SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	RADIESSE® Injectable Implant
Device Procode:	LMH
Applicant's Name and Address:	Merz North America 6501 Six Forks Road Raleigh, North Carolina 27615
Date(s) of Panel Recommendation:	None
Pre-Market Approval Application (PMA) Number:	P050052/S162
Date of FDA Notice of Approval:	March 31, 2026

The original PMA P050052 for RADIESSE® Injectable Implant 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® Injectable Implant 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. Panel Track Supplement P050052/S049 was approved on June 4, 2015 and is indicated for hand augmentation to correct volume loss in the dorsum of the hands. The SSEDs to support the indications for RADIESSE® Injectable Implant are available on the CDRH website and are incorporated by reference here.

The current supplement was submitted to expand the indication for the device.

II. INDICATIONS FOR USE

RADIESSE® Injectable Implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. It

is also indicated for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

RADIESSE® Injectable Implant is indicated for hand augmentation to correct volume loss in the dorsum of the hands.

RADIESSE® Injectable Implant diluted 1:2 with 0.9% sterile saline solution is indicated for subdermal implantation for the correction of décolleté wrinkles in patients 22 years of age and older.

III. CONTRAINDICATIONS

- RADIESSE® Injectable Implant is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- RADIESSE® Injectable Implant is 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® Injectable Implant labeling.

V. DEVICE DESCRIPTION

RADIESSE® Injectable Implant (hereinafter referred to as RADIESSE®) is an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant, whose principal component is synthetic calcium hydroxylapatite suspended in a gel carrier of glycerin, sodium carboxymethylcellulose, and sterile water for injection. RADIESSE® (1.5 mL) has a calcium hydroxylapatite particle size range of 25–45 microns. When used for the correction of wrinkles in the décolleté, RADIESSE® should be diluted in a 1:2 ratio with 0.9% sterile saline solution and injected with a 22 gauge flexible cannula.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to treat signs of aging in the décolleté region include neurotoxins, other dermal fillers, chemical peels, intense pulsed light, non-ablative and ablative lasers, and radiofrequency/ultrasound skin tightening. 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® was first approved in the United States in 2006. RADIESSE® is currently marketed worldwide including Europe, Canada and South America, and Asia. Subsequently, the product has been registered in over 73 countries. Since initial approval in the United States, over 10 million units of the RADIESSE® family of products has been sold worldwide. The product has never been withdrawn from marketing for any reason related to the safety or effectiveness of the device. As part of post-marketing surveillance, potential safety signals are monitored by trending adverse events across regions.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the RADIESSE® for correction of wrinkles in the décolleté

Adverse events (in greater than 2% of study subjects) included injection site bruising, injection site discoloration, injection site mass, and injection site pain.
Adverse events reported less frequently (in less than 2% of study subjects) included erythema, injection site pruritus, swelling, capillary fragility, injection site discomfort, injection site injury and pruritus.
Other common treatment responses associated with the use of RADIESSE® as well as for other dermal fillers as reported by patients in the study were redness, bruising, pain/discomfort (including burning/stinging), lumps/bumps, discoloration, and itching.

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

Post-marketing Surveillance

The following adverse events have been identified during post-approval use of RADIESSE® regardless of the indication, in the US and outside the US: infection, cellulitis, impetigo, loss of effect, product displacement/migration, allergic reaction, anaphylaxis, hives, rash, pruritus, urticaria, angioedema, inflammation, necrosis, granuloma, nodules, induration, erythema, skin discoloration, pustule, skin pallor, hair loss, paresthesia, ptosis, pain, headache, swelling, asymmetry, abscess, herpetic infection including herpes simplex and herpes zoster, hematoma, blanching, blistering, dizziness, festoons, flu-like symptoms, Guillain-Barre syndrome, tachypnea, ischemic reaction, lymphoid hyperplasia, nausea, pericarditis, scarring, sensitivity to cold, vascular occlusion/obstruction, vascular compromise, ocular ischemia, diplopia, visual impairment/blindness, facial muscle paralysis, Bell's palsy.

The following interventions have been reported associated with the use of the RADIESSE®: antibiotics, anti-inflammatories, corticosteroids, anti-histamines, analgesics, massage, warm compress, excision, drainage, and surgery.

IX. SUMMARY OF NON-CLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for the correction of wrinkles in the décolleté. There was no change in product manufacturing or specifications for the RADIESSE® product itself. As such, the data was previously presented in support of PMA P050052 and subsequent approved supplements. However, in support of the new indication, non-clinical assessments were carried out in relation to the process of diluting RADIESSE® 1:2 with sterile saline and injection with a cannula.

A. Laboratory Studies

The following bench tests were conducted to evaluate the performance characteristics of RADIESSE® after 1:2 dilution with sterile saline. Results can be found in **Table 1** below:

Table 1: Summary of Key Bench Testing on RADIESSE®

Test	Purpose	Results
Homogeneity	Ensures diluted RADIESSE® is homogenous with respect to solid content	Passed
Decantation stability	Ensures diluted RADIESSE® remains homogenous for 30 minutes after mixing/dilution	Passed
pH	Ensures appropriate pH of RADIESSE® after dilution	Passed
Extrusion force	Ensures extrusion force meets specification	Passed
Rheology	Ensures rheological properties meet specification	Passed
Particle Inspection/Durability	Ensures the particles of calcium hydroxylapatite (CaHA) remain unchanged after dilution	Passed
Bioburden	Ensures the product is not contaminated by the dilution process	Passed

B. Biocompatibility Testing

RADIESSE® for use in the décolleté is identical to the current, previously approved product; there are no proposed changes in design, formulation, manufacturing, or packaging. As such, the results of prior biocompatibility testing submitted and reviewed in previous P050052 supplements were leveraged for this device. However, in order to address the impact of the intended 1:2 dilution of RADIESSE® with saline by the user, a biological safety evaluation was carried out in accordance with ISO 10993-1 (Biological Evaluation of Medical Devices). This evaluation included the assessments presented in **Table 2**. All assessments passed, successfully demonstrating the biocompatibility of RADIESSE® when diluted 1:2 with sterile saline.

Table 2: Biocompatibility Assessments

Biological endpoint	Test method	ISO standard(s)	Test result
In Vitro Cytotoxicity	MTS assay, L-929 mouse fibroblast cells	ISO 10993-5	Not cytotoxic
Implantation – 14 Day	Rabbit model	ISO 10993-6	Performed as other currently marketed dermal fillers both histologically and macroscopically
Implantation – 2 Month	Rabbit model	ISO 10993-6	
Chemical Characterization and Toxicological Risk Assessment	Exhaustive extraction	ISO 10993-17 & ISO 10993-18	All identified extractables/leachables obtained showed a positive safety margin

C. Additional Studies

A human factors validation study was carried out to ensure the safety and effectiveness of diluted RADIESSE® for the intended users and uses in the intended use environments. As part of this study, users carried out a simulated use scenario which encompassed the dilution and mixing procedure as well as simulated injections of diluted product. Users were also required to complete knowledge tasks. The results of the study confirmed that the final, finished device and associated defined dilution and injection procedure met intended user needs.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (M930521003) to establish a reasonable assurance of safety and effectiveness for RADIESSE® diluted 1:2 with 0.9% sterile saline solution implanted subdermally for the correction of wrinkles in the décolleté in the US under IDE G210275. Data from this clinical study was the basis for the PMA approval decision.

A summary of the clinical study is presented below.

A. Study Design

Patients were treated between December 10, 2021 and January 12, 2023. The database for this Panel Track Supplement reflected data collected through November 15, 2023 and included 152 patients. There were 9 investigational sites.

The study was an 84-week, prospective, multicenter, randomized, evaluator-blind, parallel-group study to evaluate the safety and effectiveness of subdermal implantation of diluted RADIESSE® for the correction of moderate to severe décolleté wrinkles.

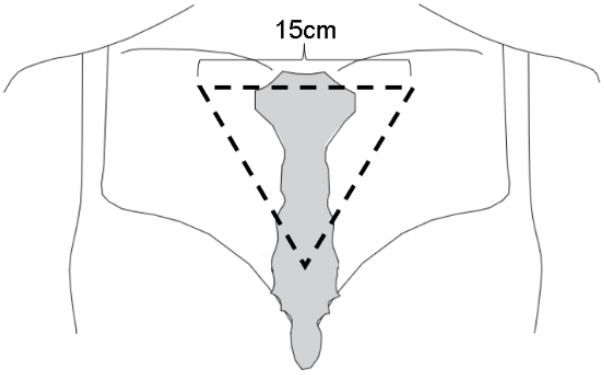
The control group was untreated control, followed by delayed treatment with diluted Radiesse®.

All eligible patients were randomized 3:1 to treatment with diluted RADIESSE® (n = 116) or to untreated control through the effectiveness assessment followed by delayed treatment with diluted RADIESSE® (n = 36). Patients randomized to treatment were scheduled to receive three treatments in total at Day 1, Week 6, and Week 12. Additionally, patients randomized to treatment had the option for retreatment at Week 36. Patients randomized to untreated control/delayed-treatment were scheduled to receive treatment at Week 24, Week 30, and Week 36 and did not have the option of a retreatment. Patients in the treatment group were followed for 84 weeks post initial treatment and patients in the untreated control/delayed treatment group were followed for 60 weeks post initial treatment. All patients exited the study at Week 84.

Treating investigators and subjects were not blinded to treatment. For the primary and secondary effectiveness assessments using the MAS Décolleté Wrinkles scales, blinded evaluators conducted the MAS Décolleté Wrinkles assessment. They were blinded to treatment assignment, they were not present during the study visits, and they did not have access to subject study records.

Each treatment consisted of subdermal implantation of RADIESSE® diluted 1:2 with 0.9% sterile saline (1.5 mL RADIESSE®:3.0 mL saline) in a defined treatment region shown in **Figure 1** below. This treatment region lies in the central area of the décolleté in an area of approximately 100 cm^2, delineated superiorly by the sternoclavicular notch, laterally by the midclavicular line and inferiorly by the superior point of the intermammary cleft. No injections were to be made in an area overlying or including breast tissue.

Figure 1: Treatment Area for Décolleté



Separately packaged from the dermal filler, the dilution and injection components used in this study consisted of one 22G x 50 mm, 2" flexible cannula with introducer needle (manufactured by TSK Laboratory), two 5 mL Luer lock syringes (BD), one Luer lock connector (Baxter Healthcare Corp.), one 18G x 1" blunt needle, and 0.9% sterile saline.

With regard to success/failure criteria, effectiveness of diluted RADIESSE® was demonstrated at Week 24 post initial injection if both of the following criteria were met: (1) the response rate in the treatment group was statistically significantly larger than 50% and (2) the responder rate for the treatment group was statistically significantly greater than that for the control /delayed-treatment group (which remained untreated at the primary endpoint evaluation). Both hypotheses for the primary endpoint need to be rejected at a one-sided significance level of 2.5%.

The lower limit of the 95% Wilson CI had to exceed the 50% response rate threshold to reject the first null hypothesis, and the lower limit of the 95% Newcombe CI had to be greater than zero to reject the second null hypothesis.

Sample size estimation assumed a 70% response rate in the treatment group, a 30% response rate in the control/delayed treatment group, a one-sided significance level α of 2.5%, and a target power of at least 90% for rejecting both hypotheses. Accounting for at most 20% missing data, approximately 152 subjects (114 subjects in the treatment group and 38 subjects in the control/delayed-treatment group) were to be randomized for this study.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the M930521003 study was limited to patients who met the following inclusion criteria:

   - Female ≥ 30 and ≤ 65 years old at the time of screening.
   - Subjects seeking improvement of décolleté wrinkles.
   - Décolleté wrinkles with a rating of moderate to severe (grade 2 to 3) on the Merz Aesthetic Scales (MAS) Décolleté Wrinkles – At Rest, as determined live by a blinded evaluator.

   Patients were not permitted to enroll in the M930521003 study if they met any of the following key exclusion criteria (Note: This is an abbreviated list of exclusion criteria; please see clinical labeling):

   - Any previous surgery, including plastic surgery or permanent surgical implant in the treatment area.
   - Previous treatment with collagen fillers, calcium hydroxylapatite, and/or long-lasting hyaluronic acid (HA) fillers in the décolleté within the previous 24 months, or with other HA fillers in the décolleté within the previous 12 months.

- Previous treatment with botulinum toxin, ablative or fractional laser, microdermabrasion, microneedling, chemical peels, and/or non-invasive skin tightening in the décolleté within the previous 6 months.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at the frequency shown in **Table 3** below. Patients in the treatment group were scheduled to be evaluated at the following timepoints: Screening, Day 1 (treatment), weeks 2, 4, 6 (treatment), weeks 8, 10, 12 (treatment), and weeks 14, 16, 24, 36 (optional retreatment), weeks 38, 40, 48, 60 and 84 post-operatively. Patients in the control / delayed treatment group were scheduled to be evaluated post-operatively at weeks 16, 24 (treatment; after completion of the primary effectiveness assessment), weeks 26, 28, 30 (treatment), 32, 34, 36 (treatment), and weeks 38, 40, 48, 60 and 84. A phone call follow up was done at 24 to 72 hours after each injection to evaluate safety. If a patient reported a safety concern during any phone call, an in-person visit was scheduled to address safety concerns.

Adverse events and complications were recorded at all visits. In addition, visual assessments (i.e., visual acuity, confrontation visual field test, and ocular motility examination) were conducted throughout the study. Pulse oximetry and neurological exams (FAST, Facial drooping, Arm weakness, Speech difficulties, and Time to call emergency services) were carried out at each treatment visit.

The key timepoints are shown below in **Table 3** summarizing safety and effectiveness.

Table 3: Schedule of Events

	Visit Timepoint	Safety Assessments	Effectiveness Assessments
Baseline and randomization	Up to 10 days prior to initial treatment	Visual assessments, AEs	MAS assessment
First treatment	**Initial treatment**	Visual assessments, CTR diary, AEs	N/A
	Up to 72h after treatment	CTR diary, AEs	N/A
	2 weeks after treatment	Visual assessments, CTR diary, AEs	N/A
	4 weeks after treatment	Visual assessments, CTR diary, AEs	N/A
Second treatment	**6 weeks post-initial treatment**	Visual assessments, CTR diary, AEs	N/A
	Up to 72h after treatment	CTR diary, AEs	N/A
	2 weeks after treatment	Visual assessments, CTR diary, AEs	N/A
	4 weeks after treatment	Visual assessments, CTR diary, AEs	N/A
Third treatment	**12 weeks post-initial treatment**	Visual assessments, CTR diary, AEs	N/A
	Up to 72h after treatment	CTR diary, AEs	N/A
	2 weeks after treatment	Visual assessments, CTR diary, AEs	N/A
	4 weeks after treatment	Visual assessments, CTR diary, AEs	MAS assessment
Primary Endpoint assessment[1]	**Week 24**	Visual assessments, AEs	MAS, iGAIS, sGAIS, and other effectiveness assessments
Optional retreatment[2]	**Week 36**	Visual assessments, CTR diary, AEs	MAS, iGAIS, sGAIS, and other effectiveness assessments
	Up to 72h after treatment	CTR diary, AEs	N/A
	2 weeks after treatment	Visual assessments, CTR diary, AEs	N/A
	4 weeks after treatment	Visual assessments, CTR diary, AEs	N/A
Follow ups	**Week 48**	Visual assessments, AEs	MAS, iGAIS, sGAIS, and other effectiveness assessments
	Week 60	Visual assessments, AEs	MAS, iGAIS, sGAIS, and other effectiveness assessments
	Week 84	Visual assessments, AEs	MAS, iGAIS, sGAIS, and other effectiveness assessments

[1] Subjects in the Control group did not receive any treatment until all primary endpoint assessments were completed. Delayed treatment was administered after this time point.

[2] Optional retreatment was only offered to subjects in the Treatment group.

3. Clinical Endpoints

With regards to safety, adverse events (AEs) were assessed at each visit by the investigator and patients reported common treatment responses (CTRs) in safety electronic diaries (eDiaries) for 28 days after each treatment. A secondary safety endpoint was established relating to the incidence of Treatment Emergent Adverse Events (TEAEs) related to treatment with diluted RADIESSE®, as reported by the treating investigator throughout the study.

With regards to effectiveness, the primary effectiveness endpoint was the proportion of responders at Week 24 on the Merz Aesthetic Scale (MAS) Décolleté Wrinkles - At Rest, as assessed live by a blinded evaluator, where response was defined as at least 1 point improvement from baseline. As for success/failure criteria, effectiveness of diluted RADIESSE® was demonstrated at Week 24 if the response rate in the treatment group was statistically significantly larger than 50% and if the responder rate for the treatment group was statistically significantly greater than that for the no-treatment control group.

Secondary effectiveness measures included:

- Proportion of responders at Week 24 on MAS Décolleté Wrinkles - Dynamic, as assessed live by a blinded evaluator, where response was defined as at least 1 point improvement from baseline.
- Proportion of subjects with any improvement, defined as a rating of + 1, + 2, or + 3 on Investigator Global Aesthetic Improvement Scale (iGAIS) at Week 24.
- Proportion of subjects with any improvement, defined as a rating of + 1, + 2, or + 3 on Subject GAIS (sGAIS) at Week 24.

4. Development and Validation of the Merz Aesthetic Scales (MAS) for Décolleté Wrinkles

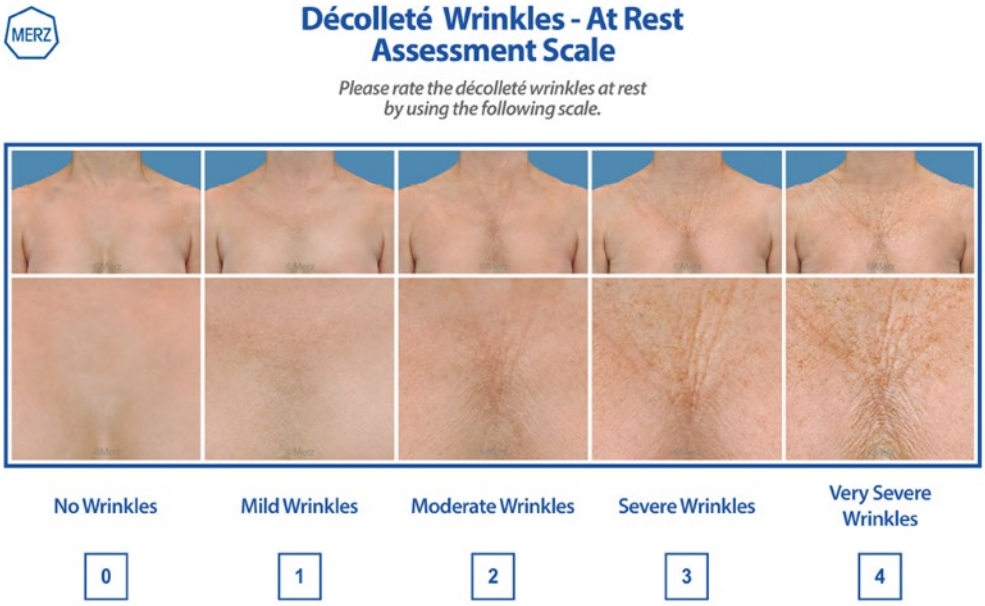
   The MAS for Décolleté Wrinkles consists of two photo numeric, 5-point (0-4) grading scales developed and validated for the assessment of décolleté wrinkles in women. As described in **Table 4** and shown in **Figure 2** and **Figure 3** below, the scales range from grade 0 (no wrinkles) to grade 4 (very severe wrinkles).

   1. Décolleté Wrinkles – At Rest: subjects with arms at rest alongside the body (**Figure 2**).
   2. Décolleté Wrinkles – Dynamic: subjects positioned with anteversion of the shoulders, each hand touching the opposite elbow with breasts leaning on the arms and the nipples positioned above the inframammary fold to diminish the effect of breast weight (**Figure 3**).

Table 4: Merz Aesthetic Scale (MAS) for Décolleté Wrinkles

Score	Grade
0	No wrinkles
1	Mild wrinkles
2	Moderate wrinkles
3	Severe wrinkles
4	Very severe wrinkles

Figure 2: MAS Décolleté Wrinkles – At Rest Scale and Photo Guide



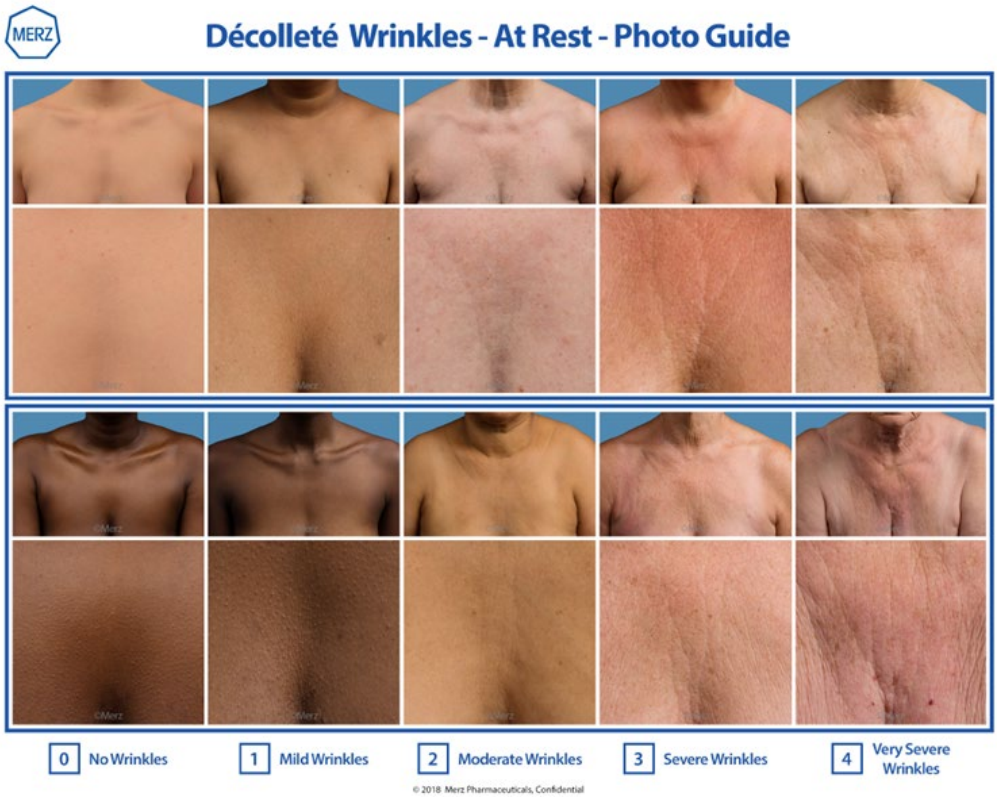
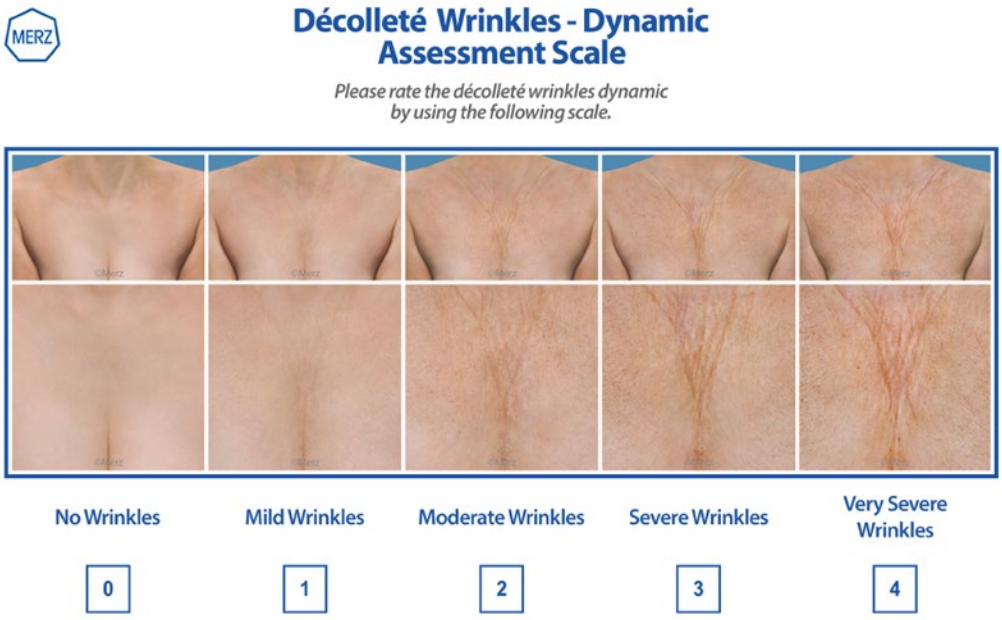
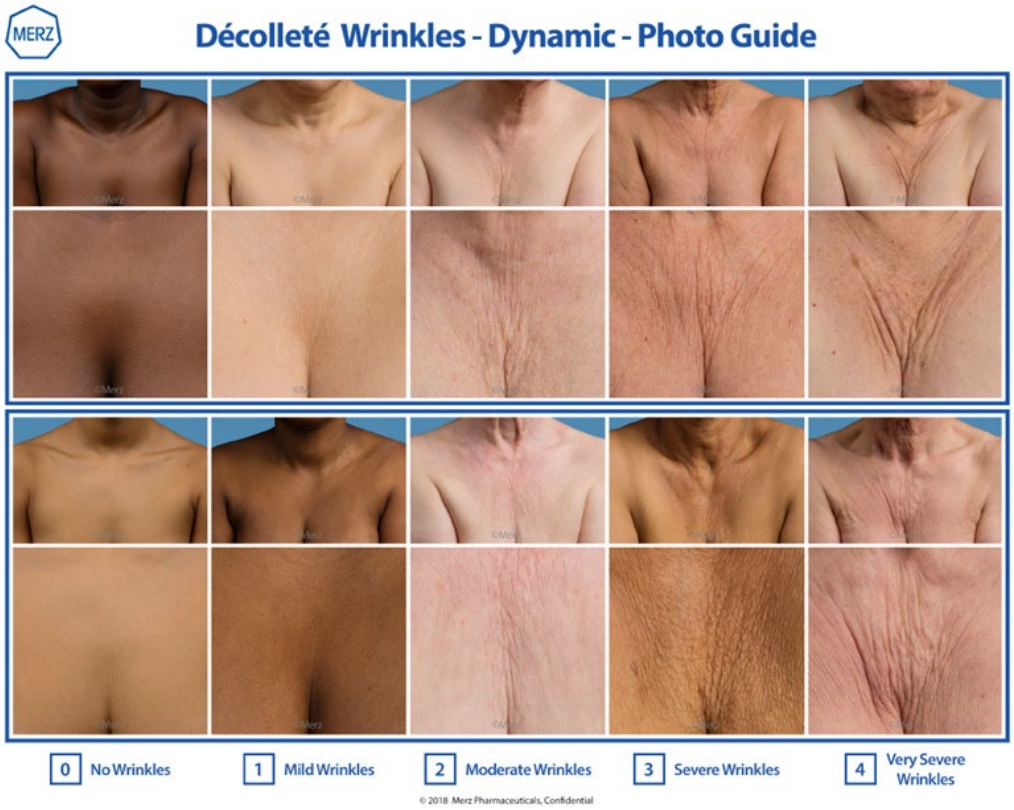


Figure 3: MAS Décolleté Wrinkles – Dynamic Scale and Photo Guide





The original validation of the MAS for décolleté wrinkles was published in 2016[1]. A subsequent live validation effort was undertaken to create photo guides for the MAS (shown above), re-confirm the reliability of the scales alongside the newly created photo guides to ease the assessment of a broader, more diverse population, and to evaluate their clinical meaningfulness.

The scale validation study conducted in two sessions demonstrated good reliability of the MAS décolleté at rest and dynamic when applied live by five trained physicians to a pool of 73 subjects with diverse severity grades and Fitzpatrick Skin Types. All raters surpassed the threshold of 0.7 in the weighted kappa coefficient and ICCs demonstrating good intra-rater and inter-rater reliability on both MAS décolleté scales with the newly developed photo guides. Additionally, experts rated pairs of images representing 1-point difference between subjects and pairs representing no difference. These findings provided strong evidence that 1-point differences across all severity grades of each of the MAS décolleté scales are clinically meaningful.

B. Accountability of PMA Cohort

At the time of database lock, 182 subjects were screened, 30 subjects did not meet the inclusion/exclusion criteria, and of 152 patients:

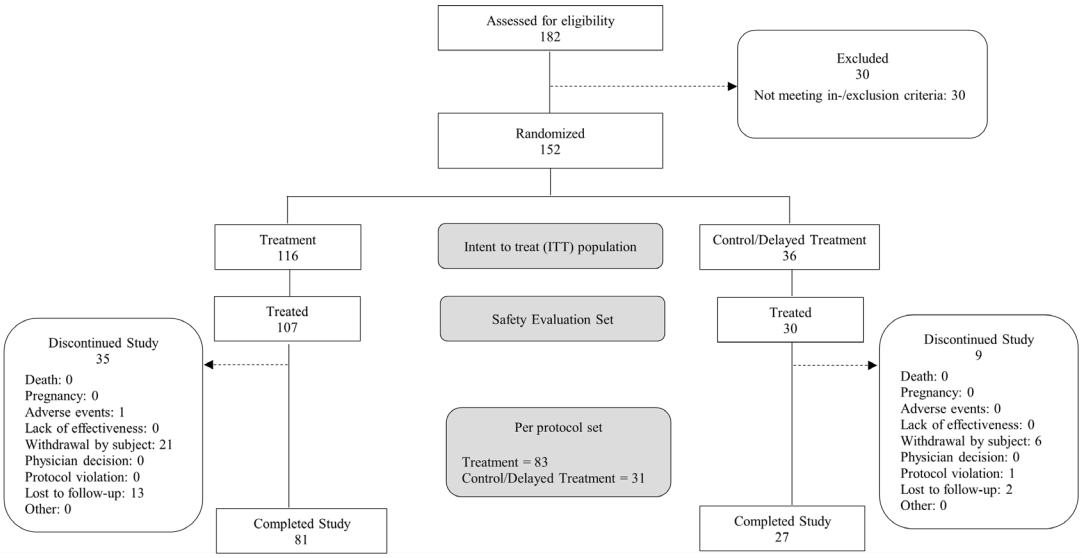
- 116 (76.3%) patients were assigned to the treatment group and 36 (23.6%) patients were assigned to the control/delayed treatment group.
- 126 patients completed the primary endpoint visit at Week 24, 95/116 patients (81.9%) in the treatment group, and 31/36 (86.1%) patients in the control/delayed-treatment group.

[1] Landau M, Geister TL, Leibou L, et al. Validated Assessment Scales for Décolleté Wrinkling and Pigmentation. Dermatol Surg. 2016;42(7):842-852.

- 108 (71.1%) patients are available for analysis at the completion of the study at week 84. 81/116 (69.8%) patients were in the treatment group and 27/36 (75.0%) patients in the control/delayed treatment group.
- 152 (100%) enrolled patients were included in the intent to treat (ITT) group. The safety evaluation set included 107/116 patients (92.2%) in the treatment group and 30/36 patients (83.3%) in the control group. The per protocol set consisted of 83/116 patients (71.6%) for the treatment group and 31/36 patients (86.1%) for the control group.

Figure 4 below summarizes the patient accountability in study M930521003.

Figure 4: Patient Accountability



NOTE: Reasons for discontinuation at any point after randomization and before completion of study are captured in the Discontinued boxes above. These include discontinuations that occurred both prior and after treatment was administered.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. The population studied in the pivotal study is representative of the adult patient population seeking nonsurgical aesthetic procedures.

An overview of the patient demographics for study are presented in **Table 5**.

Table 5: Study Demographics

	Treatment (N=116)	Control (N=36)	Total (N=152)
Sex (n (%))			
Female	116 (100.0)	36 (100.0)	152 (100.0)
Age [years]			
Mean (SD)	53.7 (7.05)	53.6 (8.08)	53.6 (7.28)
Median	54.0	56.0	54.0
Min, max	36, 65	32, 64	32, 65
Ethnicity (n (%))			
Hispanic or Latino	18 (15.5)	7 (19.4)	25 (16.4)
Not Hispanic or Latino	98 (84.5)	29 (80.6)	127 (83.6)
Race (n (%))			
White	105 (90.5)	35 (97.2)	140 (92.1)
Asian	3 (2.6)	0 (0.0)	3 (2.0)
Black or African American	5 (4.3)	1 (2.8)	6 (3.9)
American Indian or Alaska Native	1 (0.9)	0 (0.0)	1 (0.7)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
More than one race	2 (1.7)	0 (0.0)	2 (1.3)
Fitzpatrick skin type (n (%))			
I	7 (6.0)	0 (0.0)	7 (4.6)
II	30 (25.9)	8 (22.2)	38 (25.0)
III	48 (41.4)	23 (63.9)	71 (46.7)
IV	25 (21.6)	3 (8.3)	28 (18.4)
V	5 (4.3)	2 (5.6)	7 (4.6)
VI	1 (0.9)	0 (0.0)	1 (0.7)
Fitzpatrick skin type category (n (%))			
I - III	85 (73.3)	31 (86.1)	116 (76.3)
IV - VI	31 (26.7)	5 (13.9)	36 (23.7)
Baseline MAS Décolleté Wrinkles At rest severity (n (%))[1]			
Moderate = 2	81 (69.8)	24 (66.7)	105 (69.1)
Severe = 3	35 (30.2)	12 (33.3)	47 (30.9)

Max = maximum, Min = minimum, N = total number of patients in the corresponding treatment group, n = number of observations, SD = standard deviation
More than one response was allowed for race.
[1]As assessed for all patients at screening, as part of the study inclusion criteria.
Percentages based on total number of patients in intent to treat set; patients analyzed as randomized.

All patients in the study were female. Age ranged from 32 to 65 years with a mean of 53.6 years. The majority of the patients (92.1%, 140/152) self-identified as

White, 3.9% (6/152) as Black/African American, 2.0% (3/152) as Asian, and 0.7% (1/152) as American Indian or Alaska Native. As for ethnicity, 16.4% (25/152) of patients self-identified as Hispanic or Latino and 83.6% (127/152) of patients as Not Hispanic or Latino. Regarding Fitzpatrick Skin Type (FST) categories, 76.3% (116/152) patients had skin types I, II, or III, and 23.7% (36/152) had skin types IV, V, or VI.

At all treatment sessions, median retreatment injection volume was 4.5 mL (1.5 mL RADIESSE®:3.0 mL 0.9% sterile saline), which was the maximum injection volume allowed per the protocol.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety population cohort (who received treatment at least once in the study) of 137 patients available for the 21 month evaluation. The key safety outcomes for this study are presented below Tables 5 to 8.

Adverse effects that occurred in the PMA clinical study:

Adverse events (AEs) were reported by treating investigators and collected at all follow-up visits. A treatment-emergent AE (TEAE) was defined as an AE with onset date on or after the date of initial treatment. Two patients in the safety population experienced an adverse event prior to initial study treatment. Of the 137 treated patients, 11.7% (16/137) of patients had at least one TEAE that was deemed by the investigator to be related to the injection procedure or diluted RADIESSE®.

As outlined in **Table 6**, the most common treatment-related TEAEs consisted of administration site conditions including injection site bruising, injection site discoloration, injection site mass, and injection site pain.

Table 6: Patients with Treatment-Related TEAEs, >2% Incidence

	Total (N=137)	
MedDRA Preferred Term	**n**	**(%)**
Patients with at least one treatment-related TEAE	16	(11.7)
Injection site bruising	7	(5.1)
Injection site discoloration	4	(2.9)
Injection site mass	3	(2.2)
Injection site pain	3	(2.2)

The majority of treatment-related TEAEs were mild and lasted less than 52 days. None were severe, none were late onset (> 28 days after most recent injection), and all resolved without sequelae.

Table 7: Treatment-Related TEAEs by Worst Severity and Duration

	Total (n = 137)	
Patients with at least one treatment-related TEAE	**n**	**(%)**
Severity		
Mild	14	(10.2)
Moderate	2	(1.5)
Severe	0	(0)
Duration		
≤ 14 days	4	(2.9)
15 – 28 days	2	(1.5)
> 28 days	10	(7.3)

The highest incidence of treatment-related TEAEs was reported after initial treatment (7/137 patients, 5.1%), although rates remained similar over the subsequent administered treatments: 4/120 (3.3%) patients for 6 weeks post initial injection (PII), 6/119 (5.0%) patients for 12 weeks PII, and 3/68 (4.4%) patients for retreatment.

E-Diaries were used by patients to record specific signs and symptoms (Common Treatment Responses, or CTRs) experienced during each of the first 28 days after

each treatment. Patients were instructed to report the severity of each of the specified CTRs as mild, moderate, or severe. The percentages and numbers of patients reporting at least one CTR after each treatment were as follows: 80.0% (108/135) of patients after initial treatment, 69.7% (83/119) at six weeks PII, 67.2% (78/116) at 12 weeks PII, and 68.2% (45/66) after retreatment. After initial treatment (i.e., initial treatment at Day 1 or delayed treatment at Week 24), the majority of patients self-reported CTRs that were mild (57.8%; 78/135) to moderate (21.5%; 29/135) and had a maximum duration of 14 days or less (1-3 days: 25.2%, 34/135; 4-7 days: 24.4%, 33/135; and 8-14 days: 21.5%, 29/135). 8.9% (12/135) of patients experienced a CTR lasting between 15 and 28 days. Note that of the 137 patients who received treatment, 135 patients completed eDiaries.

The overall incidence, severity, and duration of CTRs were comparable in all four patient diaries (initial treatment, 6 weeks PII, 12 weeks PII, and retreatment). CTRs after initial treatment are summarized by severity in **Table 8** and by duration in **Table 9**.

Table 8: CTRs by Worst Severity After Initial Treatment

CTR	Severity M = 135		
	Mild n (%)	Moderate n (%)	Severe n (%)
Any CTR	78 (57.8)	29 (21.5)	1 (0.7)
Redness	67 (49.6)	15 (11.1)	0 (0.0)
Bruising	66 (48.9)	14 (10.4)	0 (0.0)
Pain/Discomfort (including burning/stinging)	52 (38.5)	11 (8.1)	0 (0.0)
Lumps/bumps	41 (30.4)	1 (0.7)	0 (0.0)
Swelling	36 (26.7)	6 (4.4)	0 (0.0)
Discoloration	36 (26.7)	3 (2.2)	0 (0.0)
Itching	30 (22.2)	3 (2.2)	1 (0.7)

M = number of patients with at least one entry in the eDiary. % is calculated based on M.

Table 9: CTRs by Maximum Duration After Initial Treatment

CTR	Duration M=135			
	1-3 days n (%)	4-7 days n (%)	8-14 days n (%)	15-28 days n (%)
Any CTR	34 (25.2)	33 (24.4)	29 (21.5)	12 (8.9)
Redness	46 (34.1)	26 (19.3)	9 (6.7)	1 (0.7)
Bruising	27 (20.0)	24 (17.8)	24 (17.8)	5 (3.7)
Pain/Discomfort (including burning/stinging)	43 (31.9)	13 (9.6)	5 (3.7)	2 (1.5)
Lumps/bumps	16 (11.9)	18 (13.3)	6 (4.4)	2 (1.5)
Swelling	19 (14.1)	15 (11.1)	6 (4.4)	2 (1.5)
Discoloration	17 (12.6)	11 (8.1)	7 (5.2)	4 (3.0)
Itching	26 (19.3)	3 (2.2)	3 (2.2)	2 (1.5)

M = number of patients with at least one entry in the eDiary. % is calculated based on M.

Additional safety assessments included a neurological exam (FAST: Facial drooping, Arm weakness, Speech difficulties, and Time to call emergency services), pulse oximetry, and visual assessments (i.e., visual acuity, confrontation visual field test, and ocular motility examination). No abnormal results were reported for the neurological exam, pulse oximetry, confrontation visual field tests, or ocular motility exam. For the visual acuity assessment, a total of nine patients in the study showed a ≥ 1-line change on the Snellen eye chart. These occurrences were all changes between Snellen values assessed at different visits and none of the changes manifested during a treatment visit immediately (within 60 minutes) post treatment. All of these events were determined to be unrelated to the investigational product or injection procedure and were not considered clinically significant by the treating investigators.

Breast Imaging Safety Evaluation

Following the conclusion of this pivotal trial, Merz conducted a retrospective addendum study on the same population to demonstrate the safety of treatment with diluted RADIESSE® in the décolleté and its lack of interference in mammograms and/or breast ultrasound images collected after treatment. The

defined treatment area for diluted RADIESSE® injection in the décolleté does not overlay breast tissue (see **Figure 1**); this retrospective study was initiated as a precautionary measure to provide further assurance of device safety.

Participants who received treatment in the décolleté while in the pivotal study and completed the study were invited to participate in this retrospective study. Participants were contacted approximately 17-22 months after completing their participation in the pivotal study. A total of 81 participants provided informed consent for obtaining their medical records pertaining to mammograms and/or breast ultrasound images or reports taken before and after receiving treatment with diluted RADIESSE® in the décolleté. Of those who consented, a total of 71 participants provided at least one post-treatment mammography and/or breast ultrasound image and 4 participants provided at least one post-treatment mammography and/or breast ultrasound report (as the corresponding breast images could not be obtained). Available post-treatment images were taken as early as 3 days after first treatment with diluted RADIESSE® and up to 960 days after receiving optional retreatment.

All breast images and reports were evaluated by an Adjudication Committee, composed of two board-certified radiologists with a subspeciality in breast and body imaging and with at least five years of postgraduate training. The Adjudication Committee evaluated the breast images for any potential image interference after treatment of the décolleté with diluted RADIESSE®. When asked if the product is visible on the assessed images, evaluators answered "No" for 100.0% of the breast images and reports (69/69 participants, images from 2 participants are not accessible). Additionally, for 4 participants, the Adjudication Committee evaluated mammography and/or breast ultrasound report. When asked if foreign material was reported as present in these reports, evaluators answered "No" for 100.0% of the reports (4/4 participants). None of the 81 participants who enrolled in this retrospective study reported any new treatment related TEAEs.

In summary, no product was observed the assessed participants' post treatment mammograms or breast ultrasounds and no foreign material was reported as

present in the evaluated breast imaging reports. There were no instances of interference of diluted RADIESSE® on mammogram or breast ultrasound images collected after treatment with diluted RADIESSE® in the décolleté.

2. Effectiveness Results

The analysis of effectiveness was based on the 152 evaluable patients at the 24-week time point. Multiple imputation was used to impute missing data for the primary effectiveness endpoint. Average responder rate over all imputations was computed.

Primary Effectiveness Results

Diluted RADIESSE® provided a clinically and statistically significant improvement in the correction of décolleté wrinkles compared to the no treatment control group using the MAS – At Rest. As shown in **Table 10**, the treatment response rate at Week 24 for the treatment group was 71.2% [95% Confidence Interval (CI): 61.4%, 79.4%], exceeding the targeted margin of 50%, while the response rate in the control/delayed-treatment group was 6.3% [95% CI: 1.5%, 22.9%]. The difference between the response rates was statistically significant, showing superiority over the no treatment control.

Table 10: Responder Rates on MAS – At Rest at Week 24

Responder Rates		Difference in responder rates	95% CI
Treatment	Control		
71.2%	6.3%	65.0%	[45.6%, 74.4%]

After the Week 24 primary endpoint evaluation, the responder rate on the MAS – At Rest scale remained above 60% at 60 weeks post initial injection (PII), as shown in **Table 11**.

Table 11: Treatment Group MAS Décolleté Wrinkles – At Rest Responder Rates on Observed Cases

	Treatment n/N (%)
24 weeks PII*	69/95 (72.6)
36 weeks PII	60/91 (65.9)
48 weeks PII	63/86 (73.3)
60 weeks PII	54/89 (60.7)
N = number of subjects with observed data PII = Post Initial Injection *Primary endpoint (24 weeks PII)	

Secondary Effectiveness Results

Analysis of the MAS Décolleté Wrinkles – Dynamic responder rate and the GAIS scores further supported the primary endpoint finding that treatment with diluted RADIESSE® resulted in overall aesthetic improvement of the décolleté at Week 24.

The estimated average MAS Décolleté Wrinkles-Dynamic responder rate at Week 24 was 65.8% [95% CI: 55.9%, 74.5%] among the treatment group (n=116). In the control group (n=36), the estimated average responder rate was 16.0% [95% CI: 6.8%, 33.1%].

In the ITT population, 92.6% (88/95; observed cases) of patients in the treatment group showed some level of improvement according to the iGAIS score at Week 24. This level of improvement in iGAIS score was largely sustained at further timepoints, with 85.3% of patients showing any improvement at 60 weeks Post PII and 80.2% of treatment group patients showing any improvement at 84 weeks PII.

Similarly, the majority of patients (83/95, 87.4%; observed cases) in the treatment group self-reported some level of improvement on the sGAIS at Week 24. A total of 78.4% of patients reported any improvements at 60 weeks PII and 84.0% of treatment group patients reported any improvements at 84 weeks PII.

Other Effectiveness Results – Patient Perspective

Other effectiveness measures included patient perspectives through a subject satisfaction questionnaire as well as a likelihood of retreatment survey administered to treated patients in the study.

Among the treatment group at Week 24, the majority of patients self-reported satisfaction with their appearance (79/116 patients, 84.0%), the appearance of tightened skin (76/116 patients, 85.4%), appearance of fine lines and wrinkles (72/116 patients, 80.9%), and smoothness of skin (77/116 patients, 86.5%) compared to before treatment. Each of these measures remained above 73% through the end of the study (84 weeks post initial injection).

The likelihood of retreatment survey was administered to the patients in the treatment group at Week 60. The majority of patients (73/88 patients, 83.0%) were willing to receive future diluted RADIESSE® décolleté treatment. 85.2% (75/88 patients) were likely to recommend treatment and 93.2% (82/88 patients) were willing to receive other RADIESSE® treatments.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: (FST categories (I – III versus IV – VI), race, site, ethnicity, or age group (≤54 years versus > 54 years).

The study was not specifically powered for FST, race, site, ethnicity, or age subgroups.

Comparable results were observed when stratifying MAS Décolleté Wrinkles – At Rest responder rates at Week 24 by baseline severity, median age, age group, investigational site, ethnicity, and race with responder rates favoring treatment with diluted RADIESSE® when compared to no treatment. With respect to Fitzpatrick Skin Type (FST), 48/68 (70.6%, [58.9%, 80.1%]) subjects with FST I – III and 21/27 (77.8%, [59.2%, 89.4%]) subjects with FST IV – VI were responders on the

MAS Décolleté Wrinkles – At Rest. The difference in response rates [95% CI] between treatment and control groups was 66.9% [48.2%, 76.9%] for subjects with FST I – III and 77.8% [25.4%, 89.4%] for subjects with FST IV – VI, with lower bounds of CIs greater than zero in both skin type categories.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. 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 10 Investigators of which none were full-time or part-time employees of the sponsor, and 3 had disclosable financial interests/arrangements 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: Three
- 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.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to an FDA advisory committee for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Patients treated with RADIESSE® injectable implant diluted with sterile saline showed clinically and statistically significant improvements in the appearance of décolleté wrinkles as assessed by blinded evaluators using the MAS. Diluted RADIESSE® met the pre-specified primary endpoint (responder rate for MAS Décolleté – At Rest of 71.2%) at Week 24 while the treatment response rate in the control/delayed-treatment group was 6.3%. This objective primary endpoint measure was further supported by multiple patient and investigator reported endpoints demonstrating aesthetic improvements post treatment. Both the treating investigator and the patients confirmed global aesthetic improvements in the décolleté area. Patients also reported satisfaction in their appearance after treatment and the majority shared willingness to receive future treatment.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the clinical study conducted to support PMA approval as described above. The data submitted provide a reasonable assurance that the device, when diluted in a 1:2 ratio with sterile saline, is safe for subdermal injection for the correction of wrinkles in the décolleté. The specific conclusions are:

- For initial and repeat treatments, most CTRs were mild to moderate in severity, resolved within 2 weeks, and were as expected for soft tissue filler

treatments. CTRs included redness, bruising, pain/discomfort (including burning/stinging), lumps/bumps, swelling, discoloration, and itching.

- Treatment-emergent adverse events (TEAEs) related to treatment incidence rate were 11.7% (16/137 patients). All were mild to moderate in intensity, none were late onset, and most had a duration of < 52 days. All treatment-related TEAEs resolved without sequalae.
- The most common treatment-related TEAEs were injection site bruising (7 patients, 5.1%), injection site discoloration (4 patients, 2.9%), injection site mass (3 patients, 2.2%), and injection site pain (3 patients, 2.2%).
- There were no clinically significant abnormal results from additional safety assessments conducted at each treatment visit, which included a neurological exam, pulse oximetry, and visual assessments (i.e., visual acuity, confrontation visual field test, and ocular motility examination).
- The study demonstrated an acceptable safety profile, with no treatment-related serious adverse events (SAEs) and no unexpected or atypical events with use of diluted RADIESSE® being reported.
- In the retrospective analysis of mammography, breast ultrasounds, and breast imaging reports for 71 patients injected with diluted RADIESSE® in the décolleté in the pivotal study, there was no evidence of diluted RADIESSE® visualized in the images or reports in the breast area. There were no instances of interference of diluted RADIESSE® on mammogram or breast ultrasound images collected after treatment with diluted RADIESSE® in décolleté.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the clinical study conducted to support PMA approval as described above. This was a prospective, randomized, evaluator-blind, parallel-group study, using two validated scales ensuring data robustness. In the diluted RADIESSE® treatment group, 71.2% of patients were responders on the MAS Décolleté Wrinkles – At Rest at Week 24.

Treatment with diluted RADIESSE® was significantly superior over no treatment control, for which 6.3% of patients were responders at Week 24. The findings of the primary effectiveness assessment were supported by the secondary endpoints. The estimated average MAS Décolleté Wrinkles-Dynamic responder rate at Week 24 was 65.8% [95% CI: 55.9%, 74.5%]. The GAIS investigator and subject assessments at Week 24 showed improvements in 92.6% and 87.4% of patients, respectively.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Common treatment responses (CTRs) reported by patients included redness, bruising, pain/discomfort (including burning/stinging), lumps/bumps, swelling, discoloration, and itching. Participants rated CTRs as predominantly mild to moderate in severity with a majority resolving within 2 weeks. There were no treatment-related serious TEAEs, treatment-related TEAEs of special interest, or unanticipated TEAEs. Most treatment-related TEAEs were mild in nature and all resolved without sequalae. When evaluated retrospectively, there were no instances of RADIESSE® interference on mammogram or breast ultrasound images collected after décolleté treatment.

Patient Perspective

Patient perspectives considered during the review included patient reported outcome tools and questionnaires:

- Subject GAIS
- Subject satisfaction questionnaire
- Likelihood of retreatment survey
- Use of patient eDiaries (completed by participants for 28 days after each treatment) to collect information about predefined, injection related events at the treated area.

As discussed, these patient perspectives supported a high level of satisfaction with treatment.

In conclusion, given the available information above, the data support that for the correction of décolleté wrinkles, 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 March 31, 2026.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

Conditions of Approval

A. Device-Specific Use Training Program

This approval is being granted on the condition that:

1. The device manufacturer must develop, maintain, and update as necessary, a device-specific use training program that ensures proper training in decollete anatomy and vasculature, safe injection techniques, and identification and management of potential adverse events, including intravascular complications.

2. The device-specific use training program is submitted, as a supplement, within 30 days from the date of this letter and approved by FDA prior to implementation.

3. The device-specific use training program is implemented within 6 months from the date of this letter. A report must be submitted to FDA within 30 days of

implementation to notify FDA of this milestone.

4. The device manufacturer may only distribute the device to providers that implement the device-specific use training program and ensure that providers have completed the device-specific training program.

5. The device manufacturer must submit a report to the FDA annually on the anniversary of initial marketing authorization for the device, until such time as FDA may terminate such reporting, including an assessment of the success of the device-specific training based on quantitative metrics, the number of providers who have completed the training, and any changes to the training program since the last report.

6. The device manufacturer should develop a method by which the public could verify that a provider has successfully completed the aforementioned required training program.

7. Please include in the labeling:

   a. A description of the training program and a recommendation that device usage be reserved for qualified providers with expertise in dermal filler injection.

   b. A statement regarding how the device is only for distribution to providers that have taken and successfully completed device-specific use training program.

B. Post-Approval Study

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below.

1. The Safety Study to Assess Radiographic Imaging is an open-label, multicenter, single-arm, uncontrolled safety study to assess radiographic imaging following treatment with RADIESSE® dilute in the décolleté in adult females in the United States.

a. **Study purpose/objectives:** To determine if treatment with Radiesse dilute in the décolleté interferes with radiographic imaging of the breast tissue and to assess

the safety of Radiesse dilute in the décolleté.

b. **Study design:** Participants will receive three treatments spaced six weeks apart (Week 1, Week 7, and Week 13), with each consisting of injection of 1.5mL Radiesse diluted 1:2 with sterile saline into the décolleté Imaging will be performed at baseline and 1 month after the third administration
c. **Total number of subjects**: 30 female participants between the ages of 40 and 65
d. **Length of follow-up and frequency of assessments:** Total participation 60 weeks; radiographic imaging of the breast (ultrasound and mammography) will be conducted at baseline and approximately 1 month following the third injection. Safety data (including adverse events and serious adverse events) will be collected through Week 60.
e. **Endpoint(s):** Any interference of Radiesse dilute in either breast observed in breast ultrasound or mammogram images at Week 17, as assessed by an adjudication committee composed of board-certified radiologists. Occurrence of adverse events (AEs) related to treatment with Radiesse dilute, as reported by the treating investigator throughout the study.
f. **Data analysis plan for the primary endpoints:** Radiographic images will be reviewed for interference and confirmed by the adjudication committee through the Radiology Adjudication Committee Questionnaire; AE will be monitored through the study duration.
g. **Reference to protocol:** G210275/S004 approved on May 9, 2025

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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.