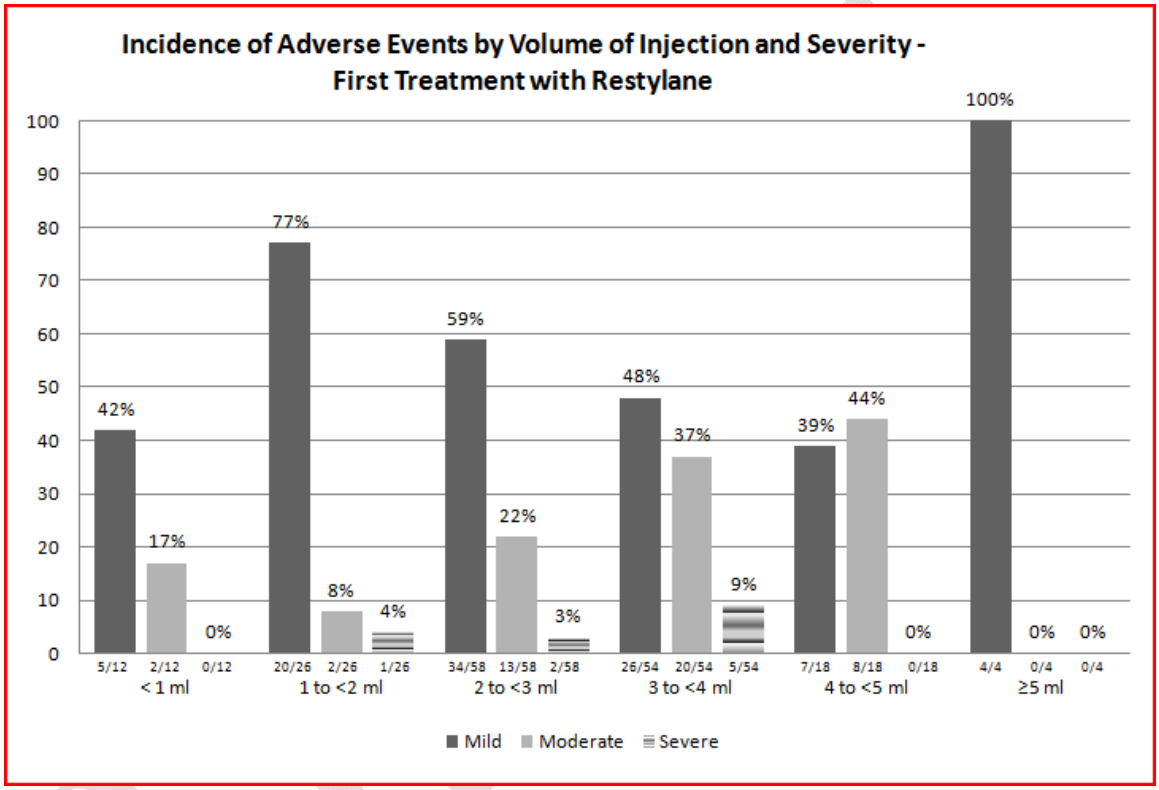
2. The relationship between Restylane dose and device safety are illustrated below. While a linear relationship between mild severity adverse events and dose was not observed, a difference in the incidence of adverse events (after first treatment) between very small (<1cc) and very large (>5cc) volumes was observed as was a possible relationship between dose and frequency of moderate and severe adverse events.

(reproduced from Table 5 (page 11) Executive Summary Addendum)



Dose was not a significant predictor of effectiveness in upper, lower, or combined lip outcomes (p=0.39, 0.34, 0.72). Based on these data, please comment on the relationship between Restylane dose and adverse event severity. Is there an appropriate maximum dose of Restylane for lip injection?

3. Study MA-1300-15 enrolled four patients under the age of 22 years (i.e., one 18 year old, one 19 year old and two 20 year olds). Three of the four subjects were retreated at Week 24 post-baseline and one subject declined retreatment for an unspecified reason. While the injected dose and product safety profile in these patients do not raise any unique questions, FDA has concern about predicting clinical outcomes for a patient population who may receive many treatments over their lifetime based on experience in four subjects. Please discuss the appropriateness of Restylane lip augmentation in patients under the age of 22. Does this patient population raise any new concerns that warrant additional Pre-market study?

4. The study enrolled 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V skin. No patients with Fitzpatrick Type VI skin were treated. Assessments of product effectiveness in this subgroup were based on 31 Restylane and 10 No Treatment patients. Please comment on the safety and effectiveness of Restylane use for lip augmentation in this patient population. Such considerations should include: 1) the data collected in the pivotal study and 2) whether previous data collected in Study MA-1400-01 (i.e., the evaluation of Restylane and Perlane injections in the nasolabial folds of 150 subjects with Fitzpatrick skin types IV, V and VI) are applicable to the proposed indication of lip augmentation.

5. The percentage of Treatment Responders (on MLFS scale) as judged by the Blinded Evaluators, Treating Investigators and Independent Photographic Reviewers are presented below for Weeks 8 and 24. The level of agreement for these decisions are reflected in the reported Weighted Kappa statistics.

Responder Analysis From Different Evaluators: Upper and Lower Lips Combined
(reproduced from Table 11 (page 17) Executive Summary Addendum)

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

Agreement Among Different Evaluators at Week 8
(reproduced from Table 10 (page 16) Executive Summary Addendum)

	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

The absolute change in MLFS from Baseline for Upper and Lower Lips at Week 8 as determined by Blinded Evaluator is presented below.

Summary of MLFS Change from Baseline (Blinded Evaluators' Assessment)
for Upper and Lower Lips at Week 8 – ITT Population
(reproduced from Table 7 (page 14) Executive Summary Addendum)

Assessment/	Statistic	No Treatment	Restylane

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Time Point		(N=45)		(N=135)	
		Observed	Change from Baseline	Observed	Change from Baseline
Upper Lip					
Week 8	n	39	39	121	121
	Mean (S.D.)	1.9 (1.0)	0.5 (0.8)	3.4 (1.0)	2.1 (1.0)
	Median	2.0	0.0	3.0	2.0
	Min, Max	1,4	0, 3	1, 5	-1, 4
	P-value	--	--	--	<0.001
Lower Lip					
Week 8	n	35	35	111	111
	Mean (S.D.)	1.9 (0.8)	0.4 (0.6)	3.4 (0.9)	1.8 (0.9)
	Median	2.0	0.0	3.0	2.0
	Min, Max	1, 3	0, 2	1, 5	-1, 4
	P-value	--	--	--	<0.001

Based on these data and other information presented in the PMA supplement, please comment on the effectiveness of Restylane in lip augmentation.

Should FDA determine the premarket data demonstrate product safety, effectiveness, and risk/benefit profile, there are some potential postmarket questions that need to be addressed. The Panel will be asked to discuss and comment on the appropriateness of the following possible Post-Approval Study questions:

6. 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 a repeat Restylane treatment (i.e., at Week 24) in 93 patients. Please discuss:

    a. Whether a Post Approval Study is recommended to evaluate the long-term safety of Restylane injections for lip augmentation. If so, please identify which adverse events that should be evaluated.

    b. Whether there is a need for long-term follow-up of a younger population to assess device safety and effectiveness after multiple re-treatments.

7. The pivotal study enrolled 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V skin. No patients were enrolled with Fitzpatrick Type VI skin. The pivotal study also enrolled 4 pediatric subjects (ages 18-21 years). If the device were to be approved, please discuss the need for inclusion of these specific populations in the Post Approval Study to further evaluate the safety and effectiveness of Restylane injections for:

    a. lip augmentation in patients with Fitzpatrick skin type IV-VI; and

    b. pediatric patients (ages 18-21 years).

8. Regarding future studies for lip augmentation, Attachment 1 to the sponsor's Executive Summary presents the 5-grade Medicis Lip Fullness Scales (MLFS) for

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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 use to improve measurements of device safety and effectiveness in lip augmentation. 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 should patient evaluations play in determining clinical safety and effectiveness (e.g., co-primary effectiveness endpoint)?

c. What issues should a sponsor consider when developing an Aesthetic Metric of Effectiveness for lip augmentation?

d. How might a sponsor determine the magnitude of a change on a lip appearance scale that correlates with a clinically significant result?

<u>Premarket Voting Questions:</u>

9. 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?

10. 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?

11. 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?

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