Belotero® Volume (+) Lidocaine Dermal Filler

Prescribing Information and Instructions for Use

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Belotero® Volume (+) Lidocaine Dermal Filler

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician or other properly licensed practitioner.

READ THE FOLLOWING INFORMATION THOROUGHLY BEFORE USING PRODUCT

DEVICE DESCRIPTION

Belotero® Volume (+) Lidocaine ("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.

INTENDED USE/INDICATIONS

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.

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.

WARNINGS

- The product must not be injected into blood vessels. Introduction of Belotero® Volume (+) into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to the underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly

after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur (see Health Care Professional Instructions).

- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled.
- Common treatment site responses consist mainly of short-term inflammatory symptoms and usually resolve within 2 weeks. Refer to the ADVERSE EVENTS section for details.
- The following have been reported following the use of dermal fillers: Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care professionals are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- Belotero® Volume (+) is packaged for single-patient use. Do not re-sterilize. Discard any unused product. Discard any partially used syringes.
- Do not use if package is open or damaged. Do not used if the product is beyond the expiration date indicated on the package.
- The safety and effectiveness for the treatment of anatomic regions other than the mid-face have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- As with all invasive procedures, Belotero® Volume (+) sessions should be conducted with aseptic technique including cleansing the patient's face prior to injection and wearing sterile gloves when injecting. Observe universal precautions to minimize risks of potential contact with patient body fluids such as blood at the injection site.
- The safety of Belotero® Volume (+) for use during pregnancy, in breastfeeding females or in patients under 21 years has not been established.
- Injections of Belotero® Volume (+) into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Belotero® Volume (+) should be used with caution in patients on immunosuppressive therapy.

- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants) may, as with any injection, experience increased bruising or bleeding at treatment sites.

- After use, treatment syringes and needles/cannulas may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.

- Belotero® Volume (+) dermal filler is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; notify Merz Ax Customer Solutions 844-469-6379.

- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer lock and needle hub connection.

- Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

ADVERSE EVENTS

A. Pivotal Study of Belotero® Volume (+) for Cheek Augmentation

In a randomized, comparator-controlled clinical study to evaluate the safety and effectiveness of Belotero® Volume (+) for correction of midface contour deficiencies or volume deficit versus a comparator product with similar indications for use, there were 152 participants randomized for treatment with Belotero® Volume (+) and 50 participants randomized for treatment with the Comparator product.

Participants were treated in the mid-face (i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region, see Figure 1). Touch-up treatments were performed at Week 4 if necessary. At the 48-week visit, after all study procedures were completed, participants in the Belotero® Volume (+) treatment groups were eligible for repeat treatment.

Electronic diary ("eDiary") forms were used by participants after each treatment to record specific signs and symptoms experienced during each of the first 28 days after initial treatment, touch-up treatment, and repeat treatment. Of the 201 participants who received initial treatment (from both the treatment and Comparator groups), 192 completed the eDiary forms. 124 out of 129 participants who received touch-up treatment completed the eDiary forms. A subset of 86 participants treated with Belotero® Volume (+) also underwent repeat treatment, with 74 participants completing eDiary forms. Participants were instructed to rate each common treatment response (CTR) listed on the diary as "Mild," "Moderate," "Severe," or "None."

After initial treatment, 82.1% of the participants treated with Belotero® Volume (+) and 83.0% of the participants treated with the Comparator reported experiencing a CTR. Participants rated CTRs after treatment with Belotero® Volume (+) as predominately mild (34.5%, 50/145) or moderate (35.9%, 52/145) in intensity, the majority (55.2%, 80/145) resolving within 2 weeks. These results were similar to the Comparator product; however, a higher percentage of participants in the Comparator group experienced treatment site responses lasting longer two weeks.
Common treatment responses reported by participants after initial treatments are summarized by maximum severity in Table 1 and by maximum duration in Table 2.

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 are summarized Table 3.

Table 1: 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 2: 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

Table 3: 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

Treatment-Related Treatment Emergent Adverse Events

Adverse Events (AEs) were reported by the Investigators throughout the entirety of the study. A treatment-emergent AE (TEAE) was defined as an AE that initially occurred or increased in severity on or after the treatment start date for the Belotero® Volume (+) or Comparator group. An AE was considered to be related to device or the injection procedure (i.e., "treatment-related") if a causal relationship between the device or the injection procedure and an AE was at least reasonably possible. Treatment site responses reported in participant diaries that lasted longer than 28 days were considered adverse events (AEs).

The severity and duration of treatment-related TEAEs occurring with a frequency of ≥ 2% reported during the study is summarized in Table 4. 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.

There were no treatment-related serious adverse events reported during the study.

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 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).

Table 4: 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.

Visual Safety Assessments

Safety assessments such as visual acuity, confrontational visual fields, ocular motility and retinal imaging were performed at the screening visit and throughout the study. A greater than one line drop in visual acuity was considered an abnormal result. All abnormal visual acuity results were determined to be non-serious and not related to treatment with either Belotero® Volume (+) or the Comparator. Fluctuations in visual acuity were attributed to differences in the times of the day when the assessment was performed, or variances on occupational exposure (i.e., prolonged duration of time in front of a screen).

Confrontational visual fields and ocular motility assessments showed that 100% of eyes were full to confrontation and had full duction and version at all timepoints.

EFFECTIVENESS

A. Pivotal Study of Belotero® Volume (+) for Cheek Augmentation

Study Design

An outside-of-United-States multicenter, evaluator-blinded, randomized, comparator-controlled pivotal non-inferiority study was conducted to evaluate the safety and effectiveness of Belotero® Volume (+) versus an FDA-approved comparator product for cheek augmentation and correction of midface contour deficiencies. The study was conducted at 10 investigational sites across Germany.

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).

Treating investigators and participants 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. 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.

Participants had in-clinic follow up visits at 2, 4, 12, 24, 36, and 48 weeks after the last treatment (initial or touch up) during the primary safety and effectiveness phase. 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.

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. The treatment area is indicated by the red oval in Figure 1. 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.

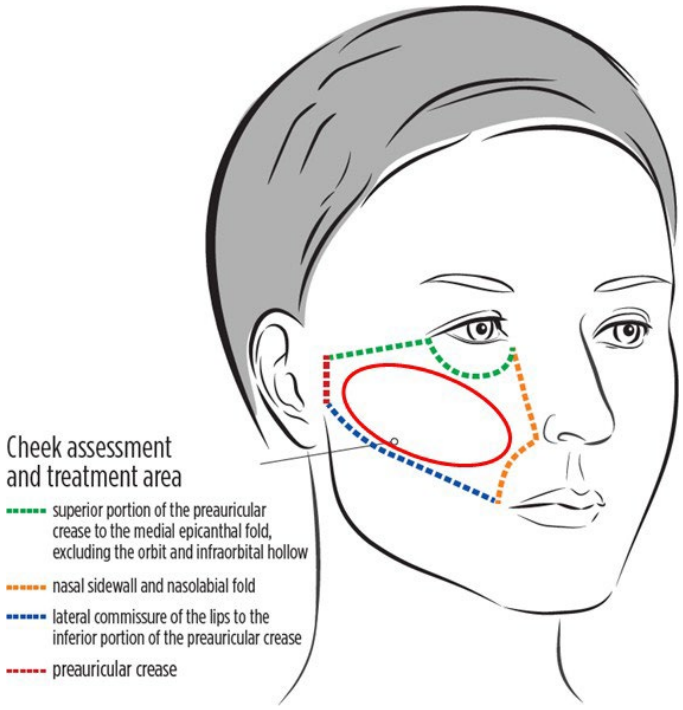


Figure 1: Cheek Assessment and Treatment Area

Study Endpoints

With regard to effectiveness, primary analysis for cheek augmentation was evaluated based on non-inferiority of Belotero® Volume (+) versus Comparator in cheek augmentation by comparing a change from baseline in the blinded evaluator's live assessment of midface fullness at 12 weeks after the last injection (i.e., initial or touch-up) using the validated[1] 5-point Merz Cheeks Fullness Assessment Scale (MCFAS) (Table 5). 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 predefined analysis of the primary endpoint was performed at cheek-level. Results of an additional analysis considered the average of both cheeks was considered.

Table 5: Merz Cheek Fullness Assessment Scale

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

Changes from baseline in MCFAS score at Week 12 at the cheek-level by injection type (cannula, needle) and were considered a key secondary endpoint of the study. Secondary effectiveness endpoints also included responder rates at Week 12, independent, noncollaborative assessments by both the investigator and the participant of the improvement in the cheeks using the 5-point Global Aesthetic Improvement Scale (GAIS), and the participants' assessment using the Satisfaction with Cheeks module of the validated FACE-Q questionnaire. Responder rates at Week 12 using the MCFAS as assessed by 3 blinded independent panel raters (IPR) using participants' photographs were also evaluated as a secondary effectiveness endpoint.

Other effectiveness endpoints included participant self-perception of age module (FACE-Q Patient-Perceived Age Visual Analog Scale), participant satisfaction with the cheeks over time, participant likelihood of seeking repeat treatment.

Analysis Methods for the Primary and Key Secondary Endpoints

Non-inferiority hypotheses were conducted for both the primary and key secondary effectiveness endpoints, with the non-inferiority margin of 0.5. The key secondary endpoint data was analyzed for cheeks treated with needles and for cheeks treated with cannula separately. 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).

Participant Demographics

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 ITTS (152 Belotero® Volume (+) group, 50 Comparator group). All 201 treated participants were included in the safety evaluation set (SES). The PPS consisted of 143/152 patients (94.1%) for the Belotero® Volume (+) group and 47/50 patients (94%) for the Comparator group.

Participant demographics (sex, age, ethnicity, race and Fitzpatrick Skin Type) for the 201 participants who received at least one treatment are shown in Table 6. The majority of participants were female and Caucasian. A minimum of 20% of the enrolled participants were Fitzpatrick Skin Type IV, V, and VI. The study population was similar to other HA dermal filler clinical studies for the same indication.

Table 6: 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.

Treatment Characteristics

The injection techniques and instruments (i.e., needle and cannula) used to administer Belotero® Volume (+) and Control treatments in the pivotal clinical study aligned with the literature review data and were similar to the results of previous clinical studies of Comparator and other HA fillers for cheek volume.

Initial treatment was administered by cannula and needle to all participants of the SES in both the Belotero® Volume (+) (n=152; 100.0%) and the Comparator (n=49; 100.0%) group. The median injection volume for initial treatment was 2.00 mL per cheek (range, 0.8 to 3.0 mL) for Belotero® Volume (+) and 2.00 mL (range, 0.6 to 3.0 mL) for the Comparator. Touch-up treatments were performed using cannulas for 81 (53.3%) participants and using needles for 85 (55.9%) participants initially treated with Belotero® Volume (+) group. Touch-up treatments for the Comparator were performed using cannulas for 29 (59.2%) participants and using needles for 37 (75.5%) participants in the safety evaluation set (SES). Injection volumes for touch-up treatments were lower, with median of 1.00 mL per cheek (range, 0.2 to 3.0 mL for Belotero® Volume (+)

and range, 0.1 to 3.0 mL for the Comparator) for all treatments and instrument groups except the Comparator injection using cannula, which had a median volume of 1.20 mL. Repeat treatment with Belotero® Volume (+) was performed on 86 (56.6%) participants using a cannula (n=78; 51.3%) or needle (n=84; 55.3%). Injection volumes for repeat treatment with Belotero® Volume (+) were consistent with touch-up treatments, with a median injection volume of 1.00 mL per cheek (range, 0.1 to 3.0 mL). Overall, the volume of Belotero® Volume (+) or Comparator product varied depending on the participant's cheek volume deficit and treatment goal.

The most common injection techniques performed at any treatment were fanning technique with cannula and serial puncture technique with needle; linear-threading was used practically equally with both instruments. Injection depth was more often supraperiosteal than subcutaneous, though injections to both depths was the most common practice.

Primary Effectiveness Results

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).

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).

The primary analysis (on cheek level) showed the primary effectiveness endpoint was met. This is confirmed by the patient level analysis which showed consistent results for both ITTS and PPS since noninferiority of Belotero® Volume (+) to the Comparator dermal filler was achieved as the upper bound of the 95% confidence intervals for the differences between Belotero® Volume (+) versus Comparator did not exceed the non-inferiority margin of δ=0.5 points (Table 7).

Table 7: Observed Change from Baseline to Week 12 on MCFAS as Assessed by Blinded Evaluator

	Treatment Group MCFAS change[1] (Week 12 - baseline) [Observed Mean Change (observed SD)]		Treatment Difference [observed Difference (95% CI)[2]]
Analysis Set	Belotero® (N = 152 randomized)	Comparator (N = 50 randomized)	(Belotero® - Comparator)
PPS Number of subjects with observed data	N=143 -1.60 (0.757)	N=47 -1.55 (0.753)	-0.05 (-0.30, 0.19)
ITTS Number of subjects with observed data	N=145 -1.60 (0.754)	N=49 -1.53 (0.746)	-0.07 (-0.33, 0.17)

[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.

Key Secondary Effectiveness Results:

As shown in Table 8 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 $\delta = 0.5$ points. Thus, non-inferiority was concluded for both techniques.

Table 8 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	-1.6 (0.78)	-1.5 (0.75)	-0.2 (-0.3,0.0)
NEEDLE	-1.6 (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 (66/143) 46.2% after Belotero® Volume (+) treatment and (16/47) 34.0% 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.

Other Effectiveness Results in the observed ITTS:

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.

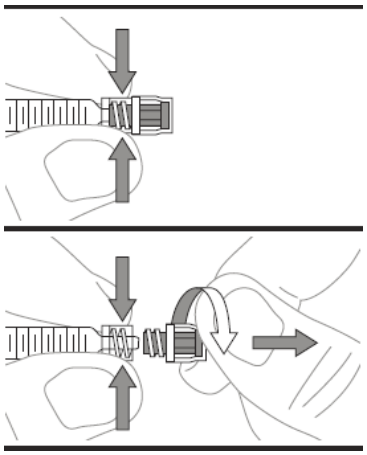
INSTRUCTIONS FOR USE

B. Attach Needle or Cannula to Syringe

To ensure proper needle attachment, use 27G needles provided or a 25G 1 ½" cannula.

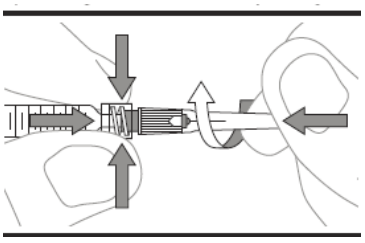
a. Open the needle/cannula packaging to expose the needle/cannula hub. When using cannulas or needles other than the needle(s) provided with Belotero® Volume (+), follow the needle or cannula manufacturer's directions.

b. While firmly gripping the Luer syringe cap, remove it from the distal end of the syringe prior to attaching the needle or cannula.



c. Holding the Luer lock fitting of the syringe, twist the needle/cannula onto the syringe. The

needle/cannula must be tightened securely to the syringe. Do not over-tighten as this may break the needle/cannula and/or dislodge the syringe.



d. Pull off the needle/cannula guard to expose the needle or cannula.

e. Prime the needle/cannula with Belotero® Volume (+) gel.

If excess implant is on the surface of the Luer lock fittings, it will need to be wiped clean with sterile gauze. Slowly push the syringe plunger until the implant material extrudes from the end of the needle/cannula. If leakage is noted at the Luer fitting, it may be necessary to remove the needle/cannula and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle/cannula.

C. Health Care Professional Instructions

1. Belotero® Volume (+) injectable gel is a crosslinked, robust, injectable gel formulation, injected using a 27G ½" or a 25G 1 ½" cannula to volumize and contour the cheek for correction of mid-face volume deficit. Merz Aesthetics® recommends the TSK SteriGlide® 25G 1 ½" cannula.

2. Educational resources are available through Merz Aesthetics®, including training in facial anatomy and vasculature, safe injection techniques, and identification and management of potential adverse events, including vascular complications. Health care professionals may contact Merz Aesthetics® for educational and training resources.

3. Before and after treatment, health care professionals are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing.

4. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

    - Ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines.[2]

    - Identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a hyaluronic acid dermal filler injection.

    - Conducting a basic neurologic examination in the event of an adverse event with central nervous system deficits

5. Prior to treatment, a complete medical history should be obtained, and the patient should

be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration.

6. Patients also should be advised that additional or supplemental implantations may be required to achieve and maintain maximum correction.

7. The patient's soft-tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of volume deficiency. Pre-treatment photographs are recommended.

8. Topical or may be used to manage pain during and after injection.After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be prepped with alcohol or another antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle/cannula.

9. If the needle/cannula is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle/cannula.

10. When using a cannula, an entry point is made in the skin with a sharp needle of appropriate size.

11. After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify the needle is not intravascular.

12. After the first small amount of material has been injected into the patient, wait 3 seconds to allow the lidocaine to take effect before proceeding with the rest of the injection.

13. The injection technique for Belotero® Volume (+) injectable gel, including the angle and orientation of the bevel, the depth (subcutaneous and/or submuscular/supraperiosteal) of injection, and the quantity administered may vary depending on the area being treated. Injection of Belotero® Volume (+) injectable gel too superficially (intradermally), or in large volumes over a small area, may result in visible and persistent lumps and/or discoloration.

14. Linear threading and fanning techniques may be used with a needle or cannula to deliver Belotero® Volume (+) injectable gel to achieve optimal results. Serial puncture may be used with a needle to deliver Belotero® Volume (+) injectable gel to achieve optimal results.

15. With supraperiosteal injections, the number of times the needle passes should be minimized to reduce the risk of bruising. If injecting in the supraperiosteal plane and then withdraw the needle or cannula, it is important to stop injecting before the needle tip reaches a more superficial plane (such as the deep dermis) to prevent material from being placed too superficially in the skin.

16. Correct to one hundred percent (100%) of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.

17. If immediate blanching occurs, the injection should be stopped, and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.[2]

18. The area of lost facial volume should appear lifted by the end of the injection. When injection is completed, the treated site may be gently massaged to mold the product tothe contour of the surrounding tissue and assure that it is evenly distributed and conforms to the contour of the surrounding tissues.

19. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.

20. With patients who have localized swelling, the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to have the patient return to the office for a supplemental or additional treatment. Note: always use a new syringe of Belotero® Volume (+) injectable gel for each return visit; do not save and reuse unfinished Belotero® Volume (+) injectable gel syringes.

21. After the initial treatment, an additional treatment may be necessary to achieve the desired level of correction. The same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as mid-face volume deficit, skin elasticity, and dermal thickness at the treatment site.

22. Patients may experience treatment site responses, which typically resolve within 2 to 4 weeks for treatment in the cheek and the chin. Ice may be applied for a brief period following treatment to minimize swelling and reduce pain.

23. The health care professional should instruct the patient to promptly report any evidence of problems possibly associated with the use of Belotero® Volume (+).

D. Patient Instructions

It is recommended that the following information be shared with patients:

- Within the first 24 hours, patients should avoid strenuous exercise and extensive sun or heat exposure. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the treatment sites.
- If the treated area is swollen, an ice pack may be applied to the site for a short period.
- To report an adverse reaction, phone the report to Merz North America, Inc. at 1-844-469-6379.

HOW SUPPLIED

Belotero® Volume (+) dermal filler is supplied in individual syringes co-packaged with sterile needles, as indicated on the carton. Belotero® Volume (+) can be injected with either a 27G ½"

needle, or a 25G 1 ½" cannula. The cannula is not supplied with Belotero® Volume (+). The volume in each syringe is stated on the syringe label and on the carton. The contents of the syringe are sterile and non-pyrogenic. Do not resterilize. Do not use if package is open or damaged. In the event that the package is open or damaged, contact Merz Ax Customer Solutions via telephone at 844-469-6379 or email complaints2@merz.com.

STORAGE

Belotero® Volume (+) must be used prior to the expiration date printed on the carton label. Store at room temperature (up to 25°C/77°F). DO NOT FREEZE.

Belotero® Volume (+) has a clear colorless (transparent) appearance. In the event that the syringe contains material that is not clear, do not use the syringe; Merz Ax Customer Solutions 844-469-6379 or email complaints2@merz.com.

To place an order, contact Merz Ax Customer Solutions, Inc. at 1-844-469-6379.

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Various features of BELOTERO® VOLUME (+) are covered by U.S. patents identified at https://merzaesthetics.com/patents/. Other U.S. and International patents to which Anteis S.A. has rights are issued, published, or pending.

IN00241-00/FEB 2025

[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.[2] Jones DH, Fitzgerald R, Cox SE, et al. Preventing and Treating Adverse Events of Injectable Fillers: Evidence-Based Recommendations From the American Society for Dermatologic Surgery Multidisciplinary Task Force. *Dermatol Surg*. 2021;47(2):214-226. doi:10.1097/DSS.0000000000002921