SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RADIESSE® (+) Lidocaine 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/S129

Date of FDA Notice of Approval: September 01, 2021

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. The SSED to support the indication is available on the CDRH website and is incorporated by reference here.

The PMA P050052/S052 for RADIESSE® (+) Lidocaine injectable implant (hereinafter referred to as RADIESSE® (+)) was approved on January 30, 2015 and is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.
The current supplement was submitted to expand the indication for the device.

II. INDICATIONS FOR USE

RADIESSE® (+) Lidocaine injectable implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

RADIESSE® (+) Lidocaine injectable implant is indicated for deep injection (subdermal and/or supraperiosteal) for soft tissue augmentation to improve moderate to severe loss of jawline contour in adults over the age of 21.

III. CONTRAINDICATIONS

- RADIESSE® (+) is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- RADIESSE® (+) is not to be used in patients with known hypersensitivity to any of the components.
- RADIESSE® (+) is not intended to be used in patients with known hypersensitivity to lidocaine or anesthetics of the amide type.
- RADIESSE® (+) is contraindicated for patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the RADIESSE® (+) labeling.

V. DEVICE DESCRIPTION

RADIESSE® (+) Lidocaine injectable implant 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, 0.3% lidocaine hydrochloride and sterile water for injection. RADIESSE® (+) (1.5cc) has a calcium hydroxylapatite particle size range of 25–45 microns and a 25-gauge Outer Diameter (O.D.) to 27 gauge Inner Diameter (I.D.) needle.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to improve moderate to severe loss of jawline contour include invasive surgery (i.e., facelift). Less invasive alternatives include radiofrequency/ ultrasound skin tightening or the use of other dermal fillers. 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 2015. RADIESSE® (+) is currently marketed worldwide including Europe, Canada and South America, and Asia. Subsequently, the product has been registered in over 57 countries. Since initial approval in the United States in 2006, over 10 million units of the Radiesse family of products has been sold worldwide. The product has never been withdrawn from marketing for any reasons 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. The distribution quantities for RADIESSE® (+) was 316, 919 in 2019 alone.

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 device.

Common treatment responses or adverse events associated with the use of RADIESSE® (+) in the jawline as reported by > 5% of patients in the clinical study include rash, swelling, firmness, lumps/bumps, bruising, redness, discoloration (not redness or bruising), itching, stinging/burning, movement or shifting of product, difficulty drinking, difficulty chewing, difficulty speaking, discomfort/pain with palpation, and discomfort/pain without palpation. RADIESSE® (+) has been marketed in the US since 2016.

There were no serious adverse events (SAEs) related to treatment that required medical intervention to prevent significant or permanent injury. Only one (1) subject had severe edema and bruising that resolved after 16 days without the requirement for additional medical treatment.
Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.

Post-marketing surveillance
The cumulative postmarketing safety database, which includes spontaneous reports from global sources, as well as case reports from the published and unpublished literature, was reviewed. A targeted review of the post-marketing reports for RADIESSE® (+) demonstrated that there were no additional adverse events with a frequency >5 for uses reported as either "jaw" or "jawline".
In addition, the following adverse events have been identified during post-approval use of RADIESSE® (with or without Lidocaine). Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to RADIESSE® injectable implant. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to RADIESSE® injectable implant: 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: antibiotics, anti-inflammatories, corticosteroids, anti-histamines, analgesics, massage, warm compress, excision, drainage, and surgery.

For the specific adverse effects that occurred in the clinical study, please see SECTION X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for the improvement of moderate to severe loss of jawline contour in adults over the age of 21. There was no change in product manufacturing or specifications used in the study. Even though cannula was used in this study, the cannula is not included in the packaging.

A. Laboratory studies

Validation testing has been completed on the device components (calcium hydroxylapatite, sterile water for irrigation, glycerin, buffer salts, and sodium carboxymethylcellulose) and the packaging for RADIESSE® (+). The in-process testing, as well as the final packaged and sterilized RADIESSE® (+) product, was validated.

The following bench tests were conducted to evaluate the performance characteristics of final, packaged and sterilized RADIESSE® (+). Results can be found in Table 1a below:

Table 1a: Summary of Key Bench Testing on RADIESSE® (+)

Test	Purpose	Results
Media Extrusion force (N)	Ensures extrusion force meets specification (<15 pounds of force, lbsf)	Passed
Rheology (tan δ)	Ensures rheological properties meet specification and integrity of gel carrier	Passed
Shelf-life testing	Ensures real-time and accelerated testing on RADIESSE® (+) syringes support a shelf life claim of 25 months	Passed
Pouch Peel Testing	Ensure the heat-sealing of the foil pouches produce consistent seal strength of 5 pounds of force.	Passed
Endotoxin (EU/mL)	Ensures endotoxin meets specification	Passed
Sterility	Ensures device is sterile, SAL of 10^{-6}	Passed
Syringe Leakage	Ensures safety testing demonstrates that the syringe, injection needle or the syringe Luer cap would not rupture with the maximum hand pressure of 30 pounds force (133 Newtons) applied to the syringe push rod	Passed
Particle Inspection/Durability	Ensures the particles of calcium hydroxylapatite (CaHA) remained unchanged after processing	Passed
Human Factors Testing	Ensures that RADIESSE® (+) can be administered into the jawline by its intended users without serious use errors.	Passed

B. Biocompatibility Testing

RADIESSE® (+) is categorized as implant devices in contact with tissue where the contact duration is more than 30 days and was subjected to *in-vitro* and *in-vivo* testing based on ISO 10993-1 (Biological Evaluation of Medical Devices), using historically accepted test methods of biomedical materials or United States Pharmacopoeia references in accordance with GLP regulations. Test results indicate RADIESSE® (+) is nontoxic and hemocompatible with no mutagenic response.

In-vivo tests assessed sensitization, irritation, tissue reaction during short-term implantation, systemic reactions, and long-term biocompatibility as seen in Table 1b and Table 1c below. It was concluded that based on these tests RADIESSE® (+) was non-sensitizing, non-irritant, and non-toxic with no concerns for long-term biocompatibility. The biocompatibility study with RADIESSE® (+) was from P050052/S052 (180-Day supplement), but the biocompatibility study with RADIESSE was from the original PMA, P050052.

Table 1b- Biocompatibility Tests Performed - Filler:

Biological endpoint/test method		Test standard/guideline	Test product	Test result
Cytotoxicity		ISO 10993-5	Radiesse(+)	Not cytotoxic
Sensitization		ISO 10993-10	Radiesse(+)	Not sensitizing
Intradermal reactivity		ISO 10993-10	Radiesse(+)	No irritation
Hemocompatibility		ISO 10993-4	Radiesse(+)	Non-hemolytic
Implantation – Up to 169 weeks intradermal in rabbits		ISO 10993-6	Radiesse(+)	Performed as other currently marketed dermal fillers both histologically and macroscopically
Systemic toxicity	**Acute systemic toxicity**	ISO 10993-11 USP <88>	Radiesse	No systemic toxicity
	Sub-chronic systemic toxicity, 13 weeks	ISO 10993-11	Radiesse	No systemic toxicity
	Material-mediated pyrogenicity study	ISO 10993-1 EP-2016 USP 41-NF 36	Radiesse(+)	No pyrogenic reaction
Genotoxicity	**Ames test**	ISO 10993-3 OECD 471	Radiesse(+)	No mutagenic response

	Mouse lymphoma	ISO 10993-3 OECD 476	Radiesse(+)	No mutagenic response or chromosomal aberration

Table 1c - Biocompatibility Tests Performed – Cannula/Needle

Biological endpoint/test method	Test standard/guideline	Test product	Test result
Cytotoxicity	ISO 10993-5	Cannula/Needle	Not cytotoxic
Sensitization	ISO 10993-10	Cannula/Needle	Not sensitizing
Intradermal reactivity	ISO 10993-10	Cannula/Needle	No irritation
Hemocompatibility	ISO 10993-4	Cannula/Needle	Non-hemolytic
Acute systemic toxicity	ISO 10993-11 USP <88>	Cannula/Needle	No systemic toxicity
Pyrogenicity study	ISO 10993-11 USP<181>	Cannula/Needle	No pyrogenic reaction

Additional animal studies evaluating RADIESSE® injectable implant in dermal soft tissue augmentation was conducted that included the product being injected into the dermis and subdermis in various animal models. These studies are contained within approved RADIESSE® injectable implant PMA P050052. These studies provided acute and chronic results that demonstrated RADIESSE® injectable implant was safe and remained durable without any evidence of CaHA particle migration.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study (M900391004) to establish a reasonable assurance of safety and effectiveness for RADIESSE® (+) for deep injection (subdermal and/or supraperiosteal) for soft tissue augmentation to improve moderate to severe loss of jawline contour in adults over the age of 21 in the US under IDE G180021. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

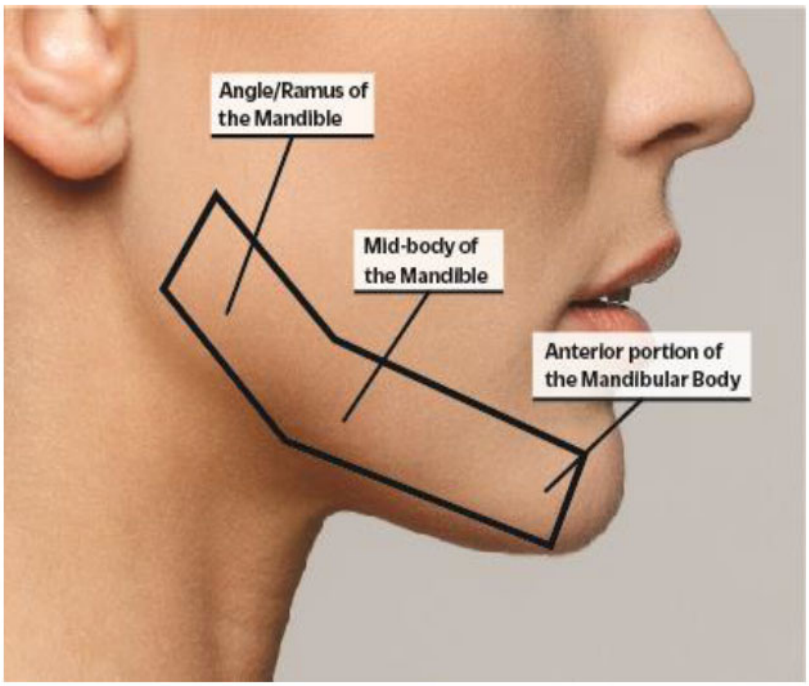
A. Study Design

Patients were treated between August 06, 2018 and January 22, 2020. The database for this Panel Track Supplement reflected data collected through March 27, 2020 and included 180 patients. There were 15 US investigational sites.

A 60-week, prospective, multicenter, randomized, controlled study was conducted at investigational sites on participants who were randomized to receive treatment (n=123) or control (delayed treatment) (n=57) with RADIESSE® (+) in both jawlines (see Figure 1). The control group consisted of patients without any treatment until the primary endpoint assessment at 12 weeks. All patients were randomized to receive treatment with either a needle (n=88) or cannula (n=87). The needle used in the study was 27 gauge ¾" Terumo injection needle approved under P050052/S078.

Separately packaged from the dermal filler, the cannula set used in the study was Sterimedix Silkann Cannula and Needle Set comprised of 27 G x 40mm (1.6''), ultrathin wall, straight cannula with luer lock fitting, and a 25 G, 12.7mm (0.5") pre-hole puncture needle, which are packaged together in a blister. The pre-hole needle is supplied to facilitate placement of the cannula. The Sterimedix Silkann Cannula and Needle Set are manufactured by Sterimedix Ltd, Worcestershire, UK (FDA Establishment Registration Number 1000614268).
Touch-up treatments were permitted 4 weeks after initial injection, if needed. After the primary endpoint assessment at 12 weeks, the control group was eligible to receive treatment and 53 control patients received treatment. All patients were followed for 48 weeks post initial treatment, at which time only the treatment group was eligible for retreatment. There was no touch up in the retreatment group. The retreated patients were followed for an additional 12 weeks with follow up examinations at 48 hours after retreatment, week 50, and week 60. All patients exited the study at week 60.

Figure 1: Treatment Area for Jawline



1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the M900391004 study was limited to patients who met the following inclusion criteria:

   - Had right and left jawline ratings of 2 or 3 (moderate or severe) on the Merz Jawline Assessment Scale (MJAS), as determined independently by the blinded evaluator and the treating investigator.

- Had the same MJAS rating on both jawlines (i.e., jawlines are symmetrical).
- Was ≥ 22 and ≤ 65 years of age.
- Had adequate understanding (reading, speaking and writing) of the local/regional language.

Patients were not permitted to enroll in the M900391004 study if they met any of the following exclusion criteria:

- Skin or fat atrophy, other than age related, in the midfacial and/or jawline region or had been diagnosed with a connective tissue disorder.
- Skin laxity and/or sun damage beyond typical for the subject's age.
- Prior surgery on the jaw or in the jawline area (including temporomandibular joint replacement or anatomical surgical modification) or had a permanent implant or graft in the lower face and/or jawline area that could interfere with effectiveness assessments.
- Ever been treated with fat injections or permanent fillers (e.g., silicone, polymethylmethacrylate (PMMA)) in the lower face and/or jawline area or planned to receive such treatments during participation in the study.
- Been treated with semi-permanent dermal fillers (e.g., poly L-lactic acid) in the lower face and/or jawline area in the past 5 years or planned to receive such treatments during participation in the study.
- Received lower face and/or jawline area treatments with porcine-based collagen fillers or with Belotero® Volume, JUVÉDERM VOLUMA®, Restylane® Lyft, RADIESSE®, or mesotherapy within the prior 24 months and/or with other hyaluronic acid (HA) products within the prior 12 months or planned to receive such treatments during participation in the study.
- Undergone oral surgery (e.g., orthodontia, extraction, implants) in the prior 30 days or planned to undergo oral surgery during participation in the study.
- Patients with any malocclusion(s) that were unstable and/or not reproducible or active/history of lockjaw.
- Patients with body mass index (BMI) of < 18.5 or ≥ 30.
- Patients who gained or lost significant weight over the prior 6 months (i.e., ≥ 2-unit change in BMI); or patients who planned to gain or lose significant weight during study participation (i.e., ≥ 2-unit change in BMI).
- Patients with jawline contour that was masked and/or difficult to differentiate from the neck due to submental fat pad(s), significant neck lipodystrophy, and/or neck skin redundancy.

2. Follow up Schedule
   All patients were scheduled to return for follow-up examinations at 2, 4, 6, 12, 24, 36 and 48 weeks after initial treatment.

All eligible patients were randomized (2:1 allocation ratio) to either treatment with RADIESSE® (+) in both jawlines or to control/delayed treatment (i.e., no treatment controls until primary endpoint assessment at Week 12, when the controls were eligible for treatment).
Patients randomized to the treatment group received an initial RADIESSE® (+) injection in both the right and left jawline and were assessed at Week 4 for a touch-up in one or both jawlines. These patients returned at Week 12 for their primary effectiveness assessment. Patients in the treatment group were eligible to receive re-treatment with RADIESSE® (+) at Week 48. Patients in the treatment group were additionally scheduled to return for follow-up at 50 weeks (if they received an optional retreatment) and 60 weeks after initial treatment.
Patients randomized to the control group remained untreated until completion of the primary endpoint assessment at Week 12; subsequently, they were treated with RADIESSE® (+) and assessed 4-weeks later for a touch-up. In case of touch-up, a visit at Week 18 was performed. Patients were scheduled to return for follow-up examinations at 24, 36, 48 and 60 weeks. These patients were not offered re-treatment. All patients were followed until the end of the study to assess long-term effectiveness and safety. Adverse events and complications were recorded at all visits. The key timepoints are shown below in the tables summarizing safety and effectiveness.

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 diaries for 28 days after each treatment.

With regards to effectiveness, the primary effectiveness endpoint was the comparison of the responder rate between the treatment group and the untreated control group at Week 12, according to the Merz Jawline Assessment Scale (MJAS), as assessed by a blinded evaluator. The validated 5-point MJAS (described in Table 2 and shown in Figure 2) ranges from grade 0 (none) to grade 4 (extreme).

Development and Validation of the Merz Jawline Assessment Scale (MJAS)

Photographs used for the creation of the MJAS© (2018 Merz North America, Inc) were obtained from subjects with a full range of jawline appearances after receiving signed photo authorization releases. Subjects were all screened by an experienced team and two subjects were selected (1 male, 1 female), whose images were morphed to represent all five grades of the MJAS scale. Scale descriptors were created for each of the five numerical grades of the scale (Table 2). After the morphed scale was created, additional photographs were selected for inclusion representing each grade of the scale, both genders, a range of ages, and a range of Fitzpatrick Skin Types. Photographs were then cropped to show the jaw aesthetic area for the lower face. The final scale

includes scale descriptors for each grade, the morphed images, and the real subject images (Figure 2).

The inter-rater and intra-rater reliability of the MJAS scale was evaluated in a live-subject rating validation study. A total of 91 subjects (mean (standard deviation) age: 38.3 (14.8) years) were recruited to ensure all MJAS grades and Fitzpatrick Skin Types were represented (I-II: n=35; III: n=28; IV: n=15; V-VI: n=13), as well as an adequate representation of males (n=33) and females (n=58). Seven (7) board-certified dermatologists or plastic surgeons familiar with jawline contour and scale development were recruited to perform live assessments. Two (2) sessions were held, separated by a 3-week interval. All 91 subjects presented one by one in person to each rater in the order of the prepared randomization sequence (Session 1). The same live subjects were assessed at the second session 3 weeks later, but in a different random sequence (Session 2).

Intra-rater reliability between Session 1 and Session 2 was evaluated for each rater by means of simple and weighted kappa statistics and intra-class correlation coefficients (ICC), including 2-sided 95% confidence intervals. The same calculations were used for evaluation of inter-rater reliability for each pair of raters and each rater against the median score of all raters. A prospective threshold of 0.70 was chosen for point estimate weighted kappa statistics and ICC as a criterion for satisfactory reliability.

The scale validation study demonstrated very good reliability of the MJAS when applied by trained physicians to live subjects. For the intra-rater assessment between the 2 live rating sessions, the percentage of exact matches between Session 1 and Session 2 ranged from 58.9% to 72.2%, the weighted kappa ranged from 0.821 to 0.908 and ICCs ranged from 0.823 to 0.909. All raters surpassed the threshold of 0.7 in the weighted kappa coefficient and ICCs demonstrating good intra-rater reliability.

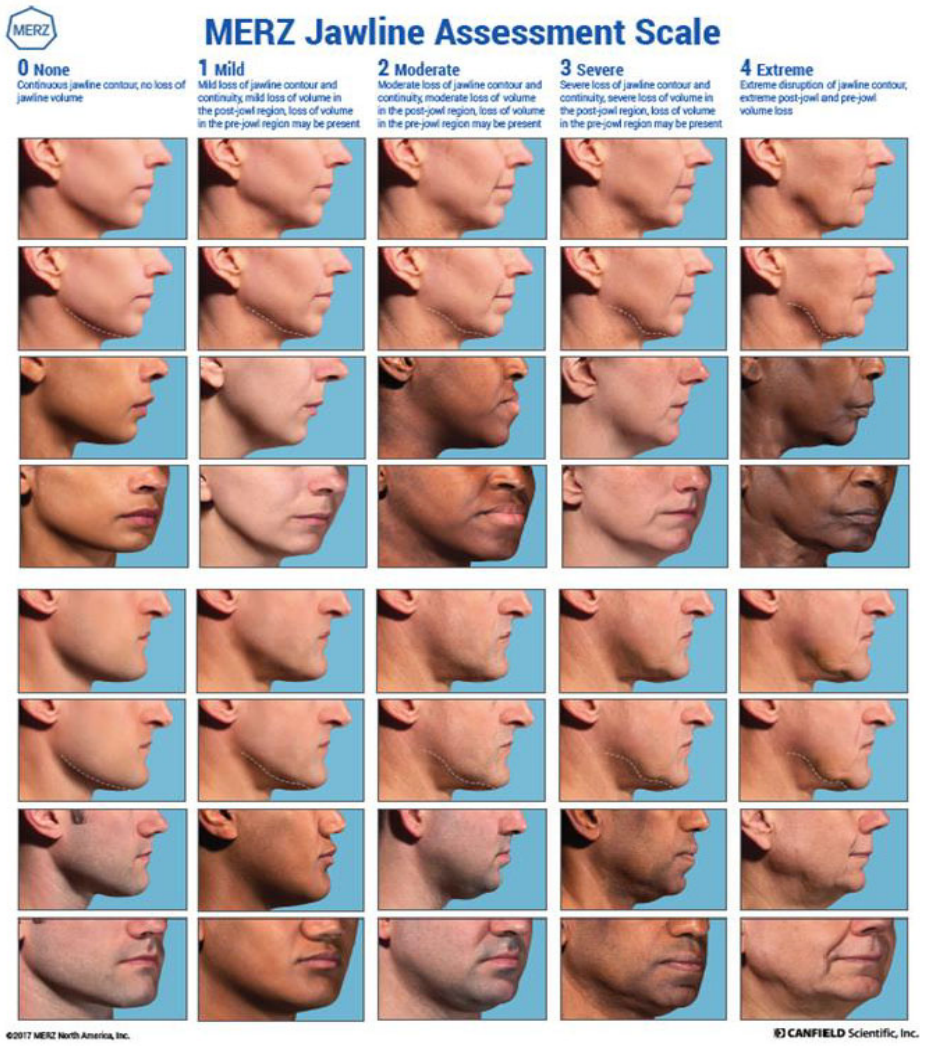
For the inter-rater assessment, the percentage of exact matches between each rater and the median ranged from 63.7% to 83.3% including Session 1 and Session 2. Weighted kappa coefficient against median ranged from 0.818 to 0.919 including both sessions and ICCs against median ranged from 0.820 to 0.920. All raters surpassed the threshold of 0.7 in the weighted kappa coefficient and ICCs against the median, demonstration of the good inter-rater reliability of the MJAS scale.

The results of this validation study demonstrated substantial intra- and inter-rater agreement among physicians using the MJAS. The 5-point MJAS scale includes scale descriptors for each grade, morphed images, and real subject images to provide standardized ratings for live, in person assessments to grade loss of jawline volume and contour.

Table 2: Merz Jawline Assessment Scale

Score	Grade	Description
0	None	Continuous jawline contour, no loss of jawline volume
1	Mild	Mild loss of jawline contour and continuity, mild loss of volume in post-jowl region, loss of volume in pre-jowl region may be present
2	Moderate	Moderate loss of jawline contour and continuity, moderate loss of volume in post-jowl region, loss of volume in pre-jowl may be present
3	Severe	Severe loss of jawline contour and continuity, severe loss of volume in post-jowl region, loss of volume in pre-jowl region may be present
4	Extreme	Extreme disruption of jawline contour, extreme post-jowl and pre-jowl volume loss

Figure 2: MERZ Jawline Assessment Scale



Secondary effectiveness endpoints assessed at Week 12 included descriptive summary of the FACE-Q™ Satisfaction with Lower Face and Jawline, and Global Aesthetic Improvement Scale (GAIS; Table 3).

Table 3: Global Aesthetic Improvement Scale

Score	Description
+ 3	Very much improved
+ 2	Much improved
+ 1	Improved
0	No change
– 1	Worse

– 2	Much worse
– 3	Very much worse

With regard to success/failure criteria, the responder rate was defined as the proportion of patients with ≥ 1-point improvement on both jawlines on the MJAS at compared to baseline. Effectiveness of RADIESSE® (+) was demonstrated at Week 12 if at least 50% of patients in the treatment group were responders and if the responder rate for the treatment group was statistically significantly greater than that for the no-treatment control group.

B. Accountability of PMA Cohort

At the time of database lock, data from all 219 patients screened in the PMA study were available for analysis (see Table 4 below). Of the 219 patients, 39 were screen failures primarily due to ineligibility, and 180 patients were enrolled and randomized per protocol.

As noted below in Table 4, 123 patients were randomized to the treatment group and 57 patients were randomized to the control/delayed-treatment group. At baseline, 55.0% (99/180) had MJAS score of 2 and 45.0% (81/180) had a score of 3. A total of 97.2% (175/180) patients were treated, of which 87 patients were treated with cannula and 88 patients were treated with needle. In total, 94.4% of patients (170/180; 117 treatment and 53 control/delayed-treatment) completed the Week 12 primary endpoint visit and 77.2% of patients (139/180; 94 treatment and 45 control/delayed-treatment) completed the 60-week study. Reasons for discontinuation of study participation are summarized in Table 5.

The intent-to-treat population included all 180 randomized patients and consisted of 123 (100.0%) patients in the treatment group and 57 (100.0%) patients in the control/delayed-treatment group. In total, 111/123 (90.2%) patients in the treatment group and 52/57 (91.2%) patients in the control/delayed-treatment group were included in the per protocol population. The safety evaluation set included all treated patients: 122/123 (99.2%) patients in the treatment group and 53/57 (93.0%) patients in the control/delayed treatment group.

Table 4: Subjects Enrolled

	Treatment		Control/DT		Total	
	n	(%)	n	(%)	n	(%)
Screened					219	
Randomized	123	(100.0)	57	(100.0)	180	(100.0)
Randomized and treated	122	(99.2)	53	(93.0)	175	(97.2)
Injection type: Cannula	62	(50.4)	25	(43.9)	87	(48.3)
Injection type: Needle	60	(48.8)	28	(49.1)	88	(48.9)

	Treatment		Control/DT		Total	
	n	(%)	n	(%)	n	(%)
Completed 12-week visit (Primary Endpoint)	117	(95.1)	53	(93.0)	170	(94.4)
Completed 60-week study	94	(76.4)	45	(78.9)	139	(77.2)
Discontinued	29	(23.6)	12	(21.1)	41	(22.8)
Intent-to-treat (ITT) population	123	(100.0)	57	(100.0)	180	(100.0)
Safety evaluation set (SES)	122	(99.2)	53	(93.0)	175	(97.2)
Per protocol (PP) population	111	(90.2)	52	(91.2)	163	(90.6)

DT = Delayed treatment; Percentages are based on the number of patients randomized

Table 5: Reasons for Discontinuation

Main reasons for discontinuation	**Total (N=180)**	
	n	**(%)**
Withdrawal by subject	21	(11.7)
Lost to follow-up	15	(8.3)
Other[1]	3	(1.7)
Adverse Event(s)[2]	1	(0.6)
Major protocol deviation and/or subject non-compliance	1	(0.6)
Physician decision	0	(0.0)
Death	0	(0.0)
Sponsor termination	0	(0.0)

[1] Discontinuation related to limitations imposed by the COVID-19 pandemic at the Week 60 visit.

[2] One subject discontinued the study before receiving treatment. The AE was coded as the preferred term "toxicity to various agents".

Percentages are based on the number of patients randomized

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.

Patient demographics and pretreatment characteristics of the RADIESSE® (+) treatment and control/delayed-treatment groups are shown in Table 6. The majority of patients were female (81.1%, 146/180 female and 18.9%, 34/180 male). Age ranged from 26 to 65 years with a mean of 55.3 years. Majority of the patients (80.6%, 145/180) self-identified as White, 13.3% (24/180) as Black/African American, 5.6% (10/180) as Asian, and 0.6% (1/180) as American Indian or Alaska Native. As for ethnicity, 17.2% (31/180) of patients self-identified as Hispanic or Latino and 82.8% (149/180) of patients as Not Hispanic or Latino. Regarding Fitzpatrick Skin Type categories, 60.6% (109/180) patients had skin types I, II, or III, and 39.4% (71/180) had skin types IV, V, or VI. All

prespecified minimum criteria for enrollment of males, diversity of races, and Fitzpatrick Skin Types (FST) detailed in the protocol were met in RADIESSE® (+) injectable implant jawline pivotal study and matched the distribution described in The American Society for Aesthetic Plastic Surgery in the 2019 Cosmetic Surgery National Data Bank Statistics.

Table 6: Subject Demographics and Baseline Characteristics

	Treatment (N=123)	Control/DT (N=57)	Total (N=180)
Gender, (n (%))			
Male	21 (17.1)	13 (22.8)	34 (18.9)
Female	102 (82.9)	44 (77.2)	146 (81.1)
Age [years]			
Mean (SD)	55.5 (7.3)	55.0 (6.6)	55.3 (7.1)
Median	57.0	55.0	56.0
Min, max	26, 65	41, 65	26, 65
Ethnicity (n (%))			
Hispanic or Latino	22 (17.9)	9 (15.8)	31 (17.2)
Not Hispanic or Latino	101 (82.1)	48 (84.2)	149 (82.8)
Race (n (%))			
White	103 (83.7)	42 (73.7)	145 (80.6)
Asian	5 (4.1)	5 (8.8)	10 (5.6)
Black or African American	14 (11.4)	10 (17.5)	24 (13.3)
American Indian or Alaska Native	1 (0.8)	0 (0.0)	1 (0.6)
Fitzpatrick skin type (n (%))			
I - III	77 (62.6)	32 (56.1)	109 (60.6)
IV - VI	46 (37.4)	25 (43.9)	71 (39.4)
MJAS score by blinded evaluator Left jawline			
2=Moderate	65 (52.8)	34 (59.6)	99 (55.0)
3=Severe	58 (47.2)	23 (40.4)	81 (45.0)
MJAS score by blinded evaluator Right jawline			
2=Moderate	65 (52.8)	34 (59.6)	99 (55.0)
3=Severe	58 (47.2)	23 (40.4)	81 (45.0)

DT= Delayed Treatment; SD = standard deviation, n = number of observations, N = number of patients in the treatment group and analysis set; More than one response is allowed for race.
MJAS = Merz jawline assessment scale

The Intent-to-Treat (ITT) population included all randomized patients (see Section X.B and Table 4 above). The safety population included all patients who were exposed to the study device at least once. The per protocol population included all patients in the ITT population without major protocol deviations.
Median initial injection volumes for each jawline (right or left) were 1.80 mL and median touch-up injection volumes were 1.10 mL for the right jawline and 1.25 mL for the left jawline. Only patients randomized to the treatment group were eligible to receive an optional retreatment. Median retreatment injection volumes were 1.40 mL for the right jawline and 1.50 mL for the left jawline.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety population cohort of 175 patients available for the 60-week evaluation. The safety population included all patients who received treatment at least once. The key safety outcomes for this study are presented below.

Adverse effects that occurred in the PMA clinical study:

Adverse events (AEs) were reported by Treating Investigators and collected at all follow-up visits. Of the 175 treated patients, 42.9% (75/175), reported an AE. A treatment-emergent AE (TEAE) was defined as an AE with onset date on or after the date of initial treatment. Overall, 26.3% (46/175) of patients had at least one TEAE that was deemed to be related to the injection procedure or RADIESSE® (+) by the investigator: 19.4% (34/175) of patients had TEAEs related to RADIESSE® (+) and 24.0% (42/175) of patients had TEAEs related to the injection procedure.

As outlined in Table 7, the most common TEAEs consisted of administration site conditions including injection site mass, injection site bruising, and injection site pain.

Table 7: Patients with TEAEs with Incidence of > 5%

	Total (N=175)	
MedDRA Preferred Term	**n**	**(%)**
Patients with at least one TEAE	74	(42.3)
Injection site mass	19	(10.9)
Injection site bruising	12	(6.9)
Injection site pain	12	(6.9)

The majority of treatment-related TEAEs were mild and resolved without sequelae (Table 8). Importantly, only 1 subject had treatment related TEAEs that were severe: injection site bruising (1 event, lasting 16 days) and injection site oedema (1 event, lasting 16 days).

Table 8: Treatment-related TEAEs by Worst Severity and Duration

	Total (N=175)		
Patients with at least one treatment-related TEAE	**n**	**(%)**	**m**
Severity			
Mild	44	(25.1)	88
Moderate	1	(0.6)	1
Severe	1	(0.6)	2

	Total (N=175)		
Patients with at least one treatment-related TEAE	**n**	**(%)**	**m**
Duration			
≤ 14 days	21	(12.0)	59
15-28 days	6	(3.4)	12
> 28 days	19	(10.9)	20

N: number of patients exposed; n: number of patients with at least one treatment-related TEAE; (%): percentage of patients with at least one treatment-related TEAE; m: number of treatment-related TEAEs (events).

For number of TEAEs, each TEAE was counted at the duration category of this event and at the severity of this event. A subject with more than one TEAE was counted once

The highest incidence of treatment related TEAEs was reported after initial treatment (initial treatment in 20.6% (36/175) of patients; touch-up in 9.8% (13/132) of patients; and retreatment in 6.6% (5/76) of patients). During the retreatment period 6.6% (5/76) of patients had a total of 5 treatment related TEAEs including: injection site mass (1 event), injection site bruising (2 events), device dislocation (1 event), and product distribution issue (1 event).

All 5 retreatment events were mild and all, but one event resolved by study end. A device dislocation event was noted during the last study visit; it was mild and required no intervention. Upon follow up in March 2021 (85 weeks after retreatment), the patient confirmed no treatment to the area was needed, and there were no ongoing adverse events since completing the study. No treatment-related serious adverse events (SAEs) and no unexpected or atypical events with use of RADIESSE® (+) were reported.

In general, treatment-related TEAEs observed in the cannula and needle subgroups were comparable in incidence, severity, and duration. Overall, no differences in safety were observed when stratifying patients by injection type (cannula versus needle), Fitzpatrick skin type categories (I-III versus IV-VI) and gender (females versus males).

For most subjects with treatment-related TEAEs (28 of 46 subjects with treatment-related TEAEs) these events began within seven (7) days of initial treatment. Hence, 16% (28/175) of all treated subjects experienced a total of 56 treatment-related TEAEs with onset within seven (7) days of initial treatment. Over the course of this study, six (6) subjects reported a total of seven (7) injection procedure related, or treatment related, events presenting > 28 days after last injection. Five (5) subjects reported 1 event, and 1 subject reported two (2) events. All events were considered mild in intensity. Details are provided in Table 9 below. All events resolved by study end except for one (1) nonserious event of

injection site nodule that remained unknown at the study end due to the subject being lost to follow up after day 100 and one (1) mild device dislocation from retreatment which resolved after the study end. None of these AEs were serious or required treatment.

Table 9: List of Treatment-Related TEAEs with Onset ≥ 28 days after last injection

MedDRA Preferred Term	Intensity	Onset (days after last injection)	Duration (days)	Outcome	Subject #
Injection site mass	Mild	68	95	Resolved	1
Injection site nodule	Mild	30	100	Unknown*	2
Injection site nodule	Mild	36	38	Resolved	3
Device dislocation	Mild	51	197	Resolved	4
Product distribution issue	Mild	59	84	Resolved	5
Injection site extravasation	Mild	129	12	Resolved	6
Injection site inflammation	Mild	129	12	Resolved	6

* Subject was lost to follow up before study end.

Electronic diaries were used by patients to record specific signs and symptoms Common Treatment Responses -CTRs) experienced during each of the first 28 days after initial, touch-up, and repeat treatments. Patients were instructed to report the severity of each of the specified CTRs as mild, moderate, severe or none. After initial treatment, 94.9% (166/175) reported at least 1 CTR after initial treatment, 77.8% (98/126) reported at least 1 CTR after touch-up treatment, and 83.8% (62/74) subject reported at least 1 CTR after repeat treatment. After initial treatment (i.e., initial treatment at Day 1 or delayed treatment at Week 12), the majority of patients self-reported CTRs that were mild (46.3%; 81/175) to moderate (46.3%; 81/175) and had a longest duration of 14 days or less (1-3 days: 12.6%, 22/175; 4-7 days: 38.9%, 68/175; and 8-14 days: 26.3%, 46/175). One patient experienced a mild CTR of discomfort/pain with palpation in both the left and right jawline lasting 29 days after initial treatment that did not require clinical intervention and resolved without sequelae.

The overall incidence, severity, and duration of CTRs were comparable in all three subject diaries (initial treatment, touch up and retreatment). Furthermore, no unexpected clinically relevant trends on CTRs incidences were identified between the needle and cannula subgroups, nor among differing Fitzpatrick Skin Types. CTRs reported by > 5% of patients after initial treatment are summarized by severity in Table 10 and by duration in Table 11.

Some differences were noted on worst CTR intensity self-reported as moderate:

- more subjects in the needle subgroup self-reported rash (needle: 6/88, 6.8% and cannula: 2/87, 2.3%), or bruising (needle: 25/88, 28.4% and cannula: 18/87, 20.7%); while

- more subjects in the cannula subgroup self-reported swelling (needle: 20/88, 22.7% and cannula: 28/87, 32.2%), firmness (needle: 11/88, 12.5% and cannula: 19/87, 21.8%), lumps/bumps (needle: 15/88, 17.0% and cannula: 33/87, 37.9%), movement or shifting of product (needle: 1/88, 1.1% and cannula: 5/87, 5.7%) or discomfort/pain with palpation (needle: 21/88, 23.9% and cannula: 26/87, 29.9%).

Some differences between needle and cannula were noted on subjects that self-reported CTRs to last 15 days or more:

- more subjects in the needle subgroup self-reported swelling (needle: 5/88, 5.7% and cannula: 2/87, 2.3%) and bruising (needle: 7/88, 8.0% and cannula: 1/87, 1.1%); while
- more subjects in the cannula subgroup self-reported firmness (needle: 3/88, 3.4% and cannula: 8/87, 9.2%), lumps/bumps (needle: 6/88, 6.8% and cannula: 10/87, 11.5%), and discomfort with palpation (needle: 2/88, 2.3% and cannula: 6/87, 6.9%).

Table 10: CTRs by worst severity occurring in > 5% of patients after initial treatment

Treatment site response	**Severity M=175**			
	None n (%)	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Any CTR	9 (5.1%)	81 (46.3%)	81 (46.3%)	4 (2.3%)
Rash	132 (75.4%)	35 (20.0%)	8 (4.6%)	0 (0.0%)
Swelling	25 (14.3%)	100 (57.1%)	48 (27.4%)	2 (1.1%)
Firmness	41 (23.4%)	103 (58.9%)	30 (17.1%)	1 (0.6%)
Lumps/Bumps	46 (26.3%)	78 (44.6%)	48 (27.4%)	3 (1.7%)
Bruising	60 (34.3%)	70 (40.0%)	43 (24.6%)	2 (1.1%)
Redness	106 (60.6%)	57 (32.6%)	12 (6.9%)	0 (0.0%)
Discoloration (not redness or bruising)	153 (87.4%)	18 (10.3%)	4 (2.3%)	0 (0.0%)
Itching	144 (82.3%)	25 (14.3%)	6 (3.4%)	0 (0.0%)
Stinging/burning	157 (89.7%)	15 (8.6%)	3 (1.7%)	0 (0.0%)
Movement or shifting of product	134 (76.6%)	35 (20.0%)	6 (3.4%)	0 (0.0%)
Difficulty drinking	166 (94.9%)	8 (4.6%)	1 (0.6%)	0 (0.0%)
Difficulty chewing	135 (77.1%)	33 (18.9%)	7 (4.0%)	0 (0.0%)
Difficulty	163 (93.1%)	11 (6.3%)	1 (0.6%)	0 (0.0%)

speaking				
Discomfort/Pain with palpation	46 (26.3%)	81 (46.3%)	47 (26.9%)	1 (0.6%)
Discomfort/Pain without palpation	88 (50.3%)	73 (41.7%)	14 (8.0%)	0 (0.0%)

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

Table 11: CTRs by maximum duration occurring in > 5% of patients after initial treatment

Treatment site response	Duration M=175					
	None n (%)	1-3 days n (%)	4-7 days n (%)	8-14 days n (%)	15-28 days n (%)	> 28 days n (%)
Any CTR	9 (5.1%)	22 (12.6%)	68 (38.9%)	46 (26.3%)	29 (16.6%)	1 (0.6%)
Rash	132 (75.4%)	38 (21.7%)	4 (2.3%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Swelling	25 (14.3%)	61 (34.9%)	67 (38.3%)	15 (8.6%)	7 (4.0%)	0 (0.0%)
Firmness	41 (23.4%)	59 (33.7%)	48 (27.4%)	16 (9.1%)	11 (6.3%)	0 (0.0%)
Lumps/Bumps	46 (26.3%)	53 (30.3%)	39 (22.3%)	21 (12.0%)	16 (9.1%)	0 (0.0%)
Bruising	60 (34.3%)	20 (11.4%)	54 (30.9%)	33 (18.9%)	8 (4.6%)	0 (0.0%)
Redness	106 (60.6%)	56 (32.0%)	13 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discoloration (not redness or bruising)	153 (87.4%)	18 (10.3%)	1 (0.6%)	2 (1.1%)	1 (0.6%)	0 (0.0%)
Itching	144 (82.3%)	19 (10.9%)	7 (4.0%)	4 (2.3%)	1 (0.6%)	0 (0.0%)
Stinging/burning	157 (89.7%)	16 (9.1%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Movement or shifting of product	134 (76.6%)	33 (18.9%)	4 (2.3%)	4 (2.3%)	0 (0.0%)	0 (0.0%)
Difficulty drinking	166 (94.9%)	9 (5.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Difficulty chewing	135 (77.1%)	32 (18.3%)	7 (4.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Difficulty speaking	163 (93.1%)	11 (6.3%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Discomfort/Pain with palpation	46 (26.3%)	56 (32.0%)	45 (25.7%)	19 (10.9%)	8 (4.6%)	1 (0.6%)
Discomfort/Pain without palpation	88 (50.3%)	59 (33.7%)	27 (15.4%)	0 (0.0%)	1 (0.6%)	0 (0.0%)

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

Jaw Function Safety Assessments: At all study visits, treating investigators performed jaw function assessments (evaluating symptoms such as difficulties with drinking, chewing, speaking, pain, sensitivity to hot/cold or any other symptoms) and intraoral exams (assessing abnormalities, such as product migration, nodule formation, ulceration, fluctuance, erythema, tenderness, occlusion instability, sensory deficiency, muscle paralysis, or any other abnormalities). Additionally, patients assessed their perception of mandibular function impairment on the Mandibular Function Impairment Questionnaire at all study visits.

No safety concerns were noted on the treating investigator jaw function assessments and intraoral exams.
Two patients had tenderness on the jaw function assessment at week 2 that resolved by week 4. Five subjects reported a score of 1 on the FIRS (Functional Impairment Rating Scale) for the patient reported mandibular function impairment questionnaire. This indicates a low level of functional impairment with no intervention needed. On intraoral examination, the investigators did not report any functional impairment. In all cases the symptoms resolved without clinical intervention over the course of the study.

Vascular occlusion assessments: Patients were instructed to report any new or unusual symptoms related to a potential vascular occlusion (e.g., signs of a stroke, changes in vision, tissue necrosis) in patient diaries for 28 days after each treatment. No events related to a potential vascular occlusion were reported over the course of the study.

2. Effectiveness Results

The analysis of effectiveness was based on the 180 evaluable patients at the primary endpoint, Week 12. Key effectiveness outcomes are presented below.

Primary Effectiveness Results

RADIESSE® (+) provided a clinically and statistically significant improvement in the contour of the jawline compared to the no treatment control group. As shown in Table 12, the treatment response rate at Week 12 for the treatment group was 75.6% (93/123), exceeding the targeted margin of 50% ($p < 0.0001$), while the treatment response rate in the control/delayed-treatment group was 8.8% (5/57). The difference between the response rates was statistically significant ($p < 0.0001$) showing superiority over the no treatment control.

Table 12: Responder Rates on MJAS at Week 12

Responder Rates		Difference in responder rates	95% CI	P – Value
Treatment	Control			
75.6% (93/123)	8.8% (5/57)	66.8%	[53.7%, 75.2%]	< 0.0001

Secondary Effectiveness Results

In the treatment group, the mean (standard deviation; SD) Rasch-transformed scores on the FACE-Q Satisfaction with Lower Face and Jawline increased from 21.5 (18.9) at baseline to 75.2 (22.3) at Week 12. The mean (SD) change from baseline to Week 12 was 53.9 (25.7) and the respective 95% confidence interval (CI) of [49.2, 58.7] excluded zero. Overall, the improvement in mean Rasch-transformed scores among treated patients

indicated that patients were more satisfied with how prominent, sculpted, nice, and smooth their jaw looked and with the profile of their jawline.

All but one subject (115/116; 99.1%) in the treatment group showed improvement on the GAIS scores as determined by the treating investigator. More specifically, the treating investigator scored 31.9% (37/116) of patients as "very much improved", 44.0% (51/116) of patients as "much improved", and 23.3% (27/116) of patients as "improved".

The majority of patients (109/116; 94.0%) in the treatment group self-reported some level of improvement on the GAIS. More specifically, patients self-reported the following improvement scores: "very much improved" in 27.6% (32/116) of patients, "much improved" in 32.8% (38/116) of patients and "improved" in 33.6% (39/116) of patients.

Other Effectiveness Results

Subject's perceived age was evaluated using the FACE-Q patient-perceived age visual analogue scale. On average, patients in the treatment group reported looking younger by 2.9 years at Week 12 when compared to baseline.

The proportion of patients that retained treatment success as assessed live by blinded evaluators using the MJAS was investigated in those patients who responded to treatment 12 weeks after initial injection. Based on observed cases, a total of 76/113 (67.3%) patients retained treatment response 48 weeks after initial treatment and before a retreatment was offered (if applicable). The 113 patients correspond to those patients that had a response 12 weeks after treatment and that also had MJAS assessment data 48 weeks after treatment. These findings support the sustained effect of RADIESSE® (+) injectable implant treatment for up to 48 weeks when injected in the jawline.

3. Subgroup Analysis

The following prespecified subgroup analyses were evaluated: injection instrument (cannula and needle; Table 13), gender (Table 14), Fitzpatrick skin type (FST; I-III and IV-VI; Table 15). Further analyses by age group (≤50 years and >50 years), race (White and Non-White), and ethnicity (Hispanic or Latino and Not Hispanic or Latino) were conducted.
Safety: No differences in safety were observed when stratifying TEAEs by the different subgroups. Overall, proportions of patients experiencing at least one treatment related TEAEs were similar for all subgroups.
Results of the subgroup analysis by age, race or ethnicity did not raise questions about the safety in these subgroups. Patients in both groups (treatment and control/delayed treatment) received treatment and safety data was analyzed for the whole population at study. See Tables 13, 14, and 15 below. Reporting rates for treatment related TEAEs were similar in the White subgroup (26.6%, 38/143) and in the Non-White subgroup (25.0%, 8/32). Regarding ethnicity, treatment related TEAEs rates were also similar in the Hispanic or Latino subgroup (30.0%, 9/30) and the Not Hispanic or Latino subgroup (25.5%, 37/145). As for age, reporting rates were similar if slightly higher in the >50

years age group (≤50 years: 17.9%, 7/39; >50 years: 28.7%, 39/136). No clinically significant tolerability concerns, regarding the injection procedure, or safety concerns associated to RADIESSE® (+) injectable implant were identified for any of the subgroups analyzed.

Effectiveness: To evaluate the consistency of the primary effectiveness analysis, results across different subgroups (i.e., injection instrument, gender, FST, age, race and ethnicity) demonstrated that the results at Week 12 were consistent with the primary analysis. Overall, the primary endpoint results for those patients who received treatment with RADIESSE® (+) were positive for all subgroups (see Tables 13, 14 and 15). MJAS responder rates for patients in the treatment group were also positive when analyzed by age (≤50 years: 73.1%, 19/26; >50 years: 76.3%, 74/97), race (White: 76.7%, 79/103; Non-White: 70.0%, 14/20), and ethnicity (Hispanic or Latino: 81.8%, 18/22; Not Hispanic or Latino: 74.3%, 75/101). Results of the subgroup analyses did not raise questions about the effectiveness in these subgroups.

For all the above subgroups, the difference in responder rates favored the treatment with RADIESSE® (+) when compared to no treatment, with lower bounds of CIs for the difference in responder rates being greater than zero.
Consistent with the high MJAS responder rates, the FACE-Q Satisfaction with Lower Face and Jawline questionnaire and the treating investigator and subject GAIS scores assessments at Week 12 also showed overall aesthetic improvements after treatment with RADIESSE® (+) when stratifying results by injection instrument (cannula versus needle), FST categories, and gender.

Table 13: Effectiveness and Safety Results by Injection Instrument

Assessment	Group	Injection Instrument	
		Cannula	Needle
EFFECTIVENESS at Week 12			
MJAS Responder Rate, % (n/N)	Treatment	77.8% (49/63)	73.3% (44/60)
	Control	7.7% (2/26)	9.7% (3/31)
FACE-Q Satisfaction with Lower Face and Jawline, mean change from baseline (SD)	Treatment	54.3 (27.9)	53.5 (23.5)
	Control	-3.6 (11.5)	-0.4 (14.8)
Treating Investigator GAIS, any improvement, % (n/N)	Treatment	100.0% (59/59)	98.2% (56/57)
Subject GAIS, any improvement, % (n/N)	Treatment	93.2% (55/59)	94.7% (54/57)
SAFETY			
Patients with at least one TEAE, % (n/N)	Total	47.1% (41/87)	37.5% (33/88)

TEAEs related to injection procedure or RADIESSE® (+), % (n/N)	Total	28.7% (25/87)	23.9% (21/88)
Patients with at least one CTR after initial treatment, % (n/N)	Total	96.6% (84/87)	93.2% (82/88)

Table 14: Effectiveness and Safety Results by Gender

Assessment	Group	Gender	
		Male	Female
EFFECTIVENESS at Week 12			
MJAS Responder Rate, % (n/N)	Treatment	66.7% (14/21)	77.5% (79/102)
	Control	15.4% (2/13)	6.8% (3/44)
FACE-Q Satisfaction with Lower Face and Jawline, mean change from baseline (SD)	Treatment	55.3 (23.1)	53.6 (26.3)
	Control	-1.8 (17.3)	-2.0 (12.4)
Treating Investigator GAIS, any improvement, % (n/N)	Treatment	100.0% (19/19)	99.0% (96/97)
Subject GAIS, any improvement, % (n/N)	Treatment	100.0% (19/19)	92.8% (90/97)
SAFETY			
Patients with at least one TEAE, % (n/N)	Total	48.4% (15/31)	41.0% (59/144)
TEAEs related to injection procedure or RADIESSE® (+), % (n/N)	Total	29.0% (9/31)	25.7% (37/144)
Patients with at least one CTR after initial treatment, % (n/N)	Total	80.6% (25/31)	97.9% (141/144)

Table 15: Effectiveness and Safety Results by Fitzpatrick Skin Type

Assessment	Group	Fitzpatrick Skin Type Subgroup	
		I-III	IV-VI
EFFECTIVENESS at Week 12			
MJAS Responder Rate, % (n/N)	Treatment	71.4% (55/77)	82.6% (38/46)
	Control	6.3% (2/32)	12.0% (3/25)
FACE-Q Satisfaction with Lower Face and Jawline, mean change from baseline (SD)	Treatment	51.3 (26.3)	58.4 (24.2)
	Control	-2.9 (10.6)	-0.4 (16.9)
Treating Investigator GAIS, any improvement, % (n/N)	Treatment	98.6% (73/77)	100.0% (42/42)

Subject GAIS, any improvement, % (n/N)	Treatment	91.9% (68/77)	97.6% (41/46)
SAFETY			
Patients with at least one TEAE, % (n/N)	Total	43.1% (47/109)	40.9% (27/66)
TEAEs related to injection procedure or RADIESSE® (+), % (n/N)	Total	27.5% (30/109)	24.2% (16/66)
Patients with at least one CTR after initial treatment, % (n/N)	Total	95.4% (104/109)	93.9% (62/66)

4. Pediatric Extrapolation

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

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 15 Investigators of which none were full-time, or part time employees of the sponsor and two investigators 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: 2
- 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

Not applicable.

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 the General and Plastic Surgery Devices Advisory Panel, 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 showed clinically and statistically significant, improvements in the contour of the jawline as assessed by blinded evaluators using the MJAS. RADIESSE® (+) met the pre-specified primary endpoint (responder rate 75.6%, 93/123) at Week 12 while the treatment response rate in the control/delayed-treatment group was 8.8% (5/57). Subgroup analyses were performed based on injection instrument (needle or cannula), Fitzpatrick skin type and age. Overall, treatment response rates for the RADIESSE® (+) group were comparable for needle (73.3%, 44/60) and cannula (77.8%, 49/63). Similar results were also observed when stratifying MJAS responder rates at Week 12 by Fitzpatrick skin type categories (I-III: 71.4%, 55/77 and IV-VI: 82.6%, 38/46) and gender (females: 77.5%, 79/102 and males: 66.7%, 14/21). This objective primary endpoint measure was further supported by multiple subject and investigator reported endpoints demonstrating aesthetic improvements post treatment.
The proportion of patients that retained treatment success as assessed live by blinded evaluators using the MJAS was investigated in those patients who responded to treatment 12 weeks after initial injection. Based on observed cases, a total of 76/113 (67.3%) patients retained treatment response 48 weeks after initial treatment and before a retreatment was offered (if applicable). These findings support the sustained effect of RADIESSE® (+) injectable implant treatment for up to 48 weeks when injected in the jawline.

Furthermore, both the treating investigator and the subject confirmed global aesthetic improvements in the jawline area. In addition, patients reported satisfaction in the lower face and jawline along with a perception of looking younger after RADIESSE® (+) treatment.

B. Safety Conclusions

The potential risks and adverse effects of the device are based on data collected in the clinical study conducted to support the indication expansion as described above as well as evaluation of device use in the Post-Marketing setting. The data submitted provide a reasonable assurance that the device is safe for deep injection (subdermal and/or supraperiosteal) for soft tissue augmentation to improve moderate to severe loss of jawline contour in adults over the age of 21. The specific conclusions are:

- For initial, touch-up, and repeat treatments, most CTRs were mild to moderate in severity, resolved within 2 weeks, and were as expected for soft tissue filler treatments.
- The most common CTRs were swelling, firmness, lumps/bumps and discomfort/pain with palpation.
- One patient experienced a mild CTR of discomfort/pain with palpation in both the left and right jawline lasting 29 days after initial treatment that did not require clinical intervention and resolved without sequelae.
- Overall, no major clinically relevant differences on CTRs incidences were identified between the needle and cannula subgroups.
- Jaw function safety assessments were evaluated at all study visits. Two patients had tenderness on the jaw function assessment at week 2 that resolved by week 4. Five subjects reported a score of 1 on the FIRS (Functional Impairment Rating Scale) for the patient reported mandibular function impairment questionnaire. This indicates a low level of functional impairment with no intervention needed. On intraoral examination, the investigators did not report any functional impairment. In all cases the symptoms resolved without clinical intervention over the course of the study.
- Treatment-emergent adverse events were generally mild to moderate in intensity.
- The most common treatment-related AEs were injection site mass, injection site bruising and injection site pain, and all others occurred in less than 5% of participants
- The study demonstrated an acceptable safety profile, with no treatment-related serious adverse events (SAEs) and no unexpected or atypical events with use of RADIESSE® (+) being reported.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The study was a prospective, multicenter, randomized, controlled, evaluator-blinded, pivotal clinical study to investigate the effectiveness and safety of RADIESSE® (+) to improve the contour of jawline by adding volume to the jawline. In the RADIESSE® (+) treatment group, 75.6% of patients were responders. RADIESSE® (+) treatment was significantly superior over no treatment control ($p < 0.0001$). The findings of the primary effectiveness assessment were supported by the secondary endpoints. The mean FACE-Q Satisfaction with Lower Face and Jawline overall Rasch-transformed score increased from 21.5 at baseline to 75.2 at Week 12, indicating that patients were more satisfied with how prominent, sculpted, nice, and smooth their jaw looked and with the profile of their jawline. The GAIS investigator and subject assessments at Week 12 showed improvements in 99.1% and 94.0% 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 rash, swelling, firmness, lumps/bumps, bruising, redness, discoloration (not redness or bruising), itching, stinging/burning, movement or shifting of product, difficulty drinking, difficulty chewing, difficulty speaking, discomfort/pain with palpation, and discomfort/pain without palpation. Participants rated CTRs as predominantly mild to moderate in severity with a majority resolving within 2 weeks. One patient experienced a mild CTR of discomfort/pain with palpation which lasted 29 days after initial treatment. Two patients had tenderness on the jaw function assessment at week 2 that resolved by week 4. Five subjects reported a score of 1 on the FIRS (Functional Impairment Rating Scale) for the patient reported mandibular function impairment questionnaire. This indicates of low level of functional impairment with no intervention needed. On intraoral examination, the investigators did not report any functional impairment. In all cases the symptoms resolved without clinical intervention over the course of the study. All treatment-related adverse events resolved either spontaneously or with treatment except for 1 nonserious event of injection site nodule that remained unknown at the study end due to the subject being lost to follow up.

The probable benefits outweigh the probable risks, as determined by the short-term adverse outcomes and rare late adverse events seen after injection, balanced against the improvement seen on the Merz Jawline Assessment Scale and patient satisfaction.

1. Patient Perspective
   Patient perspectives considered during the review included:
   - At Week 12, 94.0% (109/116) of patients treated with RADIESSE® (+) reported being "very much improved", "much improved", or "improved" on the GAIS assessment.
   - Based on the FACE-Q Satisfaction with Lower Face and Jawline questionnaire, patients reported being satisfied with how prominent, sculpted, nice, and smooth their jaw looked and with the profile of their jawline. The mean Rasch-transformed scores increased from 21.5 at baseline to 75.2 at Week 12.
   - Adverse events were obtained from sign and symptoms reported by patients during visits. Adverse events that were reported during the study are summarized in Section X.D.1 and Table 7 of this document.
   - Patient diaries, which were completed by participants for 28 days after each treatment, were used to collect information about predefined, injection related events at the treated area.

Other Considerations Relevant to Benefit-Risk
As a medical device, RADIESSE® (+) does not represent a truly novel technology, as this calcium hydroxylapatite (with and without lidocaine) product is currently FDA-approved for facial wrinkles and folds for elective aesthetic use in the adult population. Neither clinical trial nor global post-marketing data have identified any new, specific risks associated with the proposed jawline indication. The proposed

IFU employs appropriate guidance for healthcare professions and description of known risks, as well as potential warnings and precautions, employing the same risk mitigation strategy as other FDA-approved dermal fillers.

In conclusion, given the information summarized above, the data support the improvement of moderate to severe loss of jawline contour in adults over the age of 21, 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 September 01, 2021.

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.

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.

XVI. REFERENCES

None