SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RADIESSE® Injectable Implant

Device Procode: PKY, LMH

Applicant's Name and Address: Merz North America, Inc.
4133 Courtney Road
Suite 10
Franksville, WI 53126

Date(s) of Panel Recommendation: February 27, 2015

Premarket Approval Application (PMA) Number: P050052/S049

Date of FDA Notice of Approval: June 4, 2015

The original PMA (P050052) was approved on December 22, 2006, and is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Another PMA (P050037) for RADIESSE® was also approved on December 22, 2006, and is indicated for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus. The SSEDs to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for RADIESSE®.

II. INDICATIONS FOR USE

RADIESSE injectable implant is indicated for hand augmentation to correct volume loss in the dorsum of the hands.

III. CONTRAINDICATIONS

- Contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Not to be used in patients with known hypersensitivity to any of the components.
- RADIESSE® injectable implant is contraindicated for patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the RADIESSE® labeling for the dorsum of the hand.

V. DEVICE DESCRIPTION

RADIESSE® injectable implant is an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant, whose principle component is synthetic calcium hydroxylapatite (CaHA) suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. RADIESSE ® injectable implant (1.5cc and 0.8cc) has a CaHA particle size range of 25–45 microns and should be injected with a 25 gauge Outer Diameter (O.D.) to 27 gauge Inner Diameter (I.D.) needle.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for the correction of volume loss in the dorsum of the hand such as autologous fat injection. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

RADIESSE is currently marketed in Europe, Canada and South America. RADIESSE® has not been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A list of the potential adverse effects (e.g., complications) associated with the use of the device are as reported in the clinical study for RADIESSE® injection into the dorsum of the hand includes: bruising, swelling, redness, itching, pain/tenderness, hematoma, nodules/bumps/lumps, difficulty performing activities/stiffness and loss of sensation. Other adverse events reported less frequently (in less than 2% of study subjects) include vagal response, dry skin, hypersensitivity and needle pricks.

Radiesse® is approved for use in the US for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds and for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus. The clinical trial for nasolabial folds (P050052) reported the following adverse events: ecchymosis, edema, erythema, granuloma, needle jamming, nodule, pain, pruritis, soreness, numbness, contour irregularity tenderness and irritation. The clinical trial for lipoatrophy in patients with human immunodeficiency virus reported the following adverse events: ecchymosis, edema, erythema, granuloma, nodule, pain, pruritis, contour irregularities, numbness, dryness, peeling, burning sensation, whiteheads and rash.

As of November 17, 2014, the following adverse events were received from post-market surveillance for RADIESSE® injectable implant, regardless of the indication, in the US and outside the US that were not observed in clinical trials: infection, over-injection,

under-injection, loss of effect, product displacement, allergic reaction, necrosis, granuloma, exposed material, hair loss, tingling, ptosis, abscess, paralysis, superficial injection, herpetic infection, blanching, blistering, bluish color, dark circles, did not like results, dizziness, double vision, festoons, flu-like symptoms, grey discoloration, inflammation, ischemic reaction, lymphoid hyperplasia, pallor to skin, possible blood clot, scarring, sensitivity to cold, skin texture changed, tissue mass developed, vascular embolus resulting in tissue compromise, and visual loss or blindness.

The most commonly reported serious adverse events from post-market surveillance for Radiesse® with frequency greater than 5 reported events and were not observed in the clinical study were: necrosis, allergic reaction, edema, and infection.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

No new preclinical studies were presented in this PMA Supplement. RADIESSE® has previously been tested and characterized through bench and animal studies submitted in P050037 and P050052. Please refer to SSEDs for P050037 and P050052 for more information.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of RADIESSE® for hand augmentation to correct volume loss in the dorsum of the hand in the US under IDE # G110225. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between March 27, 2013 and May 9, 2013. The database for this PMA Supplement reflected data collected through May 6, 2014 and included 114 subjects. There were 6 investigational sites.

The study was a multi-center, prospective, randomized, cross-over pivotal clinical study. The duration of the study was 12 months. The treating investigator was not masked but the evaluator assessing the hands live was masked. Subjects were randomized to immediate treatment or delayed treatment in a 3:1 ratio. Immediate treatment group subjects (treatment) were treated at the onset of the study. Delayed treatment group subjects were not treated (control) for 3 months after enrollment. The control group subjects crossed over to the treatment group at 3 months. All subjects were eligible for re-treatment 6 months after initial treatment.

The statistical analysis compared the percent of subjects in the treatment and control groups that were evaluated by MHGS live assessments. The statistical hypothesis for the study was the percentage of subjects treated with RADIESSE® showing at least a one-point improvement on the Merz Hand Grading Scale (MHGS) would be superior to the percentage of subjects in the delayed-treatment group (control). All primary effectiveness analyses were performed based on the intent-to-treat (ITT) population which included all enrolled subjects that met inclusion/exclusion criteria and were scheduled for the 3 month study visit. The hypothesis tested was the comparison between the percent of subjects improved in the treatment group (BR) and the percent of subjects improved in the control group (BC) using a Fisher's Exact Test (H_0: $B_R = B_C$; H_A: $B_R > B_C$). Statistical significance was declared if the one-sided p-value of a Fisher's Exact Test is ≤ 0.025.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the pivotal study was limited to subjects who met the following inclusion criteria:

   - Has right and left hands with a rating of 2 or 3 on the validated Merz Hand Grading Scale (MHGS) as determined by a live, masked evaluator.
   - Is at least 18 years of age.
   - Has signed an informed consent.
   - Understands and accepts the obligation not to receive any other procedures in the dorsum of the hands through the end of the study.
   - Understands and accepts the obligation and is logistically able to present for all scheduled follow-up visits and meet all study requirements.

   Subjects were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria:

   - Has been treated with any dermal fillers, fat injections, has hand deformities, or has received surgery in the dorsum of the hands.
   - Has received within the past 6 months or plans to receive during the study dermal resurfacing procedures (e.g. chemical peel, dermabrasion, ablative laser resurfacing) or non-invasive skin tightening (e.g. Thermage) in the dorsum of the hands.
   - Has received in the past 2 weeks or plans to receive during the study prescription wrinkle therapies, topical steroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) in the dorsum of the hands.
   - Has received in the past 2 months or plans to receive during the study immunosuppressive medications or systemic steroids (intranasal / inhaled steroids acceptable).
   - Has an acute inflammatory process or infection, or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of adverse events.
   - Has a known bleeding disorder or is receiving medication that will likely increase the risk of bleeding as the result of injection.

- Has a known history of allergic / anaphylactic reactions including hypersensitivity to lidocaine or anesthetics of the amide type, or any of the device components.
- Has a known history of hyper- or hypo-pigmentation in the hands, keloid formation, or hypertrophic scarring.
- Is a female of child bearing potential and not using medically effective birth control or is pregnant or lactating.
- Has any other medical condition with the potential to interfere with the study or increase the risk of adverse events.
- Is enrolled or plans to enroll in an interfering study.
- Is an employee or direct relative of an employee of the investigational site or of the study sponsor.

2. Follow-up Schedule

   All subjects were scheduled to return for in-person physician follow-up examinations at 1 and 2 weeks and 1, 2, and 3 months after initial treatment. The following additional follow-up examinations are listed for each treatment group:

   No re-treatment group
   - Immediate treatment subjects: 4, 5, 6, 9 and 12 months after initial treatment
   - Delayed treatment subjects: 6, 7 and 9 months after initial treatment

   Re-treatment group (re-treatment occurred approximately 6 months after the initial treatment)
   - Immediate treatment subjects: 4, 5 and 6 after initial treatment and 3 and 6 months after re-treatment
   - Delayed treatment subjects: 6 months after initial treatment and 1 and 3 months after re-treatment

   A take-home subject diary were given to subjects to record, separately for each hand, adverse events experienced in the 30 days following initial treatment and re-treatment.

   Pre-procedure and post-procedure, the objective parameters measured during the study included live evaluation of the subjects' hands using the 5-point photometric Merz Hand Grading Scale (MHGS) and photographs of the subjects' hands.

3. Clinical Endpoints

   With regards to safety, pre-printed diary forms were used by subjects to record daily observations of symptoms experienced on both hands for 30 days after initial treatment and after re-treatment. In the diary, check boxes were provided to allow the subject to indicate whether the symptom for each hand was considered to be none, mild, moderate or severe. Adverse events were also assessed by the treating investigator at each follow-up visit. Hand function testing was conducted on subjects

to evaluate the change in hand sensation, dexterity, strength and flexibility after each injection of Radiesse® into the hand.

With regards to effectiveness, the primary effectiveness measure was the improvement on the 5-point photometric MHGS between baseline and 3 months in both hands for the treatment group versus the control group based on live evaluation by masked evaluators.

Secondary measures included the level of improvement on the (1) 5-point MHGS for each hand and for each subject after 3 months post initial treatment, (2) 5-point MHGS for each hand and for each subjects after re-treatment and (3) 5-point Global Aesthetic Improvement Scale (GAIS) performed by immediate treatment subjects by comparing their live hand appearance at 3 months after treatment to baseline, pre-treatment hand photographs.

With regard to success criteria, this was evaluated by comparing the percent of subjects in the treatment group as compared to the control group from baseline to 3-months who had ≥ 1 point improvement on the MHGS. Effectiveness was demonstrated if statistical significance was observed between the treatment group and control group.

B. Accountability of PMA Cohort

At the time of database lock, 137 subjects were screened in the clinical study but 19 failed the screening. 118 subjects were enrolled in the study but 4 withdrew from the study. Of the remaining 114 subjects, 85 randomized to the immediate treatment group and 29 randomized to the delayed treatment group (control). The delayed treatment group crossed-over the immediate treatment group after 3 months. Prior to treatment, one subject withdrew from the delayed treatment group. One hundred-thirteen (113) of 114 subjects (99%) completed the main study through 3 months. One hundred-eleven (111) of 114 subjects (97%) completed the study through 12 months.

The analysis cohort was the intent-to-treat population which included all enrolled subjects that met the inclusion/exclusion criteria and completed the 3 moth visit.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study performed in the US. Subject demographics and pre-treatment characteristics are presented in Table 1.

Table 1: Demographics and Pre-Treatment Characteristics (N = 114 Subjects)

	Treatment Group (Immediate) (N=85)	**Control Group (Delayed) (N=29)**

	Treatment Group (Immediate) (N=85)	Control Group (Delayed) (N=29)
Age (years)		
Mean	52.8	54.8
SD	8.0	10.6
Median	52.0	57.0
Range	(26 - 75)	(34 - 79)
Gender – n (%)		
Female	81 (95.3%)	28 (96.6%)
Male	4 (4.7%)	1 (3.4%)
Race – n (%)		
Caucasian	66 (77.6%)	21 (72.4%)
African American	3 (3.5%)	3 (10.3%)
Hispanic	12 (14.1%)	3 (10.3%)
Asian	3 (3.5%)	1 (3.4%)
Other	1 (1.2%)	1 (3.4%)
Fitzpatrick Skin Type – n (%)		
I	3 (3.5%)	0 (0.0%)
II	45 (52.9%)	11 (37.9%)
III	19 (22.4%)	11 (37.9%)
IV	13 (15.3%)	4 (13.8%)
V	4 (4.7%)	2 (6.9%)
VI	1 (1.2%)	1 (3.4%)
Hand Dominance – n (%)		
Right	79 (92.9%)	26 (89.7%)
Left	6 (7.1%)	3 (10.3%)

Subjects received Radiesse® mixed with 2% lidocaine hydrogen chloride (final concentration of lidocaine was 0.3%) in the dorsum of both hands. The number of injection points varied and was left to the discretion of the treating investigator. Injected aliquots had volumes of a maximum of 0.5 cc each. The volumes of Radiesse (including the volume of added lidocaine) that were injected are detailed in Table 2. The data are presented by initial treatment, re-treatment, and by the combined amount of both treatments.

Table 2: Injection Volume (cc) for 226 Hands
(N = 113 Subjects)

	Initial Treatment n = 226 Hands	Re-treatment n = 156 Hands	Combined n = 226 Hands

	Right Hand	Left Hand	Total	Right Hand	Left Hand	Total	Right Hand	Left Hand	Total
Mean	2.58	2.60	5.18	1.64	1.61	3.25	3.72	3.71	7.43
Standard Deviation	0.68	0.69	1.37	0.52	0.61	1.08	1.16	1.15	2.29
Median	2.64	2.64	5.28	1.76	1.76	3.52	3.52	3.54	7.20
Range	1.50 - 3.60	1.40 - 3.60	2.90 - 7.20	0.70 - 2.64	0.00 - 3.00	1.40 - 5.30	1.50 - 6.16	1.40 - 6.16	2.90 - 12.32

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of subjects available at each follow-up time point. A take-home subject diary were given to subjects to record, separately for each hand, adverse events experienced in the 30 days following initial treatment and re-treatment. All 113 subjects who underwent treatment (immediate treatment and delayed treatment groups) completed the diary forms. All 78 subjects who underwent re-treatment also completed the diary forms. In the diary, check boxes were provided to allow the subjects to indicate whether the symptom for each hand was considered to be none, mild, moderate or severe.

The key safety outcomes for this study are presented below and are summarized in Tables 3 to 5. Adverse events are listed in Tables 6 to 9 for after initial treatment and in Tables 10 to 13 for after re-treatment. All subjects experienced at least one adverse event. A total of 24 out of 113 subjects (21%) experienced adverse events described as "severe" such as swelling, bruising, pain, difficulty in performing activities and redness (Table 3).

Table 3: Duration of Severe Adverse Events over a 12 month period

Adverse Event Type	# of Subjects	Mean duration (days)	Median duration (days)	Range of days	Duration reported as "severe" in diary (days)
Swelling	18	17.5	12	3-57	1-8
Bruising	7	19.9	10.5	5-67	1-4
Pain	7	33.1	21.5	8-99	1-7
Difficulty in Performing Activities	3	41.8	15	3-97	1-11
Redness	4	18.5	14.5	3-37	1-2

48% of study subjects reported temporary difficulty performing activities after injection. The effects of Radiesse® on hand function were assessed by

quantitative tests and the results were determined to be uncertain. Therefore, hand function is being collected as part of the post-approval study.

The percentage of subjects (out of 113 subjects) that experienced an adverse event for greater than 14 days in the study were: 29% swelling, 25% pain, 7% nodules/bumps/lumps, 6% difficulty performing activities, 6% redness, 3% itching, 3% bruising and 1% hematoma. The subjects that experienced nodules/bumps/lumps in the dorsum of the hand reported a duration ranging from 17 to 312 days.

Table 4: Subject-Reported Adverse Events over a 12 month period (N = 113 Subjects)

Adverse Event Type	**# of Subjects With Event** (% total)	**Maximum Severity** (N, % with event)		
		Mild	Moderate	Severe
Bruising	82 (72.6%)	48 (58.5%)	29 (35.4%)	5 (6.1%)
Swelling	112 (99.1%)	22 (19.6%)	74 (66.1%)	16 (14.3%)
Redness	92 (81.4%)	40 (43.5%)	48 (52.2%)	4 (4.3%)
Itching	52 (46.0%)	35 (67.3%)	17 (32.7%)	0 (0.0%)
Pain	104 (92.0%)	46 (44.2%)	51 (49.0%)	7 (6.7%)
Hematoma	1 (0.9%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	7 (6.2%)	2 (28.6%)	5 (71.4%)	0 (0.0%)
Difficulty Performing Activities	54 (47.8%)	30 (55.6%)	21 (38.9%)	3 (5.6%)
Loss of Sensation	17 (15.0%)	10 (58.8%)	7 (41.2%)	0 (0.0%)
Other*	10 (8.8%)	4 (40.0%)	5 (50.0%)	1 (10.0%)
Total	113 (100.0%)	14 (12.4%)	78 (69.0%)	21 (18.6%)

* Other adverse events reported that were related to the device include vagal response, dry skin, hypersensitivity and needle pricks.

Table 5: Physician-Reported Adverse Events over a 12 month period (N = 113 Subjects)

Adverse Event Type	# of Subjects With Event (% total)	Maximum Severity (N, % with event)		
		Mild	Moderate	Severe
Bruising	21 (18.6%)	13 (61.9%)	6 (28.6%)	2 (9.5%)
Swelling	23 (20.4%)	7 (30.4%)	14 (60.9%)	2 (8.7%)
Redness	9 (8.0%)	5 (55.6%)	4 (44.4%)	0 (0.0%)
Itching	4 (3.5%)	3 (75.0%)	1 (25.0%)	0 (0.0%)
Pain	7 (6.2%)	4 (57.1%)	2 (28.6%)	1 (14.3%)
Hematoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nodule, Bumps/Lumps	7 (6.2%)	7 (100.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	2 (1.8%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
Loss of Sensation	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other*	13 (11.5%)	7 (53.8%)	5 (38.5%)	1 (7.7%)
Total	50 (44.2%)	24 (48.0%)	21 (42.0%)	5 (10.0%)

* Other adverse events reported that were related to the device include vagal response, dry skin, hypersensitivity and needle pricks.

After Initial Treatment

Table 6: Subjects Experiencing Adverse Events, For First Six Months from Initial Treatment Reported in Subject Diaries (N = 113 Subjects)

Adverse Event Type	# Subjects With Event		Maximum Severity		
	N	95% CI	Mild	Moderate	Severe

Bruising	73 (64.6%)	(55.0-73.4)	48 (65.8%)	22 (30.1%)	3 (4.1%)
Swelling	110 (97.3%)	(92.4-99.4)	28 (25.5%)	69 (62.7%)	13 (11.8%)
Redness	88 (77.9%)	(69.1-85.1)	46 (52.3%)	39 (44.3%)	3 (3.4%)
Itching	49 (43.4%)	(34.1-53.0)	36 (73.5%)	13 (26.5%)	0 (0.0%)
Pain	98 (86.7%)	(79.1-92.4)	48 (49.0%)	45 (45.9%)	5 (5.1%)
Hematoma	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)
Nodule, Bumps/Lumps	4 (3.5%)	(1.0-8.8)	1 (25.0%)	3 (75.0%)	0 (0.0%)
Difficulty Performing Activities	45 (39.8%)	(30.7-49.5)	26 (57.8%)	17 (37.8%)	2 (4.4%)
Loss of Sensation	11 (9.7%)	(5.0-16.8)	7 (63.6%)	4 (36.4%)	0 (0.0%)
Other	9 (8.0%)	(3.7-14.6)	4 (44.4%)	5 (55.6%)	0 (0.0%)
Total	112 (99.1%)	(95.2-100.0)	21 (18.8%)	75 (67.0%)	16 (14.3%)

Table 7: Subjects Experiencing Adverse Events, For First Six Months from Initial Treatment Reported by Physician Assessment (N = 113 Subjects)

Adverse Event Type	# Subjects With Event		Maximum Severity		
	N	95% CI	Mild	Moderate	Severe
Bruising	20 (17.7%)	(11.2-26.0)	14 (70.0%)	4 (20.0%)	2 (10.0%)
Swelling	23 (20.4%)	(13.4-29.0)	7 (30.4%)	14 (60.9%)	2 (8.7%)
Redness	9 (8.0%)	(3.7-14.6)	5 (55.6%)	4 (44.4%)	0 (0.0%)
Itching	4 (3.5%)	(1.0-8.8)	3 (75.0%)	1 (25.0%)	0 (0.0%)

Pain	7 (6.2%)	(2.5-12.3)	4 (57.1%)	2 (28.6%)	1 (14.3%)
Hematoma	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)
Nodule, Bumps/Lumps	2 (1.8%)	(0.2-6.2)	2 (100.0%)	0 (0%)	0 (0%)
Difficulty Performing Activities	2 (1.8%)	(0.2-6.2)	2 (100.0%)	0 (0%)	0 (0%)
Loss of Sensation	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)
Other	10 (8.8%)	(4.3-15.7)	6 (60.0%)	3 (30%)	1 (10%)
Total	44 (38.9%)	(29.9-48.6)	20 (45.5%)	19 (43.2%)	5 (11.4%)

Table 8: Subject-Reported Duration of Adverse Events Onset after Initial Treatment (N = 914 Events)

		Reported Adverse Events (N, % with event)				
Adverse Event Type	**All First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Bruising	133 (14.6%)	124 (93.2%)	5 (3.8%)	3 (2.3%)	1 (0.8%)	129 (97.0%)
Swelling	218 (23.9%)	218 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	218 (100.0%)
Redness	166 (18.2%)	163 (98.2%)	3 (1.8%)	0 (0.0%)	0 (0.0%)	166 (100.0%)
Pain	192 (21.0%)	180 (93.8%)	4 (2.1%)	6 (3.1%)	2 (1.0%)	184 (95.8%)
Itching	83 (9.1%)	60 (72.3%)	16 (19.3%)	6 (7.2%)	1 (1.2%)	76 (91.6%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	7 (0.8%)	2 (28.6%)	4 (57.1%)	0 (0.0%)	1 (14.3%)	6 (85.7%)
Difficulty Performing Activities	82 (9.0%)	71 (86.6%)	7 (8.5%)	4 (4.9%)	0 (0.0%)	78 (95.1%)
Loss of Sensation	16 (1.8%)	8 (50.0%)	5 (31.3%)	3 (18.8%)	0 (0.0%)	13 (81.3%)
Other	17	13	4	0	0	17

		Reported Adverse Events (N, % with event)				
Adverse Event Type	**All First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
	(1.9%)	(76.5%)	(23.5%)	(0.0%)	(0.0%)	(100.0%)
Total	914 (100.0%)	839 (91.8%)	48 (5.3%)	22 (2.4%)	5 (0.5%)	887 (97.0%)

* Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

Table 9: Physician-Reported Duration of Adverse Events after Initial Treatment (N = 117 Events)

		Reported Adverse Events (N, % with event)				
Adverse Event Type	**All First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Bruising	26 (22.2%)	23 (88.5%)	0 (0.0%)	0 (0.0%)	3 (11.5%)	23 (88.5%)
Swelling	39 (33.3%)	28 (71.8%)	10 (25.6%)	1 (2.6%)	0 (0.0%)	38 (97.4%)
Redness	15 (12.8%)	14 (93.3%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	15 (100.0%)
Pain	11 (9.4%)	5 (45.5%)	2 (18.2%)	1 (9.1%)	3 (27.3%)	7 (63.6%)
Itching	7 (6.0%)	5 (71.4%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	5 (71.4%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	3 (2.6%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)
Difficulty Performing Activities	4 (3.4%)	2 (50.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	12 (10.3%)	4 (33.3%)	0 (0.0%)	0 (0.0%)	8 (66.7%)	4 (33.3%)
Total	117 (100.0%)	83 (70.9%)	15 (12.8%)	2 (1.7%)	17 (14.5%)	98 (83.8%)

Re-treatment Adverse Events

Table 10: Subject-Reported* Adverse Events Following Initial Treatment v. Re-treatment

Reported in Subject Diaries* (N = 78 Retreated Subjects)

Adverse Event Type	# Subjects							
	Following Initial Treatment				Following Re-Treatment			
	N (%)	Max Severity			N (%)	Max Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Bruising	52 (66.7%)	34 (65.4%)	16 (30.8%)	2 (3.8%)	45 (57.7%)	27 (60.0%)	16 (35.6%)	2 (4.4%)
Swelling	75 (96.2%)	23 (30.7%)	44 (58.7%)	8 (10.7%)	68 (87.2%)	31 (45.6%)	33 (48.5%)	4 (5.9%)
Redness	60 (76.9%)	34 (56.7%)	24 (40.0%)	2 (3.3%)	42 (53.8%)	26 (61.9%)	15 (35.7%)	1 (2.4%)
Itching	33 (42.3%)	23 (69.7%)	10 (30.3%)	0 (0.0%)	16 (20.5%)	7 (43.8%)	9 (56.3%)	0 (0.0%)
Pain	65 (83.3%)	34 (52.3%)	28 (43.1%)	3 (4.6%)	47 (60.3%)	28 (59.6%)	17 (36.2%)	2 (4.3%)
Nodule, Bumps/Lumps	2 (2.6%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	3 (3.8%)	1 (33.3%)	2 (66.7%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	26 (33.3%)	15 (57.7%)	10 (38.5%)	1 (3.8%)	21 (26.9%)	15 (71.4%)	5 (23.8%)	1 (4.8%)
Loss of Sensation	8 (10.3%)	6 (75.0%)	2 (25.0%)	0 (0.0%)	6 (7.7%)	3 (50.0%)	3 (50.0%)	0 (0.0%)
Other	7 (9.0%)	3 (42.9%)	4 (57.1%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Total	77 (98.7%)	17 (22.1%)	50 (64.9%)	10 (13.0%)	73 (93.6%)	28 (38.4%)	39 (53.4%)	6 (8.2%)

*Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

Table 11: Physician-Reported Adverse Events Following Initial Treatment v. Re-treatment (N = 78 Retreated Subjects)

Adverse Event Type	# Subjects							
	Following Initial Treatment				Following Re-Treatment			
	N (%)	Max Severity			N (%)	Max Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Bruising	11 (14.1%)	9 (81.8%)	1 (9.1%)	1 (9.1%)	5 (6.4%)	3 (60.0%)	2 (40.0%)	0 (0.0%)
Swelling	12 (15.4%)	5 (41.7%)	6 (50.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Adverse Event Type	# Subjects							
	Following Initial Treatment				Following Re-Treatment			
	N (%)	Max Severity			N (%)	Max Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Redness	6 (7.7%)	3 (50.0%)	3 (50.0%)	0 (0.0%)	1 (1.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Itching	2 (2.6%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	4 (5.1%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (6.4%)	5 (100.0%)	0 (0.0%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	1 (1.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	4 (5.1%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	3 (3.8%)	1 (33.3%)	2 (66.7%)	0 (0.0%)
Total	24 (30.8%)	14 (58.3%)	9 (37.5%)	1 (4.2%)	14 (17.9%)	10 (71.4%)	4 (28.6%)	0 (0.0%)

Table 12: Subject Reported* Total Number of Adverse Events Onset after Re-treatment (N = 473 Events)

		Reported Adverse Events (N, % event type)				
Adverse Event Type	**First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Bruising	82 (17.3%)	82 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	82 (100.0%)
Swelling	133 (28.1%)	133 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	133 (100.0%)
Redness	83 (17.5%)	82 (98.8%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	83 (100.0%)
Pain	91 (19.2%)	91 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	91 (100.0%)
Itching	30 (6.3%)	30 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	30 (100.0%)
Hematoma	1	1	0	0	0	1

		Reported Adverse Events (N, % event type)				
Adverse Event Type	**First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
	(0.2%)	(100.0%)	(0.0%)	(0.0%)	(0.0%)	(100.0%)
Nodule, Bumps/Lumps	5 (1.1%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	3 (60.0%)	2 (40.0%)
Difficulty Performing Activities	36 (7.6%)	32 (88.9%)	2 (5.6%)	1 (2.8%)	1 (2.8%)	34 (94.4%)
Loss of Sensation	11 (2.3%)	9 (81.8%)	0 (0.0%)	2 (18.2%)	0 (0.0%)	9 (81.8%)
Other	1 (0.2%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Total	473 (100.0%)	461 (97.5%)	5 (1.1%)	3 (0.6%)	4 (0.8%)	466 (98.5%)

* Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

Table 13: Physician Reported Total Number of Adverse Events Onset after Re-treatment (N = 21 Events)

		Reported Adverse Events (N, % event type)				
Adverse Event Type	**First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Bruising	8 (38.1%)	7 (87.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	7 (87.5%)
Swelling	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	2 (9.5%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Itching	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nodule, Bumps/Lumps	7 (33.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	6 (85.7%)	1 (14.3%)
Difficulty	0	0	0	0	0	0

		Reported Adverse Events (N, % event type)				
Adverse Event Type	**First Onset** (N, % total)	**Week 1**	**Week 2**	**Week 3**	**Week 4 and Beyond**	**Week 1 and 2 Combined**
Performing Activities	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	4 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)	0 (0.0%)
Total	21 (100.0%)	10 (47.6%)	0 (0.0%)	0 (0.0%)	11 (52.4%)	10 (47.6%)

Adverse effects that occurred in the PMA clinical study:

Recurrent adverse events were reported in subject diaries and by the treating investigator. The recurrent adverse events are listed in Table 14 for after initial treatment and Table 15 for after re-treatment.

An adverse event was considered a recurrent adverse event, if an adverse event of the same type was reported again after greater than 3 days. A total of 58% subjects (66 out of 113) had a recurrent adverse event after the initial treatment.

Table 14: Total Number of Recurrent AEs after Initial Treatment Reported in Subject Diaries*+
(N=239 Events)

	Less Than 14 Days	**14-19 Days**	**20-29 Days**	**30-59 Days**	**Total Adverse Events per Event Type**
Bruising	4 (28.6%)	4 (28.6%)	6 (42.9%)	0 (0.0%)	14 (5.9%)
Swelling	44 (64.7%)	17 (25.0%)	6 (8.8%)	1 (1.5%)	68 (28.5%)
Redness	16 (40.0%)	10 (25.0%)	11 (27.5%)	3 (7.5%)	40 (16.7%)
Pain	43 (65.2%)	6 (9.1%)	14 (21.2%)	3 (4.5%)	66 (27.6%)
Itching	17 (54.8%)	7 (22.6%)	7 (22.6%)	0 (0.0%)	31 (13.0%)
Nodule, Bumps/Lumps	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	3 (1.3%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Difficulty Performing Activities	11 (68.8%)	1 (6.3%)	3 (18.8%)	1 (6.3)	16 (6.7%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Total	137 (57.3%)	46 (19.2%)	48 (20.1%)	8 (3.3%)	239 (100.0%)

*Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.
+ Physicians reported recurrent swelling adverse events after initial treatment from 14-19 days (2 events) and from 60 or more days (1 event).

Table 15: Total Number of Recurrent Adverse Events after Re-treatment Reported in Subject Diaries*
(N = 31 Events)

Adverse Event Type	Less Than 14 Days	14-19 Days	20-29 Days	30-59 Days	60 or More Days	Total Adverse Events per Event Type
Bruising	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	4 (33.3%)	1 (8.3%)	5 (41.7%)	2 (16.7%)	0 (0.0%)	12 (38.7%)
Redness	1 (20.0%)	2 (40.0%)	1 (20.0%)	1 (20.0%)	0 (0.0%)	5 (16.1%)
Pain	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (9.7%)
Itching	0 (0.0%)	0 (0.0%)	4 (66.7%)	2 (33.3%)	0 (0.0%)	6 (19.4%)
Nodule, Bumps/Lumps	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difficulty Performing Activities	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (9.7%)
Loss of Sensation	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	5	9	12	5	0	31

Adverse Event Type	Less Than 14 Days	14-19 Days	20-29 Days	30-59 Days	60 or More Days	Total Adverse Events per Event Type
	(16.1%)	(29.0%)	(38.7%)	(16.1%)	(0.0%)	(100.0%)

*Subject diaries recorded entries for the period of 30 days after treatment. If an event was still ongoing at the time of collection of the diary at 30 days, the resolution date was recorded and reported by phone or at next study visit.

2. Effectiveness Results

Primary effectiveness: 75.3% of subjects in the treatment group had ≥ 1 point improvement which was significantly greater than 3.4% of subjects in the control group ($p < 0.0001$) at 3 months. The study met the primary effectiveness pre-specified success criteria. There were no differences in effect due to age, hand dominance or Fitzpatrick skin type. The mean initial volume injected was 5.18cc.

Table 16: Effectiveness Summary at 3 Months Based on Live Evaluation

n (%)		p – value*
Treatment Group n = 85	Control Group n = 29	
64 (75.3%)	1 (3.4%)	<0.0001

* Fisher's exact test

Table 17 shows the MHGS results, by hand, for both the treatment and control groups at 3 months. In the treatment group there was a statistically significant improvement at 3 months when compared to the control. In addition, the treatment group showed a statistically significant improvement from baseline condition, whereas, the control group did not.

Table 17: MHGS By Hand
(N = 228 Hands*)**

	Baseline		3 Month		Change	
	Treatment Group n = 170	Control Group n = 58	Treatment Group n = 170	Control Group n = 58	Treatment Group n = 170	Control Group n = 58
Mean	2.6	2.6	1.5	2.6	-1.1	-0.1
Median	3.0	3.0	1.0	3.0	-1.0	0
Standard Deviation	0.5	0.5	0.8	0.5	0.9	0.2
Range	2 - 3	2 - 3	0 - 3	2 - 3	-3 , 1	-1 , 0
Mean Difference	0		-1.1		-1.0	

p-value - Treatment vs. Control*	0.56	<0.0001	<0.0001	
p-value - vs. Baseline**			<0.0001	0.25

* Wilcoxon Rank-Sum Test
**Wilcoxon Signed-Rank Test
*** Including the subject withdrawn prior to treatment

A sensitivity analysis per site was performed and it was found that one site (Site 7) had effectiveness scores significantly higher than all other sites. When effectiveness was evaluated excluding Site 7, the mean MHGS improvement was 0.7 versus 1.1 when site 7 was included. When effectiveness was evaluated excluding Site 7, 65.5% of subjects showing at least a 1 point improvement on the MHGS in both hands as compared to 75.3% when site 7 was included. The percent of subjects that showed $\geq$ 1 point improvement at 3 months by investigational site is provided in Table 18.

Table 18: MHGS ≥ 1 Point Improvement at 3 Months – By Investigational Site (N = 114 Subjects)

Improvement From Baseline	n (%)			
	Site 1, 2, 3	Site 4	Site 6	Site 7
	n=16	n=44	n=17	n=37
$\geq$ 2 points	0 (0%)	1 (2%)	5 (29%)	25 (68%)
1 point	8 (50%)	27 (61%)	10 (59%)	11 (30%)
0 point	7 (44%)	15 (34%)	2 (12%)	1 (3%)
< 0 point	1 (6%)	1 (2%)	0 (0%)	0 (0%)

Secondary effectiveness: The Global Aesthetic Improvement Scale (GAIS) results for the treatment group as rated by the subjects at 3 months (Table 19). Evaluation of the subject-reported results demonstrated that 166/170 hands (97.6%) were improved compared to baseline. Only 4 hands (2%) were reported as unchanged and no hands rated as being worse.

Table 19: GAIS By Hand (n = 170 Hands for 85 Subjects)

Rating	n (%)
Very Much Improved	54 (31.8%)
Much Improved	75

Rating	n (%)
	(44.1%)
Improved	37 (21.8%)
No Change	4 (2.4%)
Worse	0 (0%)
TOTAL - At Least "Improved"	**166 (97.6%)**

Extended Follow-up: Table 20 provides long term effectiveness data of Radiesse® injected into the dorsum of the hand after initial treatment (single treatment) and re-treatment of subjects that had ≥ 1 point improvement in the MHGS at 3, 6, 9 and 12 months. The mean re-treatment volume was 3.25cc.

Table 20: MHGS Ratings: ≥ 1 Point Improvement at 3, 6, 9 and 12 Months After Initial Treatment and After Re-treatment (N=113 Subjects)

Number (N) or Percentage (%) of Subjects					
Time After Initial Treatment				Time After Re-Treatment	
3 months N=113	6 months N=113	9 months N=35	12 months N=22	3 months N=78	6 months N=61
87 (77%)	82 (72.6%)	25 (71.4%)	15 (68.2%)	64 (82.1%)	54 (88.5%)

3. Subgroup Analyses
   The following preoperative characteristics were evaluated for potential association with outcomes: age, injection volume and Fitzpatrick skin type.

   The subgroup analysis for age did not identify differences in the incidence of device-related adverse events. However, there is a significant increase in the incidence of:
   - bruising with increased initial injection volume ($p = 0.0477$);
   - redness and pain with increased re-treatment injection volume ($p = 0.0071$ and $p = 0.0148$ respectively); and
   - difficulty performing activities for Fitzpatrick Skin Types IV-VI as compared to Fitzpatrick Skin Types I-III ($p = 0.0251$).

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information

concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 6 treating investigators, 4 sub-investigators and 8 masked evaluators from which 14 clinical investigators had no disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

The pivotal clinical study included 3 clinical investigators that had disclosable financial interests/arrangements with Merz as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Canadian Clinical Study: This study was conducted in Canada to assess the sensitivity of the Merz Hand Grading Scale (MHGS) to detect changes in hand appearance one month after treatment. The method of injection was similar to the clinical study conducted in the US (i.e., skin tenting with small bolus injections).

The study enrolled 30 subjects who were treated with Radiesse® with 20 subjects randomized to the immediate treatment group (treatment) and 10 subjects to the delayed treatment group (control). After 4 weeks, the control group was crossed-over to the treatment group. All subjects were followed for a total of 4 weeks after injection and evaluated by MHGS ratings (live evaluation), Global Aesthetic Improvement Scale (GAIS) ratings (photo evaluation), hand function testing, and adverse events reporting by subject diaries. Hand function was assessed by range of motion, touch sensation, functional dexterity, grip strength and pinch strength.

The effectiveness outcome of the study was that 100% of treated hands showed a $\geq$ 1 point improvement at Weeks 2 and 4. Subjects rated 92.5% of hands and treating investigators rated 100% of hands as at least "Improved" on the GAIS. A summary of the adverse event reporting indicated that a total of 146 adverse events were reported in subject diaries with onset and duration ranging from 0-30 days. 15% of adverse events in subject diaries had onset of greater than 14 days post-treatment. A total of 95 adverse events were reported by

treating investigator. Five subjects reported "severe" adverse events (e.g., pain, swelling, bruising, and redness).

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on February 27, 2015, the General and Plastic Surgery Devices Panel voted 11-3 that there is a reasonable assurance the device is safe, 12-2 that there is reasonable assurance that the device is effective, and 9-1-4 with one abstained that the benefits of the device outweigh the risks in subjects who meet the criteria specified in the proposed indication.

The advisory committee agreed when comparing Radiesse® treatment versus control groups at 3 months supported product effectiveness. The advisory committee commented on the variability that was observed between sites in regards to the amount of improvement. The panel concurred that the variability may be due to inconsistent use of the MHGS and/or injector technique.

The advisory committee recommended that the labeling should identify a clear list of precautions, contraindications, and warnings in the labeling.

The advisory committee recommended that the sponsor conduct post-approval studies to evaluate the following:

- Adverse event profile of subjects with very severe loss of fatty tissue; i.e., marked visibility of veins and tendons (4 on the Merz Hand Grading Scale (MHGS)). The advisory committee had concerns that more adverse events may occur in these types of subjects because they will most likely require larger volumes of Radiesse® than was administered in the clinical study.
- Effects of Radiesse® on hand function. The advisory committee noted that the data captured for the hand function testing was variable and was difficult to interpret; therefore adequate testing and data needs to be captured in order to understand the effects of hand function after Radiesse® injection.
- Short-term and long-term studies to assess hand imaging post-injection of Radiesse® into the dorsum of the hand. The advisory committee expressed concerns about the radiopaque properties of Radiesse®, and the absence of data that evaluated the potential impact of Radiesse® on hand imaging.

The FDA's Executive Summary and meeting transcript may be assessed at the following webpage:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/UCM435297.pdf

B. FDA's Post-Panel Action

After the panel meeting, FDA completed review of the product labeling and post-approval study design by incorporating the panel's recommendation.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Radiesse® met the pre-specified primary endpoint. The data indicates that Radiesse® is effective in correcting volume loss in the dorsum of the hand at the 3-month primary effectiveness time point.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The adverse effects of the device are based on data collected in the clinical studies conducted to support PMA approval as described above as well as evaluation of the device use in the post-market setting. The submitted data provided a reasonable assurance that the device is safe for hand augmentation to correct volume loss in the dorsum of the hand. The specific conclusions are:

- All subjects experienced at least one adverse event. The majority of adverse events were reported as having a maximum severity of mild or moderate for swelling, pain, redness, bruising, difficulty performing in activities, itching, loss of sensation, nodule/bumps/lumps, hematoma and other. 21% of subjects reported a total of 64 severe adverse events. 48% of study subjects reported temporary difficulty performing activities after injection. Adverse event reported by subjects and physicians related to nodule/lumps/bumps was 11.5% with duration ranging from 17 to 312 days.

- Adverse events that lasted for greater than 14 days for subjects were swelling, pain, nodules/bumps/lumps, difficulty performing activities, redness, bruising and hematoma.

- 58% of the subjects experienced recurrent adverse events (defined as an event that recurs more than 3 days after resolution of the previous event). 25% of the recurrent AEs occurred between 2-4 weeks after initial treatment.

- There is a significant increase in incidence of device related adverse events with increased initial injection volume (bruising), increased re-treatment injection volume (redness and pain), and Fitzpatrick Skin Types IV-VI (difficulty in performing activities).

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The study was a well-designed prospective, randomized, cross-over, masked live evaluation study designed to evaluate the safety and effectiveness of Radiesse for hand augmentation for 12 months. The primary effectiveness endpoint was improvement of ≥ 1 point on the MHGS (Merz Hand Grading Scale) between baseline and 12 weeks both by subject and by hands, using ratings from the live, masked evaluators at each site based on the ITT population.

64 of 85 subjects (75.3%) in the immediate treatment group showed a ≥ 1 point on the MHGS between baseline and 3 months as compared to 1 of 29 subjects (3.4%) in the control group. This difference is clinically meaningful and statistically significant. There were no differences in effect due to age, hand dominance or Fitzpatrick skin type. Although not validated, GAIS is a commonly used scale in the study of devices used for aesthetic improvement. Almost every subject in the treated group (97.6%) thought that the appearance of both of their hands had at least "Improved" on the GAIS at 3 months.

The duration of the treatment effect defined as a ≥ 1 point improvement on the MHGS was 68.2% of subjects after 12 months from initial treatment which was assessed live masked evaluation. The GAIS which was self-assessed by subjects was determined to be 86.4% after 12 months from initial treatment.

All subjects experienced at least one adverse event which included swelling, pain, redness, bruising, difficulty performing in activities, itching, loss of sensation, nodule/bumps/lumps, hematoma and other. A total of 24 out of 113 subjects (21%) experienced adverse events described as "severe" such as swelling, bruising, pain, difficulty in performing activities and redness. Total duration of adverse events was 1-312 days. Most adverse events resolved within 14 days however, 29% of subjects reported having swelling greater than 14 days in duration. Several adverse events were reported to last for greater than 14 days, and included pain, nodules/bumps/lumps, difficulty performing activities, redness, bruising and hematoma. 58% of the subjects experienced recurrent adverse events such as swelling, pain, redness, bruising, itching, difficulty performing activities and other. The number of adverse events reported was greater when subjects received high injection volumes versus low injection volumes. No serious adverse events related to the device were reported. All adverse events resolved either spontaneously or with treatment.

The probable benefits outweigh the probable risks, as determined by no observed serious adverse event outcomes that were related to the device, and all adverse events resolved, balanced against the improvement seen on the MHGS at 3 and 12 months and the lack of subjects dropping out of the study.

In conclusion given the available information above, the data supports that for hand augmentation to correct volume loss in the dorsum of the hand, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on June 4, 2015. The final conditions of approval cited in the approval order are described below.

1. *Radiesse Radiological Evaluation Study:* This is a prospective, open-label, single-site, descriptive study, designed to evaluate whether Radiesse interferes with radiological assessment by obscuring the bones of the hand. Twenty newly enrolled subjects with MHGS grade 2, 3, and 4 at baseline (10 subjects with MHGS 4 and 10 subjects with MHGS 2 and 3) will be treated with Radiesse in the dorsum of the hands and have the opportunity to receive up to 3 repeat treatments over 2 years of follow-up.

   X-rays of the hands will be taken in all study participants at the following time points: baseline (before initial treatment) and at 1- and 6-months. In addition, 12-month x-rays will be taken in subjects whose bones were not visible on the 6-month x-ray. To evaluate the appearance of cumulative injections over time, 24-month x-rays will be taken in all subjects who received 4 Radiesse treatments during the 2-year study. Each digital radiographic image will be assessed by two blinded, licensed radiologists to determine whether the bones are visible on x-ray.

   Safety endpoints include adverse events reported by treating physicians and by subjects and hand function assessments based on hand function testing and the Michigan Hand Questionnaire. Effectiveness endpoints include MHGS ratings by a masked evaluator and subject-reported GAIS score. After initial treatment, all subjects will be seen at in-clinic follow-up visits at 1-, 6-, 12-, and 24-months. In addition, pre- and post-safety evaluations will be performed for each repeat treatment on the same day of injection.

2. *Radiesse New Enrollment Study:* This is a prospective, multi-center, open-label study, designed to evaluate the safety and effectiveness of Radiesse treatment in MHGS grade 4 subjects. In addition, this study will provide safety data after multiple repeat treatments. A total of 250 subjects with MHGS grades 2, 3 and 4 at baseline (at least 50% MHGS 4) will be enrolled in at least 5 sites and maximum of 12 sites in the U.S. Study participants will receive an initial Radiesse injection in the dorsum of the hands and have the opportunity to receive up to 3 repeat treatments over 2 years of follow-up. After initial treatment, all subjects will be seen at in-clinic follow-up visits at 1-,

6-, 12-, and 24-months. In addition, pre- and post-safety evaluations will be performed for each repeat treatment on the day of injection.

A non-inferiority hypothesis test will be conducted, comparing the 6-month rate of device/injection-related severe adverse events (primary study endpoint) in MHGS 4 versus MHGS 2 and 3 subjects combined, with an expected event rate of 17% and a 12% non-inferiority margin. A total of 244 subjects (n=122 in each group) at 6 months are required to ensure 80% power to conduct the hypothesis test. Based on an expected attrition rate of 5% per year, a minimum of 225 evaluable subjects are required to provide 2 years follow-up data. Safety and effectiveness data that are collected after 6 months and up to 2 years will be presented descriptively.

The effect of Radiesse injection on hand function will be evaluated with hand function testing and the Michigan Hand Questionnaire. The hand function tests will consist of the following: range of motion assessed by passive and active flexion/extension of the MCP joints; functional dexterity assessed using a 16-hole pegboard test; hand strength measured with a Jamar dynamometer (including grip strength, two-point tip pinch strength test, lateral pinch strength test, and three-jaw chuck pinch strength test); and sensation assessed by monofilament testing on the dorsum of the hands. Training of evaluators who will be conducting the hand function tests will be provided by an instructional video of a qualified physical or occupational therapist and an on-site sponsor trainer. Hand function testing will be performed in all subjects at baseline (prior to injection) and at 1-, 6-, 12-, and 24-months. In addition, pre-injection testing of hand function will be performed for each repeat treatment on the day of injection, and 1 month post-injection for repeat treatments.

For the first 10 subjects enrolled at each site (minimum of 50 subjects across all sites), hand function testing will be performed by 2 independent evaluators. These data will provide an assessment of inter- and intra-rater variability in hand function measures within and between sites.

Other safety endpoints include adverse events reported by treating physicians and by subjects. Effectiveness endpoints include MHGS ratings by a masked evaluator and subject-reported GAIS score. Hand photographs will be taken for safety and effectiveness evaluation at the following times: enrollment and 24-months (study exit) in all subjects; and at any follow-up visit in subjects who experience a serious or medically concerning adverse event.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling. *(See General hints)*

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.