I. General Information

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	Belotero® Volume (+)
Device Procode:	LMH
Applicant's Name and Address:	Merz North America, Inc. 6501 Six Forks Road Raleigh, NC 27615 United States of America
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P250020
Date of FDA Notice of Approval:	May 19, 2026

II. Indications for Use

Belotero® Volume (+) is indicated for deep (subcutaneous and/or supraperiosteal) injection to improve volume deficit in the mid-face or to correct mid-face contour deficiencies in adults 22 years or older.

III. Contraindications

- Belotero® Volume (+) is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history of multiple severe allergies.
- Belotero® Volume (+) contains lidocaine and is contraindicated for patients with known hypersensitivity to lidocaine or anesthetics of the amide type.
- Belotero® Volume (+) contains trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.

IV. Warnings and Precautions

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

V. Device Description

Belotero® Volume (+) is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenous gel implant. It consists of hyaluronic acid (HA) of non-animal origin, which is crosslinked with BDDE (1,4-butanediol diglycidyl ether) and formulated to a concentration of 26 mg/mL with 0.3% mg/mL lidocaine in a physiological phosphate buffer.

Belotero® Volume (+) is a dermal filler injected under the facial skin. Once in place, it helps restore volume of your midface. Belotero® Volume (+) may also be used to increase fullness of your cheeks.

VI. Alternative Practices and Procedures

There are several other alternatives for the correction of volume loss or contour deficiencies in the mid-face including another hyaluronic acid dermal filler product, autologous fat injection or transposition, plasma gel injection, surgery, and acellular dermal graft treatment. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with their physician to select the method that best meets expectations and lifestyle.

VII. Marketing History

Belotero® Volume (+) is currently registered globally in approximately eighty-five countries including Australia, Brazil, Canada, China, Chile, Columbia, the European Union, Mexico, and United Kingdom. The product has not been withdrawn from marketing for any reason related to safety or effectiveness.

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.

Adverse events reported in the pivotal clinical study at a frequency greater than 2% include injection site swelling (10.5%), injection site pain (9.2%), injection site hematoma (7.9%), injection site induration (5.3%), and injection site mass (2.0%). Adverse events reported at less than 2% frequency include injection site erythema, injection site nodule, injection site deformation, injection site dryness, injection site exfoliation, injection site indentation, injection site irritation, injection site edema, injection site pruritus, neuralgia, skin disorder, and skin wrinkling.

Additionally, the following rare but serious adverse events that are associated with intravascular injection of other dermal filler material in the face have been reported in the literature: vision impairment (acute or permanent), blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

The following additional adverse events were observed with similar dermal filler implants and are considered as potential risks for this device: abscess, angioedema, infection, dizziness, fever, hypoesthesia, induration, nausea, numbness, peeling, presyncope, rash, burning sensation, syncope, inflammation, pruritus/itching, swelling, skin discoloration.

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

IX. Summary of Nonclinical Studies

A. Laboratory Studies

Belotero® Volume (+) has been characterized by the following physical and chemical analysis (Table 1).

Table 1 Physical and Chemical Analyses

Test	Results
Appearance	Pass
pH	Pass
Osmolarity	Pass
Mean of Ejection Force	Pass
Rheological properties: Elastic modulus G'	Pass
Rheological properties: Tan δ	Pass
Extractable Volume	Pass
NaHA Content	Pass
Lidocaine hydrochloride content	Pass
2,6 DMA content	Pass
Residual BDDE content	Pass
Endotoxin content	Pass
Protein content	Pass

Sterilization – Pre-filled syringes were sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle was validated according to ISO 17665-1 sterilization standard. The validated sterilization cycle provided a Sterility Assurance Level (SAL) of 10^{-6}.

Stability / Shelf life - Packaged product data has been collected at 25°C/60% relative humidity and was evaluated for conformance to microbiological, physical, and chemical properties. Conformance with all specifications was confirmed.

B. Biocompatibility Studies

The biocompatibility studies were performed in accordance with the current Good Laboratory Practices Regulations (21 CFR § 58), ISO 10993 and FDA's biocompatibility guidance "Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management". The results of the biocompatibility tests are summarized in Table 2 below.

Table 2 Biocompatibility Results

Biological Endpoint	Method	ISO Standard	Results
Cytotoxicity	ISO MTS Cytotoxicity Test - L-929 Mouse Fibroblast Cells	ISO 10993-5	EMEM extracts showed slight cytotoxic potential to L-929 mouse fibroblast cells at 100% (full strength) and at the dilution 50% (v/v). No evidence for cytotoxicity and/or cell lysis at dilutions of 25% and 12.5% (v/v).
Dermal Sensitization	ISO Guinea Pig Maximization Sensitization Test	ISO 10993-10	Non-sensitizing
Intracutaneous Reactivity/Irritation	ISO Intracutaneous Reactivity / Irritation in rabbits	ISO 10993-10	Non-irritant
Acute Systemic Toxicity	ISO Acute Systemic Toxicity in mice	ISO 10993-11	No evidence of systemic toxicity or mortality after intraperitoneal injection
Chronic Systemic Toxicity	26-Week Sub-chronic systemic toxicity in rats	ISO 10993-11	Repeated subcutaneous injections to male and female rats, at Day 1 and Day 29 were not associated with any systemic toxicity throughout the observation period of 26 weeks
Pyrogenicity	Material Mediated; Bacterial Endotoxin	USP-NF	Non-pyrogenic
Genotoxicity	Bacterial Reverse Mutation Test – AMES Assay; Mouse Lymphoma Assay; Micronucleus Assay	ISO 10993-3	Non-mutagenic Non-genotoxic
Implantation/ Chronic Local Tissue and Degradation Effects	167-Week Implantation study in a mini-pig model	ISO 10993-6	Local Tissue Effects: Non-irritant *In vivo* Degradation: These advanced levels of article degradation, together with the minimal local tissue reaction observed at the last time point of 167 weeks (steady-state) are compatible with the late time frame as per the ISO 10993-6 standard

Carcinogenicity risks: The excess cancer risks for Belotero® Volume (+) are in the same range of acceptable cancer risks as other previously approved dermal filler products.

X. Summary of Primary Clinical Study

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of deep (subcutaneous and/or supraperiosteal) injection with Belotero® Volume (+) for improving volume deficit in the mid-face or correction of mid-face contour deficiencies in Germany. Data from this clinical study were the basis for the PMA approval decision.

A summary of the clinical study is presented below.

I. Study Design

Patients were treated between May 25, 2021 and May 25, 2022. The database for this PMA reflected data collected through May 16, 2023 and included 202 patients. There were 10 investigational sites, all in Germany.

The study was an outside-of-United States (OUS), multicenter, evaluator-blinded, randomized, comparator-controlled pivotal non-inferiority clinical study.

The control group was a legally marketed alternative with similar indications for use (i.e., "comparator").

All eligible participants were randomized in a ratio of 3:3:1:1 to one of four treatment groups:
(1) Belotero® Volume (+) in the left cheek via needle and in the right cheek via cannula (n=76);
(2) Belotero® Volume (+) in the left cheek via cannula and in the right cheek via needle (n=76);
(3) Comparator in the left cheek via needle and in the right cheek via cannula (n=26); or
(4) Comparator in the left cheek via needle and in the right cheek via cannula (n=24).

Participants underwent treatment at the onset of the study and optional touch-up treatment 4 weeks after initial treatment, if deemed necessary to achieve optimal aesthetic improvement. The total duration of the study was up to 76 weeks after baseline, depending on treatment group and retreatment. The treatment area is indicated by the red oval in Figure 1.

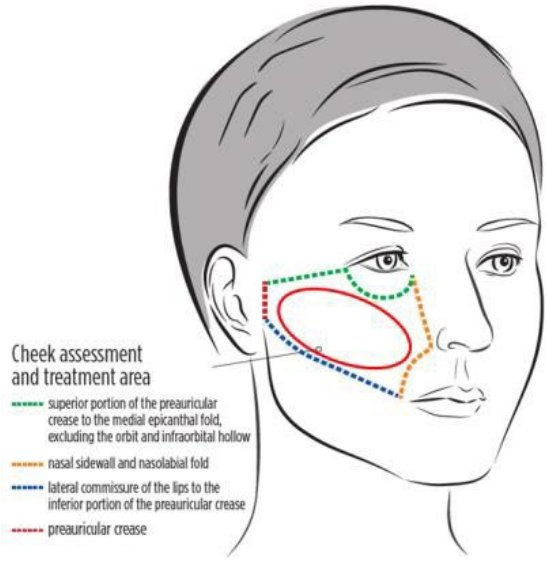


Figure 1: Cheek Assessment and Treatment Area

Treating investigators and subjects were not blinded to treatment. For the primary and secondary effectiveness assessments using the Merz Cheek Fullness Assessment Scale (MCFAS), blinded evaluators conducted the MCFAS assessment (Table 3). Blinded evaluators were board-certified plastic surgeons, dermatologists or qualified healthcare practitioners, who were trained and qualified by the sponsor to perform scale-grading assessments.

Table 3 Merz Cheek Fullness Assessment Scale[1]

Score	Rating	Description
0	Full Cheek	Full cheek region, tear trough may be present
1	Mildly Sunken Cheek	Mildly flattened cheek region, tear trough may be present
2	Moderately Sunken Cheek	Moderately sunken cheek, tear trough may be present
3	Severely Sunken Cheek	Severely sunken cheek with marked cheek volume loss, tear trough present
4	Very Severely Sunken Cheek	Very severely sunken cheek with extensive cheek volume loss, distinct tear trough

[1] Moradi A, Bloom JD, Verma A, Duncan AW. Validation of a Midfacial Scale and Its Use in a Randomized, Evaluator-Blinded Study of CPM-HA-V. J Drugs Dermatol. 2024;23(1):1284-1291. doi:10.36849/JDD.7981.

With regard to success/failure criteria, effectiveness of Belotero® Volume (+) was demonstrated at Week 12 post-initial or touch-up injection if the change from baseline in the treatment group was statistically non-inferior to that of the comparator group. The analysis was based on the average MCFAS scores of both cheeks for each participant at each time point. Non-inferiority was to be concluded at a one-sided significance level of 2.5% (equivalent to a two-sided 95% confidence interval). The null hypothesis of non-inferiority would be rejected if the upper bound of the 95% confidence interval for the difference in mean change from baseline (Belotero® Volume (+) minus Comparator) was below the non-inferiority margin of 0.5.

The sample size of approximately 200 subjects (150 Belotero® Volume (+), 50 Comparator) was justified based on power considerations assuming a standard deviation of 0.45–0.60, as observed in a pilot study, 10% attrition, and ≥80–90% power to demonstrate non-inferiority, while also ensuring adequate safety exposure to detect events with approximately 2% incidence.

1. Clinical Inclusion and Exclusion Criteria

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

   • Had a symmetrical rating of 2 (moderate) or 3 (severe) for right and left cheek on the MCFAS, as determined independently by the blinded evaluator and the treating investigator. The blinded evaluator and the treating investigator must each have had the same MCFAS ratings assigned for the right and left cheeks. However, blinded evaluator and treating investigator must not have collaborated or discussed their MCFAS rating.

   • Desired cheek augmentation to correct volume deficit in the midface and was willing to receive sufficient volume to achieve at least a 1-point improvement on the MCFAS.

   • Female or male subject, who was ≥18 and ≤70 years of age at the onset of the study.

   • Had adequate understanding (reading, speaking, and writing) of the local/regional language.

   Patients were not permitted to enroll in the clinical study if they met any of the following

exclusion criteria:

• Skin or fat atrophy in the midfacial region other than that related to age.

• Subjects with body mass index of <18.5 or ≥30.

• Acute inflammatory process or active infection at the injection site (e.g., acne, eczema, streptococcus infections), or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of AEs.

• Prior surgery, including midfacial plastic surgery, or had a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments.

• Received midfacial region treatments with porcine-based collagen fillers or with RADIESSE® or with volumizing hyaluronic acid (HA) fillers, such as, but not limited to Juvéderm® Voluma, Restylane® Lyft within the past 24 months and/or with other HA fillers or mesotherapy within the past 12 months or planned to receive such treatments during participation in the study.

• Received facial dermal therapies (i.e., facial ablative or fractional laser, dermabrasion, chemical peels, non-invasive skin-tightening [e.g., Ultherapy®, Thermage®] and surgical procedures) in the midfacial region within the past 12 months or planned to receive them in the facial region during participation in the study.

2. Follow-up Schedule

All patients were scheduled to return for follow-up in-clinic examinations at 2, 4, 12, 24, 36, and 48 weeks after the last treatment (initial or touch up) postoperatively. Participants who received a touch-up treatment at Week 4 also had a safety follow-up visit at Week 6.

At the 48-week visit, after all study procedures were completed, participants in the Belotero® Volume (+) treatment groups were eligible for repeat treatment and participants in the Comparator group exited the study. If repeat treatment was performed, another 2 week in-person safety assessment was scheduled. All participants in the Belotero® Volume (+) treatment group were followed for safety and effectiveness and had visits scheduled at Week 60 and Week 72.

Preoperatively, the following evaluations were performed: pregnancy test (for females of childbearing potential), height and weight measurements for body mass index (BMI), FACE-Q assessments (satisfaction with cheeks, patient-perceived age visual analog scale (VAS)), blinded evaluator MCFAS assessment, treating investigator MCFAS assessment, and visual safety assessments (visual acuity test, confrontation visual field test, ocular motility test and retinal photography).

Table 4 provides the objective parameters that were assessed during the study. Adverse events and complications were recorded at all visits during the study.

Table 4 Objective Assessments Performed During the Study

	Visit Timepoint	Safety Assessments	Effectiveness Assessments
Day 1 / Baseline	**Initial treatment**	Visual safety assessments Evaluation of pain Common treatment response (CTR) diary Adverse events (AEs)	N/A
	Up to 72h after treatment	CTR diary AEs	N/A
	2 weeks after treatment	Visual safety assessments CTR diary AEs	N/A
Optional touch-up treatment	**Week 4** post-initial treatment	Visual safety assessments CTR diary AEs	MCFAS
	Up to 72h after treatment[1]	CTR diary AEs	N/A
	2 weeks after treatment[1]	Visual safety assessments CTR diary AEs	N/A
Primary Endpoint assessment	**Week 12** post-last treatment	CTR diary AEs	MCFAS, investigator Global Aesthetic Improvement Scale (iGAIS), subject Global Aesthetic Improvement Scale (sGAIS), and FACE-Q
Maintenance Phase	**Week 24** post-last treatment	AEs	MCFAS, iGAIS, sGAIS, and FACE-Q
Maintenance Phase	**Week 36** post-last treatment	AEs	MCFAS, iGAIS, sGAIS, and FACE-Q
Optional retreatment[2]	**Week 48** post-last treatment	Visual safety assessments AEs	MCFAS, iGAIS, sGAIS, and FACE-Q
	Up to 72h after treatment[3]	CTR diary AEs	N/A
	2 weeks after treatment[3]	Visual safety assessments CTR diary AEs	N/A
Retreatment Phase	**Week 60** post-initial treatment / touch-up or 12 weeks post retreatment	Visual safety assessments CTR diary AEs	MCFAS, iGAIS, sGAIS, and FACE-Q

	Visit Timepoint	Safety Assessments	Effectiveness Assessments
Retreatment Phase	**Week 72** post-initial treatment / touch-up or 24 weeks post retreatment	Visual safety assessments AEs	MCFAS, iGAIS, sGAIS, and FACE-Q and likelihood of retreatment survey

[1] Safety follow up assessments were only for participants who received a touch-up at Week 4.
[2] Optional retreatment was only offered to participants in the Belotero® Volume (+) treatment groups.
[3] Safety follow up assessments were only for participants who received optional retreatment at Week 48 post-initial treatment.

All participants received a safety follow-up phone call 72 hours after each treatment (i.e., initial, touch up, optional retreatment).The Treating Investigator (TI) determined the appropriate volume of Belotero® Volume (+) or Comparator product to be injected in the midface (injection volumes did not exceed 12 mL (6 mL per cheek) for initial and touch-up treatment combined, and another 6 mL for Belotero® Volume (+) repeat treatment. Participants were in the Belotero® Volume (+) group received treatment in one cheek with the co-packaged 27G ½" needle and a 25G 1 ½" cannula in the other cheek according to the randomization assigned at the start of the study.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, Belotero® Volume (+) was evaluated by:

a) the incidence of related serious adverse events (SAEs) or delayed-onset AEs (>21 days after treatment) following the first treatment including touch-up until week 48,

b) the presence, location, severity, and duration of AEs and SAEs,

c) incidence, severity, and duration of common treatment responses (CTRs) reported in subject diaries for 28 days following the injections,

d) pain sensation immediately after and 30 minutes following the injection at baseline.

With regard to effectiveness, the primary effectiveness endpoint was the change from baseline to Week 12 after initial or touch-up injection on MCFAS as assessed by a blinded evaluator. The average of both cheeks was considered.

The key secondary effectiveness endpoint was the change from baseline to Week 12 on the MCFAS as assessed by a blinded evaluator by injection type (either cannula or needle).

Other secondary effectiveness endpoints included:

a) Responder rates at Week 12 (where a responder is defined as a ≥ 1-point improvement on both cheeks for MCFAS) when comparing the change from baseline to Week 12

b) Independent, non-collaborative assessments by both the investigator and the participant of the improvement in the cheeks using the 5-point Global Aesthetic Improvement Scale (GAIS)

c) The participants' assessment using the Satisfaction with Cheeks module of the validated FACE-Q questionnaire

Responder rates at Week 12 using MCFAS as assessed by 3 blinded independent panel raters (IPR) using participants' photographs were also evaluated as a secondary effectiveness endpoint.

Hypotheses and Analysis Methods for the Primary and Key Secondary Endpoints

Non-inferiority hypotheses were pre-specified for both the primary and key secondary effectiveness endpoints, with a shared non-inferiority margin of 0.5.

The primary effectiveness endpoint was analyzed at the subject level (i.e., using the average MCFAS scores of both cheeks for each participant at each time point). An ANCOVA model with baseline MCFAS score, treatment group, order of injection, and study site as main effect terms was used to estimate the treatment effect. The results are presented for all randomized participants (intent-to-treat set/ITTS) and all randomized participants without major protocol deviation (Per Protocol Set/PPS).
The observed mean change in MCFAS from baseline to Week 12 post-last injection (initial or touch-up) is reported for each treatment arm, alongside both the observed and ANCOVA-based between-group differences in mean change from baseline. A by-subject bootstrapped 95% confidence interval (CI) is also provided for the observed between-group difference.

The key secondary endpoint data was analyzed on the cheek-level using two separate analyses, one for cheeks treated with needle and the other for cheeks treated with cannula, using an ANCOVA model with baseline MCFAS, treatment group, order of injection, and center as main effect terms in the PPS.

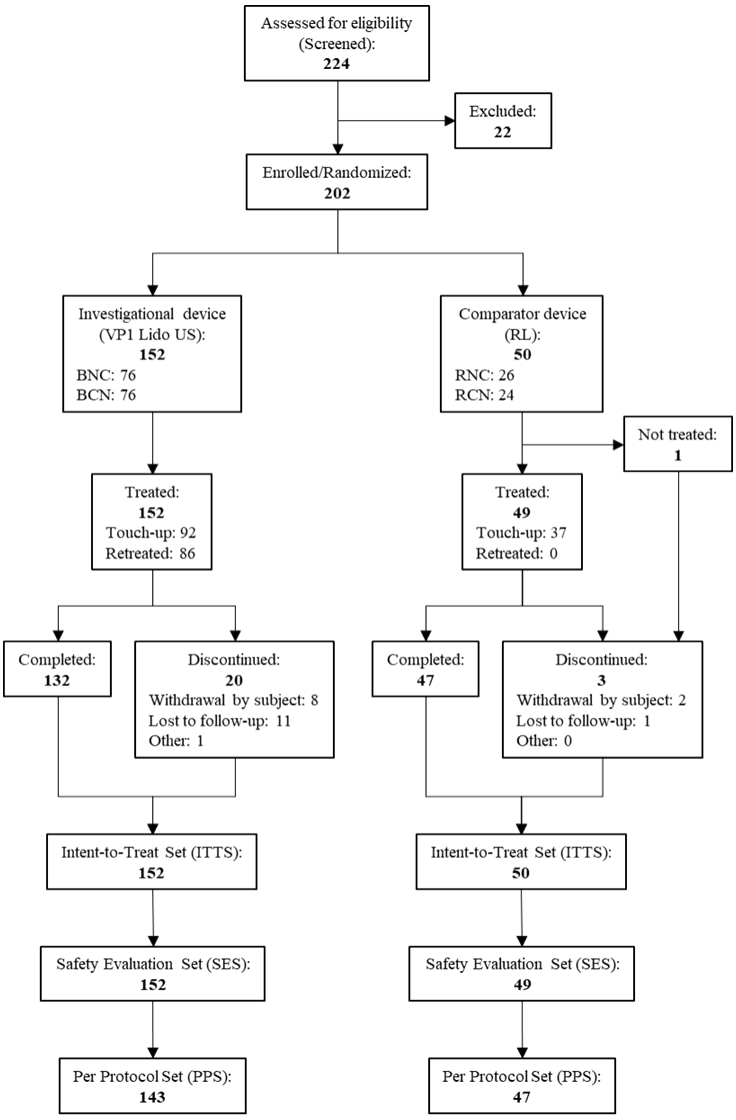
The one-sided familywise type I error rate $\alpha = 2.5\%$ was controlled by a hierarchical test design. This means that the key secondary endpoint analyses could only be tested after the primary endpoint showed non-inferiority.

II. Accountability of PMA Cohort

At the time of database lock, 202 patients enrolled in the PMA study, 179 (88.6%) participants are available for analysis at the completion of the study (Week 72 for participants randomized to Belotero® Volume (+), Week 48 for participants randomized to the Comparator).

Figure 2 provides an overview of the subject disposition for the pivotal study.

Figure 2 Subject Disposition



202 participants were randomized, with 152 in the Belotero® Volume (+) treatment group and 50 assigned to the Comparator product treatment group. One participant from the Comparator group discontinued the study before first treatment. Of the 202 randomized participants, 179 (88.6%) completed the study, whereas 23 (11.4%) discontinued the study prematurely. All 202 randomized participants were included in the intent-to-treat (ITT) set. All 201 treated participants were included in the safety evaluation set (SES).

III. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a dermal filler investigation for similar indications performed in the US. The majority of participants were female and Caucasian. A minimum of 20% of the enrolled participants were Fitzpatrick Skin Type IV, V, and VI. Table 5 provides an overview of pivotal study demographics.

Table 5 Pivotal Study Demographics, SES

Characteristic		Belotero® Volume (+) (N=152) % (n/N)	Comparator (N = 49) % (n/N)	Total (N=201) % (n/N)
Sex	Male	11.8% (18/152)	16.3% (8/49)	12.9% (26/201)
	Female	88.2% (134/152)	83.7% (41/49)	87.1% (175/201)
Age (years)	Mean (SD)	48.3 (9.85)	48.7 (9.65)	48.4 (9.78)
	Range (min, max)	(23-69)	(26-69)	(23-69)
Ethnicity	Hispanic or Latino	0.7% (1/152)	6.1% (3/49)	2.0% (4/201)
	Not Hispanic and not Latino	99.3% (151/152)	93.9% (46/49)	98.0% (197/201)
Race	White	89.5% (136/152)	91.8% (45/49)	90.0% (181/201)
	Black or African American	5.3% (8/152)	4.1% (2/49)	5.0% (10/201)
	Asian	3.3% (5/152)	2.0% (1/49)	3.0% (6/201)
	Other	0.7% (1/152)	2.0% (1/49)	1.0% (2/201)
	More than One Race	1.3% (2/152)	0.0% (0/49)	1.0% (2/201)
Fitzpatrick Skin Type	I	1.3% (2/152)	4.1% (2/49)	2.0% (4/201)
	II	32.2% (49/152)	24.5% (12/49)	30.3% (61/201)
	III	38.2% (58/152)	40.8% (20/49)	38.8% (78/201)
	IV	17.8% (27/152)	22.4% (11/49)	18.9% (38/201)
	V	9.2% (14/152)	6.1% (3/49)	8.5% (17/201)
	VI	1.3% (2/152)	2.0% (1/49)	1.5% (3/201)
BMI	Mean (SD)	23.05 (2.690)	23.52 (2.788)	23.17 (2.715)
	Range (min, max)	(17.9-29.8)	(19.1-31.1)	(17.9-31.1)

BMI = Body Mass Index, Max = maximum, Min = minimum, n = number of observations, N = number of participants in the treatment group and analysis set, SD = standard deviation, SES = Safety Evaluation Set. Percentages based on total number of pooled treatment groups.

IV. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Safety Evaluation Set (SES) cohort of 201 patients, available up to the final evaluation, 48 weeks post-last injection follow up visit. The key safety outcomes are presented below in Tables 6 to 8. Adverse effects are reported in Table 9.

- **Common Treatment Responses (CTRs)**

Electronic diaries were used by subjects who received treatment to record specific signs and symptoms experienced during the month after treatment. Subjects were instructed to rate each CTR listed in the diary as 'mild', moderate', severe' or 'none'.

Table 6 provides Common Treatment Site Responses (CTRs) by severity and Table 7 provides CTRs by maximum duration.

Table 6 Incidence of Common Treatment Site Responses (CTRs) Overall and by Maximum Severity, Initial Treatment for Cheek Augmentation, SES

Common Treatment Response	Belotero® Volume (+) (N = 152 / M = 145)				Comparator (N = 49 / M = 47)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)
Overall	82.1% (119/145)	34.5% (50/145)	35.9% (52/145)	11.7% (17/145)	83.0% (39/47)	31.9% (15/47)	42.6% (20/47)	8.5% (4/47)
Swelling	66.9% (97/145)	35.9% (52/145)	26.2% (38/145)	4.8% (7/145)	74.5% (35/47)	42.6% (20/47)	27.7% (13/47)	4.3% (2/47)
Lumps/Bumps	64.1% (93/145)	38.6% (56/145)	21.4% (31/145)	4.1% (6/145)	63.8% (30/47)	44.7% (21/47)	17.0% (8/47)	2.1% (1/47)
Pain / Tenderness	58.6% (85/145)	36.6% (53/145)	20.0% (29/145)	2.1% (3/145)	68.1% (32/47)	40.4% (19/47)	27.7% (13/47)	0.0% (0/47)
Firmness	45.5% (66/145)	28.3% (41/145)	13.8% (20/145)	3.4% (5/145)	44.7% (21/47)	27.7% (13/47)	14.9% (7/47)	2.1% (1/47)
Bruising	42.1% (61/145)	27.6% (40/145)	11.0% (16/145)	3.4% (5/145)	40.4% (19/47)	23.4% (11/47)	17.0% (8/47)	0.0% (0/47)
Redness	37.2% (54/145)	23.4% (34/145)	11.7% (17/145)	2.1% (3/145)	38.3% (18/47)	27.7% (13/47)	8.5% (4/47)	2.1% (1/47)
Stinging / Burning	28.3% (41/145)	21.4% (31/145)	5.5% (8/145)	1.4% (2/145)	23.4% (11/47)	17.0% (8/47)	4.3% (2/47)	2.1% (1/47)
Discoloration (not bruising or redness)	17.2% (25/145)	14.5% (21/145)	2.8% (4/145)	0.0% (0/145)	12.8% (6/47)	12.8% (6/47)	0.0% (0/47)	0.0% (0/47)
Itching	14.5% (21/145)	12.4% (18/145)	2.1% (3/145)	0.0% (0/145)	4.3% (2/47)	4.3% (2/47)	0.0% (0/47)	0.0% (0/47)

A participant's maximum severity was counted for each category of the CTRs.

N = Total number of participants in the corresponding treatment group; M = number of participants in the corresponding treatment group with any diary data. Percentages are based on M.

SES= Safety Evaluation Set

Table 7 Incidence of Common Treatment Site Responses (CTRs) Overall and by Maximum Duration, Initial Treatment for Cheek Augmentation, SES

Common Treatment Response	Belotero® Volume (+) (N = 152 / M = 145)					Comparator (N = 49 / M = 47)				
	Total % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)	Total % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)
Overall	82.1% (119/145)	14.5% (21/145)	21.4% (31/145)	19.3% (28/145)	26.9% (39/145)	83.0% (39/47)	12.8% (6/47)	21.3% (10/47)	14.9% (7/47)	34.0% (16/47)
Swelling	66.9% (97/145)	22.8% (33/145)	24.8% (36/145)	13.1% (19/145)	6.2% (9/145)	74.5% (35/47)	31.9% (15/47)	27.7% (13/47)	10.6% (5/47)	4.3% (2/47)
Lumps / Bumps	64.1% (93/145)	21.4% (31/145)	24.1% (35/145)	7.6% (11/145)	11.0% (16/145)	63.8% (30/47)	17.0% (8/47)	17.0% (8/47)	14.9% (7/47)	14.9% (7/47)
Pain / Tenderness	58.6% (85/145)	24.8% (36/145)	15.2% (22/145)	9.7% (14/145)	9.0% (13/145)	68.1% (32/47)	25.5% (12/47)	23.4% (11/47)	10.6% (5/47)	8.5% (4/47)
Firmness	45.5% (66/145)	14.5% (21/145)	15.2% (22/145)	6.2% (9/145)	9.7% (14/145)	44.7% (21/47)	14.9% (7/47)	10.6% (5/47)	4.3% (2/47)	14.9% (7/47)
Bruising	42.1% (61/145)	15.9% (23/145)	9.7% (14/145)	11.0% (16/145)	5.5% (8/145)	40.4% (19/47)	14.9% (7/47)	17.0% (8/47)	4.3% (2/47)	4.3% (2/47)
Redness	37.2% (54/145)	24.1% (35/145)	10.3% (15/145)	2.1% (3/145)	0.7% (1/145)	38.3% (18/47)	31.9% (15/47)	6.4% (3/47)	0.0% (0/47)	0.0% (0/47)
Stinging / Burning	28.3% (41/145)	22.8% (33/145)	3.4% (5/145)	1.4% (2/145)	0.7% (1/145)	23.4% (11/47)	17.0% (8/47)	6.4% (3/47)	0.0% (0/47)	0.0% (0/47)
Discoloration (not bruising or redness)	17.2% (25/145)	11.7% (17/145)	4.1% (6/145)	1.4% (2/145)	0.0% (0/145)	12.8% (6/47)	6.4% (3/47)	2.1% (1/47)	0.0% (0/47)	4.3% (2/47)
Itching	14.5% (21/145)	9.0% (13/145)	2.1% (3/145)	2.8% (4/145)	0.7% (1/145)	4.3% (2/47)	2.1% (1/47)	2.1% (1/47)	0.0% (0/47)	0.0% (0/47)

A participant's maximum duration was counted for each category of the CTRs.

N = Total number of participants in the corresponding treatment group; M = number of participants in the corresponding treatment group with any diary data. Percentages are based on M.

SES = Safety Evaluation Set

The CTRs most frequently reported after treatment with either Belotero® Volume (+) or the Comparator included swelling, lumps/bumps, and pain/tenderness, with a slightly higher proportion of participants experiencing swelling and pain/tenderness in the Comparator group. Based on the data from the participants who completed eDiaries, treatment site responses following touch-up and repeat treatment with Belotero® Volume (+) were less frequent than initial treatment. Treatment site responses following repeat treatment with Belotero® Volume (+) were less severe. The incidences of treatment site responses after initial treatment with cannula compared to needle were similar. Treatment site responses reported by participants after initial treatment with cannula

and needle for the Belotero® Volume (+) treatment arm are summarized in Table 8.

Table 8: Incidences of CTRs by Cannulas and Needles, Initial Treatment of Belotero® Volume Lidocaine

Common Treatment Response	**Total** (N = 152 / M = 145)	
	Cannula	**Needle**
Overall	76.6% (111/145)	77.9% (113/145)
Swelling	62.8% (91/145)	63.4% (92/145)
Lumps / Bumps	50.3% (73/145)	57.2% (83/145)
Pain / Tenderness	53.8% (78/145)	52.4% (76/145)
Firmness	40.7% (59/145)	41.4% (60/145)
Redness	30.3% (44/145)	36.6% (53/145)
Bruising	25.5% (37/145)	37.2% (54/145)
Stinging / Burning	23.4% (34/145)	23.4% (34/145)
Discoloration (not bruising or redness)	10.3% (15/145)	13.8% (20/145)
Itching	9.0% (13/145)	12.4% (18/145)

N = Total number of participants in the corresponding treatment group; M = number of participants in the corresponding treatment group with any diary data. Percentages are based on M.

SES = Safety Evaluation Set

- **Adverse Effects**

Adverse events (AEs) were reported by Treating Investigators at all follow-up visits, where applicable. Table 9 provides an overall summary of Treatment-Related Treatment Emergent Adverse Events (TEAE). The most frequently reported treatment related TEAE after any treatment with Belotero® Volume (+) group was injection site swelling. Most treatment-related TEAEs were mild (82.7%) and, overall, no severe treatment-related TEAEs were reported throughout the study. All treatment-related TEAEs were resolved at the end of the study, with the majority of treatment-related TEAEs lasting 1 to 7 days in the Belotero® Volume (+) group, except for 2 participants with had treatment-related TEAEs with an unknown outcome: one participant was discontinued the study (lost to follow-up) and in the other case the report (injection site pain) was derived from the eDiary data.

Treatment-related TEAEs occurring in < 2% of subjects after initial and touch-up treatment, for both treatment groups, included injection site nodule, injection site deformation, injection site dryness, injection site exfoliation, injection site indentation, injection site irritation, injection site edema, injection site pruritus, neuralgia, skin disorder, and skin wrinkling.

Table 9 Treatment-Related TEAEs Occurring ≥ 2% of Participants by Adverse Event Preferred Term, SES

Adverse Event	Belotero® Volume (+) Initial/Touch-Up (N=152)		Comparator Initial/Touch-Up (N=49)		Belotero® Volume (+) Repeat Treatment (N=86)	
	Participants % (n/N)	Number of Events	Participants % (n/N)	Number of Events	Participants % (n/N)	Number of Events
Injection site swelling	10.5% (16 /152)	21	10.2% (5/49)	5	4.7% (4/86)	7
Injection site pain	9.2% (14/152)	17	12.2% (6/49)	9	2.3% (2/86)	3
Injection site hematoma	7.9% (12/152)	12	4.1% (2/49)	2	4.7% (4/86)	5
Injection site induration	5.3% (8/152)	8	10.2% (5/49)	5	4.7% (4/86)	4
Injection site mass	2.0% (3/152)	3	12.2% (6/49)	7	2.3% (2/86)	2
Injection site erythema	1.3% (2/152)	2	2.0% (1/49)	1	0.0% (0/86)	0
Headache	0.7% (1/152)	1	2.0% (1/49)	1	0.0% (0/86)	0
Injection site bruising	0.0% (0/152)	0	2.0% (1/49)	1	0.0% (0/86)	0
Skin burning sensation	0.0% (0/152)	0	2.0% (1/49)	1	0.0% (0/86)	0

N = number of participants in the treatment group and analysis set, n = number of participants in respective subset, m = number of treatment-related TEAEs. Percentages are based on N. SES = Safety Evaluation Set

A participant with more than one treatment-related TEAE within an Adverse Event (SOC/Preferred Term) was counted once.

Treatment-Related Delayed-Onset TEAEs:

Four participants (2.6%) who received treatment with Belotero® Volume (+) reported a total of 4 treatment-related delayed-onset TEAEs (i.e., >21 days after treatment): 1 injection site induration, 1 injection site edema, 1 injection site pain, and 1 event of skin disorder (reported as skin blemishes). No treatment-related delayed-onset TEAEs occurred at time points more than 1 month post any treatment. All 4 treatment-related delayed-onset TEAEs were rated as mild and resolved, except for injection site pain with an unknown outcome (participant lost to follow-up).

The treatment-related delayed-onset TEAEs injection site induration and injection site edema were linked to cannula treatment, while injection site pain was related to needle treatment. The treatment-related delayed-onset TEAE skin disorder was linked to both cannula and needle treatment.

No treatment-related delayed-onset TEAEs were reported after repeat treatment.

Safety Subgroup Analyses:

In Belotero® Volume (+) group the proportion of participants with treatment related TEAEs were similar by cannula (21.7 %, n=33/152) and by needle (21.1 %, n=32/152). Proportions of female participants who reported treatment related TEAEs (29.1%, n=39/134) were comparable to rates of male participants (27.8%, n=5/18) in Belotero® Volume (+) group. In Belotero® Volume (+) group, the proportion of treatment-related TEAEs reported in participants with Fitzpatrick Skin Type (FST) I-III (31.2%, n=34/109) was slightly higher than the rate for participants with FST IV-VI (23.3%, n=10/43).

2. Effectiveness Results:

No imputation was performed for missing primary or key secondary endpoints data. Among all randomized subjects (ITTS), the rates of missing data were low; only 9 of 202 subjects (4.5%) had missing primary endpoint data. Key effectiveness outcomes are presented in Table 10 and described below.

Primary Effectiveness Results

Table 10 Observed Subject-level MCFAS Change from Baseline to Week 12 Post-Last Injection (Initial or Touch Up) as Assessed by Blinded Evaluator

	Treatment Group MCFAS change[1] (Week 12 - baseline) N Mean Change (SD)		**Treatment Difference** Difference (95% CI)[2]	**Treatment Difference** ANCOVA-based Difference (95% CI)[3]
Analysis Set	**Belotero® Volume (+) (N = 152 ITTS)**	**Comparator (N = 50 ITTS)**	**(Belotero® Volume (+) - Comparator)**	**(Belotero® Volume (+) - Comparator)**
PPS	143 -1.60 (0.757)	47 -1.55 (0.753)	-0.05 (-0.30, 0.19)	-0.13 (-0.31, 0.06)
Observed ITTS	145 -1.60 (0.754)	49 -1.53 (0.746)	-0.07 (-0.33, 0.17)	-0.13 (-0.31, 0.05)

[1] The MCFAS score for each subject is the average of left and right cheeks.
[2] This is the 95% by-subject bootstrapped confidence interval for the observed difference.
[3] This is the subject-level ANCOVA-based 95% confidence interval for the difference.

In the PPS, the observed mean change in MCFAS from baseline to Week 12 post-last injection was -1.60 for Belotero® Volume (+) and -1.55 for the Comparator. The observed difference (Belotero® Volume (+) minus Comparator) was -0.05 with a corresponding 95% CI of (-0.30, 0.19) and the subject-level ANCOVA-based difference was -0.13 with a corresponding 95% CI of (-0.31, 0.06).

Similarly in the observed ITTS, the observed mean change in MCFAS from baseline to Week 12 post-last injection was -1.60 for Belotero® Volume (+) and -1.53 for the Comparator. The observed difference (Belotero® Volume (+) minus Comparator) was -0.07 with a corresponding 95% CI of (-0.33, 0.17) and the subject-level ANCOVA-based

difference was -0.13 with a corresponding 95% CI of (-0.31, 0.05).

In both the PPS and observed ITTS, the upper bounds of the 95% CIs for the subject-level differences did not exceed the non-inferiority margin (δ=0.5) supporting non-inferiority of Belotero® Volume (+) to the Comparator with respect to the change in MCFAS from baseline to Week 12 post-last injection.

Key Secondary Effectiveness Results:

As shown in Table 11 the ANCOVA-based treatment difference (Belotero® Volume (+) - comparator) was −0.2 (95% CI: −0.3, 0.0) for the cannula injection technique and −0.1 (95% CI: −0.3, 0.1) for the needle injection technique in the PPS. The 95% CI upper bounds of both injection techniques did not exceed the pre-specified non-inferiority margin of δ = 0.5 points. Thus, non-inferiority was concluded for both techniques.

Table 11 Observed MCFAS Change from Baseline to Week 12 post-last injection (initial or touch-up) at the cheek-level as Assessed by Blinded-Evaluator, by injection type [PPS]

	Treatment Group MCFAS change (Week 12 - baseline) Mean (SD)		**Treatment Difference** ANCOVA-based Difference (95% CI)
Injection Type	**Belotero® Volume (+) (N = 143)**	**Comparator (N = 47)**	**(Belotero® Volume (+)-Comparator)**
CANNULA	-1.60 (0.78)	-1.5 (0.75)	-0.2 (-0.3,0.0)
NEEDLE	-1.60 (0.76)	-1.6 (0.77)	-0.1 (-0.3,0.1)

Other Secondary Effectiveness Results in the PPS:

MCFAS

The responder rates according to the MCFAS assessed at Week 12 by the blinded evaluator were very similar, with Belotero® Volume (+) at 95.8% (137/143) and the Comparator at 95.7% (45/47).

MCFAS-based responder rates at Week 12, as assessed by 3 blinded board-certified IPRs using participant photographs, where a responder was defined as a participant with ≥1-point improvement from baseline on both cheeks as scored by at least 2 blinded reviewers (as opposed to by a single blinded live evaluator assessment performed for the primary analysis), were 46.2% (66/143) after Belotero® Volume (+) treatment and 34.0% (16/47) after Comparator treatment. The responder rate difference of 12.1% in favor of Belotero® Volume (+) at Week 12, according to the MCFAS, supports that Belotero® Volume (+) treatment is non-inferior to Comparator.

These differences between live blinded evaluators and IPRs utilizing the MCFAS likely reflect the inherent limitations of photographic evaluation, which relies on two-dimensional images and may not capture all clinically relevant aspects of cheek fullness.

GAIS

At Week 12, 97.9% (140/143) of participants assessed by investigator and 95.1% (136/143) participants assessed by self-assessment reported noticeable aesthetic improvements with Belotero® Volume (+) treatment. Investigators and participants in the Comparator group also reported aesthetic improvement with treatment at Week 12 (100% [47/47] and 95.7% [45/47], respectively).

FACE-Q Questionnaire

Participant satisfaction with cheeks, as measured by the FACE-Q Satisfaction with Cheeks questionnaire indicate significant improvements after treatment. In the Belotero® Volume (+) treatment group, mean Rasch-transformed scores increased from 39.3 at baseline to 76.1 at Week 12. In the Comparator group, mean scores increased from 35.7 at baseline to 78.6 at Week 12. The Rasch-transformed scores have a possible range from 0 to 100. 0 indicates the worst and 100 the best score.

<u>Other Effectiveness Results in the observed ITTS</u>:

The proportion of participants treated with Belotero® Volume (+) that achieved a ≥2-point improvement for both cheeks according to the MCFAS at Week 12, as assessed by blinded evaluator, was 49.0% (71/145).

At Week 24, 79.0% of participants (109/138) treated with Belotero® Volume (+) reported looking younger than their age.

The overall satisfaction of participants treated with Belotero® Volume (+) was further substantiated by the majority (82.0%) (109/133) of participants responding that they would likely have future Belotero® Volume (+) cheek augmentation treatment on the end-of-study survey.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness: FST, race, age, sex, ethnicity, and injection instrument. The study was not specifically powered for these subgroups.

Safety Analysis

FST: Overall, the proportion of subjects with at least one treatment-related treatment-emergent adverse event (TEAE) in subjects with FST IV-VI was lower (25.9%, 24 treatment-related TEAEs) and with FST V (29.4%) compared to the proportion of subjects with FST I-III (31.5%, 87 treatment-related TEAEs) with no treatment-related TEAES being reported for FST VI subjects. The difference is even more pronounced in the Belotero® Volume (+) group with 23.3% of subjects with FST IV-VI and 28.6% of subjects with FST V reporting at least one treatment-related TEAE compared to 31.2% of subjects reporting at least one treatment-related TEAE with FST I-III. For the Comparator group there is no difference in rate of treatment-related TEAEs between FST I-III, FST V and FST IV-VI subgroups. Overall and in the Belotero® Volume (+) group, the preferred terms of treatment-related TEAEs that were reported in more than 5% of subjects with FST I-III included injection site pain, injection site swelling, injection site induration, injection site hematoma, in subjects with FST IV-VI included injection site pain, injection site swelling, injection site haematoma and in subjects with FST V included injection site pain, injection site haematoma, injection site indentation, injection site oedema.

Race: In terms of race, subjects were analyzed separately as white, black or African American, Asian, Other and more than one race. Overall, the proportion of subjects with at least one treatment-related TEAE was highest in subjects with the race white (30.4%), followed by subjects with Asian race (16.7%).

Age: In terms of age, safety data were grouped into subjects of 22-29 years, 30-50 years and more than 50 years. Overall, the proportion of subjects with at least one treatment-related TEAE was similar between those aged 30-50 years (30.0%) and those subjects more than 50 years (32.6%) old, whereas the proportion among subjects aged 18-29 years was lower (8.3%). This was similar in the Belotero® Volume (+) group with 27.8% of subjects aged between 30-50 years reported at least one treatment-related TEAE and 32.9% of subjects aged more than 50 years reported at least one treatment-related TEAE and only 10% of subjects aged 22-29 years reported at least one treatment-related TEAE.

Sex: In terms of sex, treatment-related TEAEs were analyzed in female and male subjects separately. Overall, the proportion of female subjects with at least one treatment-related TEAE (30.3%) was similar to the proportion of male subjects with at least one treatment-related TEAE (26.9%). The same pattern could be found in the Belotero® Volume (+) group, with 29.1% of female subjects reporting at least one treatment-related TEAE and 27.8% of male subjects reporting at least one treatment-related TEAE.

Ethnicity: In terms of ethnicity, treatment-related TEAEs were analyzed for Hispanic or

Latino vs. Not Hispanic or Latino. The proportion of subjects with at least one treatment-related TEAE with Hispanic or Latino ethnicity (50.0%) is higher compared to the proportion of subjects with at least one treatment-related TEAE with not Hispanic or Latino ethnicity (29.4%). In the Belotero® Volume (+) group, there was only one Hispanic or Latino subject. This subject reported a treatment-related TEAE (100%) while the percentage of subjects in the Not Hispanic or Latino was 28.5%.

Injection Instrument: In terms of injection instrument, all subjects were treated with needle and cannula. For each subject, one cheek was treated with needle and the other with cannula. Treatment-related TEAEs were analyzed by the affected treatment area. Some treatment-related TEAEs occurred only on the cheek treated with cannula or other on the cheek treated with needles. In the Belotero® Volume (+) group, the proportion of subjects with at least one treatment-related TEAE that only affected the cheek treated with needle was 11.2% and similar compared to 9.9% of subjects in the Belotero® Volume (+) group with at least one treatment-related TEAE which only affected the side treated with cannula.

Effectiveness:

The clinical effectiveness of Belotero® Volume (+) was assessed by addressing the observed subject-level changes from baseline to week 12 (primary endpoint visit) based on the blinded evaluators MCFAS ratings regarding subjects' sex, race, FST, age, and injection type.

Table 12 Observed MCFAS Change from Baseline to Week 12 post-last injection (initial or touch-up) at the subject-level as Assessed by Blinded-Evaluator [observed ITTS]

Subgroup	Treatment Group MCFAS change (Week 12 - baseline) mean (SD)	
	Belotero	**Comparator**
Sex		
Female	N = 128 -1.64 (0.756)	N = 41 -1.54 (0.753)
Male	N = 17 -1.29 (0.686)	N = 8 -1.50 (0.756)
Race		
White	N = 133 -1.63 (0.750)	N = 45 -1.49 (0.753)
Black	N = 6 -1.50 (1.049)	N = 2 -2.50 (0.707)
Asian	N = 3 -1 (0.000)	N = 1 -1
Other	N = 1 -1	N = 1 -2
More than One Race	N = 2 -1.50 (0.707)	

Subgroup	Treatment Group MCFAS change (Week 12 - baseline) mean (SD)	
Fitzpatrick Skin Type		
Type I-III	N = 107 -1.52 (0.715)	N = 34 -1.50 (0.674)
Type IV=VI	N = 38 -1.83 (0.824)	N = 15 -1.60 (0.910)
Age		
18-29 years	N = 9 -1.22 (0.667)	N = 2 -1 (0.000)
30-50 years	N = 68 -1.62 (0.702)	N = 28 -1.59 (0.806)
> 50 years	N = 68 -1.64 (0.810)	N = 19 -1.50 (0.687)
Injection Type		
Cannula	N = 145 -1.6 (0.78)	N = 49 -1.5 (0.74)
Needle	N = 145 -1.6 (0.76)	N = 49 -1.6 (0.77)

These observed mean changes appear to be similar between treatment groups across the subgroups listed.

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. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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 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

Belotero® Volume (+) met the pre-specified primary endpoint, and the secondary endpoints to support product effectiveness.

Non-inferiority of Belotero® Volume (+) versus an approved HA dermal filler (Restylane Lyft Lidocaine) was achieved for the primary endpoint with respect to the mean change in MCFAS from baseline to Week 12 in both the PPS and observed ITTS. The upper bounds of the 95% CIs for the subject-level differences in MCFAS change from baseline to 12 weeks after treatment or touch-up, between Belotero® Volume (+) and Comparator did not exceed the non-inferiority margin of δ=0.5 points.

Similar results were shown for needle treatment and cannula treatment, respectively; thus, non-inferiority was also demonstrated for these 2 injection methods.

The data confirms that Belotero® Volume (+) is effective for cheek augmentation to improve volume deficit in the mid-face or to correct mid-face contour deficiencies in adults age 22 or older.

The observed mean MCFAS changes from Baseline to Week 12 post-last injection (initial or touch-up) at the subject-level as Assessed by Blinded-Evaluator, appear to be similar between treatment groups across the subgroups of sex, race, age group, Fitzpatrick Skin Type, and injection type.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies and animal studies, as well as data collected in the clinical study conducted to support the indication for use. The safety evaluation included incidence and type of any adverse events (AEs) and serious adverse events (SAEs) separately for Maintenance Phase and Retreatment Phase. The maintenance phase started with first treatment (baseline) and ended at 48 weeks after post last treatment (i.e. either initial treatment or touch-up if applicable). The retreatment phase started at 48 weeks post last injection and ended at the end-of-study visit. In addition, the incidence, severity and duration of common treatment responses (CTRs) were collected in subject diaries for 28 days following each treatment The data submitted provide a reasonable assurance that the device is safe for injections in the supraperiosteal and/or subcutaneous plane for the improvement of the volume

deficit in the midface or correction of mid-face contour deficiencies in adults. See data above.

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 pivotal study was a prospective, comparator control study using a validated scale and blinded, live evaluations. The effectiveness of the treatment was evaluated by an independent assessment of blinded rater using a validated tool (MCFAS) (Primary Endpoint) as well as via patient reported outcome assessments and treating investigator assessment (Secondary Endpoints). Based on the results, Belotero® Volume (+) is an effective treatment for the correction of volume loss in the mid-face area.

At Week 48 Post Initial Injection/Touch-up, for Belotero® Volume (+) subjects: 68.1% reported they 'look younger', 25.9% reported they 'look my age', and 5.9% reported they 'look older'; for the Comparator subjects: 66.0% reported they 'look younger', 27.7% reported they 'look my age', and 6.4% reported they 'look older'. Results indicate for a majority of subjects that duration of effect remains.

At the last study visit, subjects randomized to Belotero® Volume (+) were asked how likely they would be to have future Belotero® Volume (+) treatments in the mid-face. The majority of subjects (82.0%) responded that they are willing to receive future Belotero® Volume (+) cheek augmentation treatment on the end-of-study survey.

The probable risks of the device are also based on data collected in a clinical study that supports PMA approval as described above. This study had no treatment-related SAEs and no unexpected or atypical events with use of Belotero® Volume (+) reported. Treatment related TEAEs were generally mild to moderate in intensity. Treatment-related delayed-onset TEAEs were reported in 4 subjects after Belotero® Volume (+) treatment, but only single events at PT level were delayed. The maximum onset reported was approximately one month (no specific day was given as onset day, but it occurred the month after IMD injection). All 4 treatment-related delayed-onset TEAEs were rated as mild, and mainly resolved; thus, these do not present any further safety concerns.

1. Patient Perspective

Patient perspectives considered during the review included:

- Subject GAIS
- Time Course of FACE-Q Satisfaction with Cheeks
- Time Course of FACE-Q Patient Perceived Age VAS
- Pain Assessment
- Likelihood of Retreatment

In conclusion, given the available information above, the data support the use of Belotero® Volume (+) for cheek augmentation to improve volume deficit in the mid-face or to correct mid-face contour deficiencies in adults 22 years or older, and the probable benefits outweigh the probable risks.

D. Overall Conclusion

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 May 19, 2026.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality Management System (QMSR) 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.