Belotero® Intense (+) Lidocaine Dermal Filler

Prescribing Information and Instructions for Use

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Belotero® Intense (+) 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. For Prescription Use Only.

READ THE FOLLOWING INFORMATION THOROUGHLY BEFORE USING PRODUCT

DEVICE DESCRIPTION

Belotero® Intense (+) Lidocaine ("Belotero® Intense (+)") 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 25.5 mg/mL with 3 mg/mL lidocaine in a physiological phosphate buffer. Belotero® Intense (+) is supplied in a prefilled syringe co-packaged with two sterile 27G 1/2" needles.

INTENDED USE/INDICATIONS

Belotero® Intense (+) Lidocaine is indicated for submucosal and/or subcutaneous implantation for lip augmentation in adults over the age of 21.

CONTRAINDICATIONS

- Belotero® Intense (+) is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history of multiple severe allergies.
- Belotero® Intense (+) contains lidocaine and is contraindicated for patients with known hypersensitivity to lidocaine or anesthetics of the amide type.
- Belotero® Intense (+) 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® Intense (+) 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 Instructions16).

- 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 injection site reactions consist mainly of short-term inflammatory symptoms starting early after treatment and lasting 15-28 days. Refer to the ADVERSE EVENTS section for details.
- Do not use in a patient with a history of developing scars or keloids.

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® Intense (+) is packaged for single-patient use. Do not resterilize. 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 lips with Belotero® Intense (+) 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® Intense (+) 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® Intense (+) for use during pregnancy or in breastfeeding females has not been established.
- Injections of Belotero® Intense (+) into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Belotero® Intense (+) 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 may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.

- Belotero® Intense (+) 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.

- The patient should be informed that they should minimize exposure of the treated area to excessive sun or heat, UV lamp exposure, Turkish baths, and extreme cold weather until any initial swelling and redness have resolved and puncture sites have healed.

- Laser treatment, chemical peeling, or any other procedure based on active dermal response performed after treatment with Belotero® Intense (+) may increase the risk of an inflammatory reaction at the injection site. Similarly, the administration of Belotero® Intense (+) before the skin has healed completely after such a procedure may also increase the risk of inflammatory reactions.

ADVERSE EVENTS

A. Pivotal Study of Belotero® Intense (+) for Lip Augmentation

In the randomized, evaluator blinded, comparator-controlled clinical study to evaluate the safety and effectiveness of Belotero® Intense (+) for lip augmentation versus a comparator product with similar indications for use, participants were randomized and treated with either Belotero® Intense (+) (n=165) or the control (n=55) product.

Participants used electronic diary (“eDiary”) forms to record specific signs and symptoms of experienced during the first 28 days after initial treatment, touch-up treatment (if performed), and repeat treatment (if performed). Participants were instructed to rate each common treatment response (CTR) listed on the diary as “Mild,” “Moderate,” “Severe,” or “None.”

The severity and duration of CTRs reported by >5% of participants in either treatment group who completed post-treatment eDiaries after initial treatment, touch-up treatment (if performed), and repeat treatment (if performed) are summarized in Table 1 through Table 6. The majority of CTRs were mild or moderate in intensity and resolved within 15-28 days. The incidences, severity and duration of CTRs reported after the touch-up and repeat treatments with Belotero® Intense (+) were generally the similar to the initial treatment.

Table 1: Common Treatment Site Responses by Maximum Severity After Initial Treatment Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) (N = 165 / M = 164)				Comparator (N = 55 / M = 55)			
	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	88.4% (145/164)	24.4% (40/164)	59.1% (97/164)	4.9% (8/164)	80.0% (44/55)	23.6% (13/55)	45.5% (25/55)	10.9% (6/55)
Upper Lip								
Swelling	83.5% (137/164)	37.2% (61/164)	43.9% (72/164)	2.4% (4/164)	76.4% (42/55)	30.9% (17/55)	36.4% (20/55)	9.1% (5/55)
Lumps / Bumps	72.6% (119/164)	47.6% (78/164)	24.4% (40/164)	0.6% (1/164)	56.4% (31/55)	34.5% (19/55)	20.0% (11/55)	1.8% (1/55)
Bruising	72.0% (118/164)	40.2% (66/164)	29.3% (48/164)	2.4% (4/164)	49.1% (27/55)	32.7% (18/55)	14.5% (8/55)	1.8% (1/55)
Soreness	70.1% (115/164)	54.3% (89/164)	15.2% (25/164)	0.6% (1/164)	61.8% (34/55)	38.2% (21/55)	21.8% (12/55)	1.8% (1/55)
Redness	67.7% (111/164)	52.4% (86/164)	14.0% (23/164)	1.2% (2/164)	58.2% (32/55)	41.8% (23/55)	16.4% (9/55)	0.0% (0/55)
Pain / Tenderness	67.1% (110/164)	49.4% (81/164)	16.5% (27/164)	1.2% (2/164)	61.8% (34/55)	36.4% (20/55)	23.6% (13/55)	1.8% (1/55)
Firmness / Hardness	65.2% (107/164)	42.7% (70/164)	22.0% (36/164)	0.6% (1/164)	60.0% (33/55)	38.2% (21/55)	18.2% (10/55)	3.6% (2/55)
Discoloration	28.7% (47/164)	22.6% (37/164)	5.5% (9/164)	0.6% (1/164)	18.2% (10/55)	16.4% (9/55)	1.8% (1/55)	0.0% (0/55)
Burning / Stinging	23.8% (39/164)	20.7% (34/164)	3.0% (5/164)	0.0% (0/164)	27.3% (15/55)	18.2% (10/55)	9.1% (5/55)	0.0% (0/55)
Itching	14.0% (23/164)	14.0% (23/164)	0.0% (0/164)	0.0% (0/164)	20.0% (11/55)	16.4% (9/55)	3.6% (2/55)	0.0% (0/55)
Lower Lip								
Swelling	77.4% (127/164)	37.8% (62/164)	37.8% (62/164)	1.8% (3/164)	76.4% (42/55)	38.2% (21/55)	36.4% (20/55)	1.8% (1/55)
Lumps / Bumps	70.1% (115/164)	47.6% (78/164)	21.3% (35/164)	1.2% (2/164)	58.2% (32/55)	40.0% (22/55)	18.2% (10/55)	0.0% (0/55)
Bruising	67.7% (111/164)	38.4% (63/164)	26.8% (44/164)	2.4% (4/164)	56.4% (31/55)	38.2% (21/55)	18.2% (10/55)	0.0% (0/55)
Pain / Tenderness	65.9% (108/164)	50.0% (82/164)	15.2% (25/164)	0.6% (1/164)	61.8% (34/55)	34.5% (19/55)	25.5% (14/55)	1.8% (1/55)
Firmness / Hardness	65.2% (107/164)	46.3.% (76/164)	18.3% (30/164)	0.6% (1/164)	58.2% (32/55)	36.4% (20/55)	20.0% (11/55)	1.8% (1/55)
Soreness	61.6% (101/164)	47.6% (78/164)	13.4% (22/164)	0.6% (1/164)	63.6% (35/55)	40.0% (22/55)	21.8% (12/55)	1.8% (1/55)
Redness	59.1%	44.5%	12.8%	1.8%	54.5%	32.7%	21.8%	0.0%

Common Treatment Response	Belotero® Intense (+) (N = 165 / M = 164)				Comparator (N = 55 / M = 55)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
	(97/164)	(73/164)	(21/164)	(3/164)	(30/55)	(18/55)	(12/55)	(0/55)
Discoloration	29.9% (49/164)	25.6% (42/164)	3.7% (6/164)	0.6% (1/164)	20.0% (11/55)	16.4% (9/55)	3.6% (2/55)	0.0% (0/55)
Burning / Stinging	22.0% (36/164)	18.3% (30/164)	3.7% (6/164)	0.0% (0/164)	34.5% (19/55)	23.6% (13/55)	10.9% (6/55)	0.0% (0/55)
Itching	12.8% (21/164)	12.8% (21/164)	0.0% (0/164)	0.0% (0/164)	21.8% (12/55)	18.2% (10/55)	3.6% (2/55)	0.0% (0/55)

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

Table 2: Common Treatment Site Responses by Maximum Severity After Applicable Touch-up Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) (N = 117 / M = 117)				Comparator (N = 41 / M = 41)			
	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	82.9% (97/117)	39.3% (46/117)	40.2% (47/117)	3.4% (4/117)	78.0% (32/41)	17.1% (7/41)	53.7% (22/41)	7.3% (3/41)
Upper Lip								
Swelling	71.8% (84/117)	47.9% (56/117)	20.5% (24/117)	3.4% (4/117)	75.6% (31/41)	29.3% (12/41)	39.0% (16/41)	7.3% (3/41)
Lumps / Bumps	57.3% (67/117)	38.5% (45/117)	18.8% (22/117)	0.0% (0/117)	58.5% (24/41)	43.9% (18/41)	14.6% (6/41)	0.0% (0/41)
Bruising	57.3% (67/117)	45.3% (53/117)	12.0% (14/117)	0.0% (0/117)	46.3% (19/41)	31.7% (13/41)	14.6% (6/41)	0.0% (0/41)
Pain / Tenderness	57.3% (67/117)	47.0% (55/117)	10.3% (12/117)	0.0% (0/117)	73.2% (30/41)	56.1% (23/41)	17.1% (7/41)	0.0% (0/41)
Firmness / Hardness	54.7% (64/117)	41.9% (49/117)	12.8% (15/117)	0.0% (0/117)	68.3% (28/41)	48.8% (20/41)	19.5% (8/41)	0.0% (0/41)
Soreness	53.0% (62/117)	42.7% (50/117)	10.3% (12/117)	0.0% (0/117)	70.7% (29/41)	56.1% (23/41)	14.6% (6/41)	0.0% (0/41)
Redness	43.6% (51/117)	29.9% (35/117)	13.7% (16/117)	0.0% (0/117)	58.5% (24/41)	39.0% (16/41)	19.5% (8/41)	0.0% (0/41)
Discoloration	17.9% (21/117)	17.1% (20/117)	0.9% (1/117)	0.0% (0/117)	17.1% (7/41)	12.2% (5/41)	4.9% (2/41)	0.0% (0/41)
Burning / Stinging	16.2% (19/117)	11.1% (13/117)	5.1% (6/117)	0.0% (0/117)	31.2% (13/41)	29.3% (12/41)	2.4% (1/41)	0.0% (0/41)
Itching	7.7% (9/117)	6.0% (7/117)	1.7% (2/117)	0.0% (0/117)	12.2% (5/41)	12.2% (5/41)	0.0% (0/41)	0.0% (0/41)
Lower Lip								
Firmness / Hardness	48.7% (57/117)	35.9% (42/117)	12.8% (15/117)	0.0% (0/117)	65.9% (27/41)	39.0% (16/41)	26.8% (11/41)	0.0% (0/41)
Lumps / Bumps	47.9% (56/117)	32.5% (38/117)	15.4% (18/117)	0.0% (0/117)	48.8% (20/41)	24.4% (10/41)	24.4% (10/41)	0.0% (0/41)
Pain / Tenderness	47.9% (56/117)	38.5% (45/117)	9.4% (11/117)	0.0% (0/117)	73.2% (30/41)	56.1% (23/41)	17.1% (7/41)	0.0% (0/41)

Common Treatment Response	Belotero® Intense (+) (N = 117 / M = 117)				Comparator (N = 41 / M = 41)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Bruising	47.0% (55/117)	35.0% (41/117)	12.0% (14/117)	0.0% (0/117)	53.7% (22/41)	29.3% (12/41)	24.4% (10/41)	0.0% (0/41)
Soreness	46.2% (54/117)	36.8% (43/117)	9.4% (11/117)	0.0% (0/117)	65.9% (27/41)	43.9% (18/41)	22.0% (9/41)	0.0% (0/41)
Swelling	39.3% (71/117)	39.3% (46/117)	20.5% (24/117)	0.9% (1/117)	75.6% (31/41)	34.1% (14/41)	36.6% (15/41)	4.9% (2/41)
Redness	39.3% (46/117)	30.8% (36/117)	8.5% (10/117)	0.0% (0/117)	53.7% (22/41)	41.5% (17/41)	12.2% (5/41)	0.0% (0/41)
Discoloration	14.5% (17/117)	12.8% (15/117)	1.7% (2/117)	0.0% (0/117)	17.1% (7/41)	14.6% (6/41)	2.4% (1/41)	0.0% (0/41)
Burning / Stinging	14.5% (17/117)	12.0% (14/117)	2.6% (3/117)	0.0% (0/117)	26.2% (11/41)	22.0% (9/41)	4.9% (2/41)	0.0% (0/41)
Itching	4.3% (5/117)	2.6% (3/117)	1.7% (2/117)	0.0% (0/117)	9.8% (4/41)	9.8% (4/41)	0.0% (0/41)	0.0% (0/41)

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

Table 3: Common Treatment Site Responses by Maximum Severity After Optional Retreatment Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) (N = 116 / M = 114)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Overall	71.9% (82/114)	29.8% (34/114)	38.6% (44/114)	3.5% (4/114)
Upper Lip				
Swelling	67.5% (77/114)	40.4% (46/114)	36.3% (30/114)	0.9% (1/114)
Firmness / Hardness	60.5% (69/114)	42.1% (48/114)	17.5% (20/114)	0.9% (1/114)
Pain / Tenderness	56.1% (64/114)	44.7% (51/114)	11.4% (13/114)	0.0% (0/114)
Soreness	55.3% (63/114)	45.6% (52/114)	9.6% (11/114)	0.0% (0/114)
Bruising	54.4% (62/114)	30.7% (35/114)	22.8% (26/114)	0.9% (1/114)
Lumps / Bumps	54.4% (62/114)	43.0% (49/114)	11.4% (13/114)	0.0% (0/114)
Redness	52.6% (60/114)	37.7% (43/114)	14.9% (17/114)	0.0% (0/114)
Burning / Stinging	17.5% (20/114)	13.2% (15/114)	3.5% (4/114)	0.9% (1/114)
Discoloration	15.8% (18/114)	13.2% (15/114)	2.6% (3/114)	0.0% (0/114)
Itching	10.5% (12/114)	8.8% (10/114)	1.8% (2/114)	0.0% (0/114)

Common Treatment Response	Belotero® Intense (+) (N = 116 / M = 114)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Lower Lip				
Swelling	60.5% (69/114)	41.2% (47/114)	18.4% (21/114)	0.9% (1/114)
Firmness / Hardness	53.5% (61/114)	41.2% (47/114)	11.4% (13/114)	0.9% (1/114)
Pain / Tenderness	50.9% (58/114)	41.2% (47/114)	9.6% (11/114)	0.0% (0/114)
Soreness	50.9% (58/114)	43.0% (49/114)	7.9% (9/114)	0.0% (0/114)
Bruising	50.0% (57/114)	32.5% (37/114)	17.5% (20/114)	0.0% (0/114)
Lumps / Bumps	49.1% (56/114)	36.8% (42/114)	12.3% (14/114)	0.0% (0/114)
Redness	43.0% (49/114)	34.2% (39/114)	8.8% (10/114)	0.0% (0/114)
Burning / Stinging	18.4% (21/114)	15.8% (18/114)	2.6% (3/114)	0.0% (0/114)
Discoloration	14.0% (16/114)	10.5% (12/114)	2.6% (3/114)	0.9% (1/114)
Itching	6.1% (7/114)	5.3% (6/114)	0.9% (1/114)	0.0% (0/114)

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

Table 4: Common Treatment Site Responses by Maximum Duration After Initial Treatment Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) (N = 165 / M = 164)					Comparator (N = 55 / M = 55)				
	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	88.4% (145/164)	0.0% (0/164)	1.8% (3/164)	2.4% (4/164)	84.1% (138/164)	80.0% (44/55)	0.0% (0/55)	1.8% (1/55)	0.0% (0/55)	78.2% (43/55)
Upper Lip										
Swelling	83.5% (137/164)	13.4% (22/164)	28.0% (46/164)	13.4% (22/164)	28.7% (47/164)	76.4% (42/55)	14.5% (8/55)	25.5% (14/55)	1.8% (1/55)	34.5% (19/55)
Lumps / Bumps	72.6% (119/164)	9.1% (15/164)	4.9% (8/164)	5.5% (9/164)	53.0% (87/164)	56.4% (31/55)	10.9% (6/55)	9.1% (5/55)	0.0% (0/55)	36.4% (20/55)
Bruising	72.0% (118/164)	6.7% (11/164)	28.0% (46/164)	20.1% (33/164)	17.1% (28/164)	49.1% (27/55)	14.5% (8/55)	16.4% (9/55)	1.8% (1/55)	16.4% (9/55)
Soreness	70.1% (115/164)	23.2% (38/164)	12.8% (21/164)	15.2% (25/164)	18.9% (31/164)	61.8% (34/55)	21.8% (12/55)	18.2% (10/55)	3.6% (2/55)	18.2% (10/55)
Redness	67.7% (111/164)	27.4% (45/164)	16.5% (27/164)	11.0% (18/164)	12.8% (21/164)	58.2% (32/55)	20.0% (11/55)	18.2% (10/55)	1.8% (1/55)	18.2% (10/55)
Pain / Tenderness	67.1% (110/164)	15.2% (25/164)	16.5% (27/164)	12.8% (21/164)	22.6% (37/164)	61.8% (34/55)	20.0% (11/55)	18.2% (10/55)	1.8% (1/55)	21.8% (12/55)
Firmness / Hardness	65.2% (107/164)	9.8% (16/164)	11.6% (19/164)	14.6% (24/164)	29.3% (48/164)	60.0% (33/55)	18.2% (10/55)	7.3% (4/55)	7.3% (4/55)	27.3% (15/55)

Discoloration	28.7% (47/164)	11.0% (18/164)	9.1% (15/164)	3.0% (5/164)	5.5% (9/164)	18.2% (10/55)	5.5% (3/55)	5.5% (3/55)	0.0% (0/55)	7.3% (4/55)
Burning / Stinging	23.8% (39/164)	15.2.% (25/164)	3.0% (5/164)	1.8% (3/164)	3.7% (6/164)	27.3% (15/55)	18.2% (10/55)	1.8% (1/55)	0.0% (0/55)	7.3% (4/55)
Itching	14.0% (23/164)	7.9% (13/164)	1.8% (3/164)	1.2% (2/164)	3.0% (5/164)	20.0% (11/55)	5.5% (3/55)	3.6% (2/55)	0.0% (0/55)	10.9% (6/55)
Lower Lip										
Swelling	77.4% (127/164)	10.4% (17/164)	26.2% (43/164)	17.1% (28/164)	23.8% (39/164)	76.4% (42/55)	20.0% (11/55)	16.4% (9/55)	3.6% (2/55)	36.4% (20/55)
Lumps / Bumps	70.1% (115/164)	11.6% (19/164)	5.5% (9/164)	5.5% (9/164)	47.6% (78/164)	58.2% (32/55)	12.7% (7/55)	5.5% (3/55)	1.8% (1/55)	38.2% (21/55)
Bruising	67.7% (111/164)	10.4% (17/164)	25.0% (41/164)	16.5% (27/164)	15.9% (26/164)	56.4% (31/55)	9.1% (5/55)	18.2% (10/55)	3.6% (2/55)	25.5% (14/55)
Pain / Tenderness	65.9% (108/164)	18.9% (31/164)	14.6% (24/164)	16.5% (27/164)	15.9% (26/164)	61.8% (34/55)	12.7% (7/55)	12.7% (7/55)	9.1% (5/55)	27.3% (15/55)
Firmness / Hardness	65.2% (107/164)	16.5% (27/164)	9.8% (16/164)	15.2% (25/164)	23.8% (39/164)	58.2% (32/55)	18.2% (10/55)	5.5% (3/55)	5.5% (3/55)	29.1% (16/55)
Soreness	61.6% (101/164)	16.5% (27/164)	14.6% (24/164)	17.1% (28/164)	13.4% (22/164)	63.6% (35/55)	12.7% (7/55)	16.4% (9/55)	9.1% (5/55)	25.5% (14/55)
Redness	59.1% (97/164)	23.8% (39/164)	13.4% (22/164)	12.2% (20/164)	9.8% (16/164)	54.5% (30/55)	16.4% (9/55)	18.2% (10/55)	1.8% (1/55)	18.2% (10/55)
Discoloration	29.9% (49/164)	15.9% (26/164)	6.1% (10/164)	4.9% (8/164)	3.0% (5/164)	20.0% (11/55)	7.3% (4/55)	5.5% (3/55)	0.0% (0/55)	7.3% (4/55)
Burning / Stinging	22.0% (36/164)	14.0% (23/164)	3.7% (6/164)	1.8% (3/164)	2.4% (4/164)	34.5% (19/55)	21.8% (12/55)	7.3% (4/55)	0.0% (0/55)	5.5% (3/55)
Itching	12.8% (21/164)	7.9% (13/164)	1.2% (2/164)	0.6% (1/164)	3.0% (5/164)	21.8% (12/55)	10.9% (6/55)	1.8% (1/55)	0.0% (0/55)	9.1% (5/55)

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

Table 5: Common Treatment Site Responses by Maximum Duration After Applicable Touch-Up Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) (N = 117 / M = 117)					Comparator (N = 41 / M = 41)				
	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	82.9% (97/117)	0.0% (0/117)	1.7% (2/117)	3.4% (4/117)	77.8% (91/117)	78.5% (32/41)	0.0% (0/41)	2.4% (1/41)	0.0% (0/41)	75.6% (31/41)
Upper Lip										
Bruising	82.9% (97/117)	14.5% (17/117)	16.2% (19/117)	11.1% (13/117)	15.4% (18/117)	46.3% (19/41)	7.3% (3/41)	7.3% (3/41)	7.3% (3/41)	24.4% (10/41)
Swelling	71.8% (84/117)	17.1% (20/117)	21.4% (25/117)	8.5% (10/117)	24.8% (29/117)	75.6% (31/41)	12.2% (5/41)	19.5% (8/41)	7.3% (3/41)	36.6% (15/41)
Lumps / Bumps	57.3% (67/117)	10.3% (12/117)	6.0% (7/117)	4.3% (5117)	36.8% (43/117)	58.5% (24/41)	17.1% (7/41)	7.3% (3/41)	2.4% (1/41)	31.7% (13/41)
Pain / Tenderness	57.3% (67/117)	17.9% (21/117)	10.3% (12/117)	8.5% (10/117)	20.5% (24/117)	73.2% (30/41)	31.7% (13/41)	7.3% (3/41)	12.2% (5/41)	22.0% (9/41)
Firmness / Hardness	54.7% (64/117)	12.0% (14/117)	11.1% (13/117)	6.0% (7/117)	25.6% (30/117)	68.3% (28/41)	22.2% (9/41)	4.9% (2/41)	4.9% (2/41)	36.6% (15/41)
Soreness	53.0%	16.2%	6.8%	6.8%	23.1%	70.7%	34.1%	7.3%	4.9%	24.4%

	(62/117)	(19/117)	(8/117)	(8/117)	(27/117)	(29/41)	(14/41)	(3/41)	(2/41)	(10/41)
Redness	43.6% (51/117)	19.7% (23/117)	8.5% (10/117)	6.0% (7/117)	9.4% (11/117)	58.5% (24/41)	31.7% (13/41)	4.9% (2/41)	2.4% (1/41)	19.5% (8/41)
Discoloration	17.9% (21/117)	9.4% (11/117)	2.6% (3/117)	1.7% (2/117)	4.3% (5/117)	17.1% (7/41)	4.9% (2/41)	2.4% (1/41)	0.0% (0/41)	9.8% (4/41)
Burning / Stinging	16.2% (19/117)	8.5% (10/117)	0.9% (1/117)	2.6% (3/117)	4.3% (5/117)	31.7% (13/41)	24.4% (10/41)	2.4% (1/41)	0.0% (0/41)	4.9% (2/41)
Itching	7.7% (9/117)	3.4% (4/117)	0.9% (1/117)	0.9% (1/117)	2.6% (3/117)	12.2% (5/41)	4.9% (2/41)	2.4% (1/41)	0.0% (0/41)	4.9% (2/41)
Lower Lip										
Swelling	60.7% (71/117)	12.8% (15/117)	15.4% (18/117)	14.5% (17/117)	17.9% (21/117)	75.6% (31/41)	9.8% (4/41)	24.4% (10/41)	4.9% (2/41)	36.6% (15/41)
Firmness / Hardness	49.6% (58/117)	7.7% (9/117)	6.8% (9/117)	6.0% (7/117)	28.2% (33/117)	65.9% (27/41)	17.1% (7/41)	4.9% (2/41)	2.4% (1/41)	41.5% (17/41)
Lumps / Bumps	47.9% (56/117)	6.0% (7/117)	4.3% (5/117)	6.0% (7/117)	31.6% (37/117)	48.8% (20/41)	2.4% (1/41)	7.3% (3/41)	0.0% (0/41)	39.0% (16/41)
Pain / Tenderness	47.9% (56/117)	16.2% (19/117)	12.0% (14/117)	4.3% (5/117)	15.4% (18/117)	73.2% (30/41)	26.8% (11/41)	9.8% (4/41)	9.8% (4/41)	26.8% (11/41)
Bruising	47.0% (55/117)	12.8% (15/117)	8.5% (10/117)	11.1% (13/117)	14.5% (17/117)	53.7% (22/41)	14.6% (6/41)	9.8% (4/41)	4.9% (2/41)	24.4% (10/41)
Soreness	46.2% (5/117)	17.9% (21/117)	6.8% (8/117)	7.7% (9/117)	13.7% (16/117)	65.9% (27/41)	22.0% (9/41)	17.1% (7/41)	2.4% (1/41)	24.4% (10/41)
Redness	39.3% (46/117)	13.7% (16/117)	8.5% (10/117)	4.3% (5/117)	12.8% (15/117)	53.7% (22/41)	29.3% (12/41)	7.3% (3/41)	0.0% (0/41)	17.1% (7/41)
Discoloration	14.5% (17/117)	7.7% (9/117)	2.6% (3/117)	1.7% (2/117)	2.6% (3/117)	17.1% (7/41)	4.9% (2/41)	4.9% (2/41)	0.0% (0/41)	7.3% (3/41)
Burning / Stinging	14.5% (17/117)	8.5% (10/117)	1.7% (2/117)	0.9% (1/117)	3.4% (4/117)	26.8% (11/41)	22.0% (9/41)	2.4% (1/41)	0.0% (0/41)	2.4% (1/41)
Itching	4.3% (5/117)	1.7% (2/117)	0.9% (1/117)	0.0% (0/117)	1.7% (2/117)	9.8% (4/41)	4.9% (2/41)	2.4% (1/41)	0.0% (0/41)	2.4% (1/41)

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

Table 6: Common Treatment Site Responses by Maximum Duration After Optional Retreatment Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) (N = 116 / M = 114)				
	Total % (n/M)	1-3 Days % (n/M)	4-7 Days % (n/M)	8-14 Days % (n/M)	15-28 Days % (n/M)
Overall	71.9% (82/114)	0.0% (0/114)	0.0% (0/114)	0.0% (0/114)	71.9% (82/114)
Upper Lip					
Swelling	67.5% (77/114)	10.5% (12/114)	20.2% (23/114)	12.3% (14/114)	24.6% (28/114)
Lumps / Bumps	54.4% (62/114)	7.9% (9/114)	6.1% (7/114)	4.4% (5/114)	36.0% (41/114)
Bruising	54.4% (62/114)	7.0% (8/114)	14.0% (16/114)	13.2% (15/114)	20.2% (23/114)
Soreness	55.3% (63/114)	13.2% (15/114)	13.2% (15/114)	11.4% (13/114)	17.5% (20/114)
Redness	52.6%	22.8%	11.4%	7.0%	11.4%

	(60/114)	(26/114)	(13/114)	(8/114)	(13/114)
Pain / Tenderness	56.1% (64/114)	14.9% (17/114)	13.2% (15/114)	11.4% (13/114)	16.7% (19/114)
Firmness / Hardness	60.5% (69/114)	10.5% (12/114)	7.0% (8/114)	12.3% (14/114)	30.7% (35/114)
Discoloration	15.8% (18/114)	8.8% (10/114)	0.9% (1/114)	2.6% (3/114)	3.5% (4/114)
Burning / Stinging	17.5% (20/114)	9.6% (11/114)	2.6% (3/114)	2.6% (3/114)	2.6% (3/114)
Itching	10.5% (12/114)	5.3% (6/114)	2.6% (3/114)	0.9% (1/114)	1.8% (2/114)
Lower Lip					
Swelling	60.5% (69/114)	12.3% (14/114)	18.4% (21/114)	12.3% (14/114)	17.5% (20/114)
Lumps / Bumps	49.1% (56/114)	12.3% (14/114)	4.4% (5/114)	7.0% (8/114)	25.4% (29/114)
Bruising	50.0% (57/114)	8.8% (10/114)	20.2% (23/114)	7.9% (9/114)	13.2% (15/114)
Pain / Tenderness	50.9% (58/114)	17.5% (20/114)	7.9% (9/114)	10.5% (12/114)	14.9% (17/114)
Firmness / Hardness	53.5% (61/114)	9.6% (11/114)	8.8% (10/114)	9.6% (11/114)	25.4% (29/114)
Soreness	50.9% (58/114)	14.9% (17/114)	12.3% (14/114)	9.6% (11/114)	14.0% (16/114)
Redness	43.0% (49/114)	17.5% (20/114)	9.6% (11/114)	6.1% (7/114)	9.6% (11/114)
Discoloration	14.0% (16/114)	5.3% (6/114)	1.8% (2/114)	3.5% (4/114)	3.5% (4/114)
Burning / Stinging	18.4% (21/114)	10.5% (12/114)	1.8% (2/114)	2.6% (3/114)	3.5% (4/114)
Itching	6.1% (7/114)	1.8% (2/114)	2.6% (3/114)	0.0% (0/114)	1.8% (2/114)

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

Treatment-Related Treatment Emergent Adverse Events

Adverse Events (AEs) were also reported by the Treating Investigators at follow-up visits. 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® Intense (+) or comparator group. An AE was considered to be related to the device or the injection procedure (i.e., "treatment-related") if a causal relationship between the device or the injection procedure and the AE was at least reasonably possible. CTRs that lasted beyond 28 days were considered AEs.

After initial treatment (or touch-up treatment if performed), a total of 73 treatment-related TEAEs were reported in 17.0% (28/165) of participants treated with Belotero® Intense (+). Thirty (30) treatment-related TEAEs were reported in 14.5% (8/55) of participants treated with the comparator product. After repeat treatment in the Belotero® Intense (+) group, a total of 38 treatment-related TEAEs were reported in 11.2% (13/116) of participants. Related TEAEs occurring in > 5% of treated participants in either treatment group are summarized in Table 7. Overall, related TEAEs

were typically mild in intensity, and all resolved without sequelae. There were no serious treatment-related adverse events reported.

Table 7: Treatment-Related TEAE > 5% of Treated Participants for Lip Augmentation by Adverse Event Preferred Term

Adverse Event	Belotero® Intense (+) Initial Treatment (N=165)		Comparator Initial Treatment (N=55)		Belotero® Intense (+) Repeat Treatment (N=116)	
	Participants % (n/N)	Number of Events	Participants % (n/N)	Number of Events	Participants % (n/N)	Number of Events
Overall	17.0% (28/165)	73	14.5% (8/55)	30	11.2% (13/116)	38
Injection site mass	14.5% (24/165)	44	10.9% (6/55)	14	8.6% (10/116)	15
Injection site induration	4.2% (7/165)	12	7.3% (4/55)	7	4.3% (5/116)	9

N = number of participants in the treatment group and analysis set, n = number of participants in respective subset, Percentages are based on N.
A participant with more than one treatment-related TEAE within an Adverse Event was counted once.

Common treatment-related TEAEs included injection site mass, induration and swelling. Other related TEAEs reported by ≤ 5% of participants after initial (or touch-up treatment) Belotero® Intense (+) treatment included (in order of number of participants who experienced the event): injection site swelling, pain, discoloration, bruising, erythema, edema, and oral herpes. After repeat treatment, treatment-related TEAEs occurring in ≤ 5% of participants included (in order of number of participants experiences the event): injection site pain, swelling, bruising, discoloration, and erythema. Related TEAEs generally resolved in an average of 43.5 days for participants treated with Belotero® Intense (+) and in an average of 50.6 days for participants treated with the comparator group. All treatment-related TEAEs were resolved by the end of the study.

Safety Subgroup Analyses

Subgroup analyses were completed to analyze treatment-related AEs by Fitzpatrick Skin Phototype, age, gender, race and ethnicity. No increased safety risks were observed for any specific groups.

Treatment-Related Delayed-Onset TEAEs

In the clinical study, 4 participants experienced treatment related TEAEs > 21 days after Belotero® Intense (+) initial treatment or touch-up treatment. These delayed onset reactions included: injection site bumps (mass) (1.8%, 3/165 participants); induration (0.6%, 1/165 participants); edema (0.6%, 1/165 participants); and pain (0.6%, 1/165 participants). Five participants experienced delayed-onset treatment-related TEAEs after repeat treatment with Belotero® Intense (+), including: injection site bumps (mass) (3.4%, 4/165 participants); induration (1.7%, 2/165 participants); pain (1.7%, 2/165 participants); discoloration (0.9%, 1/165 participants); and erythema (0.9%, 1/165 participants). Delayed-onset TEAEs were mild in intensity and resolved without sequelae. Generally, the time to onset ranged from 23 to 29 days after the last treatment (initial, touch-up or repeat), with only one case of edema with a time of onset of 102 days. This case was mild and resolved within 17 days.

Other Safety Assessments

Vision safety assessments were performed at the screening visit and throughout the study. All abnormal visual acuity results were evaluated by the investigator and determined to be non-serious and not related to treatment with either Belotero® Intense (+) or the comparator.

Lip safety assessments such as functional features of the lips, lip sensitivity and sensation, lip symmetry, and movement were evaluated at the screening visit and throughout the study. None of the lip assessments were remarkable or presented any safety concerns after treatment with either Belotero® Intense (+) or the comparator.

Treating investigators conducted a neurological exam 30 minutes after each treatment visit. No abnormal neurological results were reported during the study.

EFFECTIVENESS

A. Pivotal Study of Belotero® Intense (+) for Lip Augmentation

Study Design

A multicenter, evaluator-blinded, randomized, comparator-controlled pivotal clinical study was conducted to evaluate the safety and effectiveness of Belotero® Intense (+) versus an FDA-approved comparator product for injection into the lips. The control group was a legally marketed alternative with similar indications for use. A total of 220 participants were randomized and received treatment with either Belotero® Intense (+) (n=165) or comparator (n=55) at the outset of the study. An optional touch-up treatment was performed approximately 4 weeks after the initial treatment, if deemed necessary, to achieve optimal correction.

The follow up period consisted of safety and effectiveness in-clinic visits at 2, 4, 8, 16, 24, 36, and 48 weeks after the last treatment. Participants randomized to initial treatment with Belotero® Intense (+) treatment were eligible for repeat treatment, with post repeat treatment follow-up period for a total of 12 weeks.

Study Endpoints

The primary effectiveness measure for the study was the analysis of non-inferiority of Belotero® Intense (+) relative to the comparator product based on the mean change from baseline to Week 8 in mean lip fullness according to blinded evaluator assessment using the validated[1] 5-point Merz Lip Fullness Assessment Scale (MLFAS). The co-primary effectiveness endpoint was the responder rate at Week 8 according to the MLFAS, as assessed live by blinded evaluator. Responders were defined as participants with ≥ 1-point MLFAS improvement compared to baseline on treated lip(s).

Secondary measures included assessments by both the investigator and the participant of the global aesthetic improvement at Week 8 using the Global Aesthetic Improvement Scale (GAIS), and the participants' assessments at Week 8 using the *Satisfaction with Lips* module of the validated FACE-Q questionnaire. Responder rates at Week 8 using MLFAS as assessed by 3 blinded

independent panel raters (IPR) using participant photographs were also evaluated as a secondary effectiveness endpoint.

Additional effectiveness measures included the blinded evaluator's assessments of participants' average of treated lip fullness using MLFAS, and upper and lower lip fullness. Time course of participants' satisfaction with lip treatment using the *Satisfaction with Outcomes* and *Psychological Function* modules of the FACE-Q. Participants' self-perception of lip hydration and appearance using, as well as the par assessments of willingness to undergo treatment again.

Study endpoints relating to product safety are discussed in the ADVERSE EVENTS section.

Participant Demographics

Participant demographics and pretreatment characteristics of the Belotero® Intense (+) and control groups are presented in Table 8.

Table 8: Demographics

Characteristic		Belotero® Intense (+) (N=165) % (n/N)	Comparator (N = 55) % (n/N)	Total (N=220) % (n/N)
Sex	Male	2.4% (4/165)	7.3% (4/55)	3.6% (8/220)
	Female	97.6% (161/165)	92.7% (51/55)	96.4% (212/220)
Age (years)	Mean (SD)	46.5 (12.26)	47.3 (10.26)	46.7 (11.77)
	Range (min, max)	(21-65)	(24-65)	(21-65)
Ethnicity	Hispanic or Latino	20.0% (33/165)	25.5% (14/55)	21.4% (47/220)
	Not Hispanic or Latino	80.0% (132/165)	74.5% (41/55)	78.6% (173/220)
Race	White	92.7% (153/165)	90.9% (50/55)	92.3% (203/220)
	Black or African American	3.6% (6/165)	3.6% (2/55)	3.6% (8/220)
	Asian	0.6% (1/165)	1.8% (1/55)	0.9% (2/220)
	More than One Race	3.0% (5/165)	3.6% (2/55)	3.2% (7/220)
Fitzpatrick Skin Type	I	3.6% (6/165)	3.6% (2/55)	3.6% % (8/220)
	II	43.6% (72/165)	40.0% (22/55)	42.7% (94/220)
	III	30.3% (50/165)	27.3% (15/55)	29.5% (65/220)
	IV	13.3% (22/165)	18.2% (10/55)	14.5% (32/220)
	V	6.7% (11/165)	10.9% (6/55)	7.7% (17/220)
	VI	2.4% (4/165)	0.0% (0/55)	1.8% (4/220)

Max = maximum, Min = minimum, n = number of observations, N = number of participants in the treatment group and analysis set, SD = standard deviation, Percentages based on N.

Treatment Characteristics

Belotero® Intense (+) was injected into the subcutaneous and/or submucosal plane. A tunneling technique, fanning technique, or a combination was used to achieve optimal results.

The overall total median volume Belotero® Intense (+) injected to achieve optimal outcomes was 1.6 mL during initial/touch-up treatment. Participants received a median volume of 0.8 mL in the upper lip, 0.8 mL in the lower lip. Injection volumes into the lips after repeat treatment tended to be lower, with the typical total median injection volume to achieve optimal correction after repeat treatment being approximately 0.9 mL. Similar injection volumes were used in participants treated with the comparator device.

The maximum volume of Belotero® Intense (+) evaluated in the clinical study was 1.5 mL per lip (3.0 mL total per treatment session/day). Repeat treatments may be performed based on individual participant needs; however, the total annual treatment volume should not exceed 6.0 mL.

Effectiveness Results

For Belotero® Intense (+), the analysis of effectiveness was based on 158 evaluable participants (PPS) and 162 evaluable participants (ITT observed cases) at the primary endpoint visit at Week 8. The comparator group had 52 evaluable participants (PPS and ITT observed cases) at the Week 8 time point. Key effectiveness outcomes are presented in Table 9 and Table 10

The co-primary and primary effectiveness endpoints were met. MLFAS responder rate of participants treated with Belotero® Intense (+) at Week 8 post-last treatment demonstrated a treatment effect statistically significantly greater than the prespecified performance goal of 50%, as the lower limit of the two-sided 95% confidence interval exceeded the target margin of 50%. In the PPS, 91.1% (144/158) of participants treated with Belotero® Intense (+) and 90.4% (47/52) of participants treated with the comparator showed a ≥ 1-point improvement in overall lip fullness, with an observed mean change from baseline to Week 8 post-last treatment on the MLFAS of 1.3 for participants treated with Belotero® Intense (+) and 1.2 for participants treated with comparator. The study met the goal of demonstrating noninferiority of Belotero® Intense (+) compared to comparator, as the lower bound of the two-sided 95% confidence interval for difference between groups was > -0.5 point. The analysis results based on observed cases in the ITT population are consistent with the primary analysis result based on the PPS.

Table 9: Co-primary: Responder Rate in MLFAS at Week 8 Post-Last Treatment as Assessed by the Blinded Evaluator

	PPS Belotero® Intense (+) (N=158)	ITT (Observed Cases) Belotero® Intense (+) (N=162)
Responder rate, n/N (%)	144/158 (91.1%)	148/162 (91.4%)
Two-sided 95% CI*	(85.6, 95.1)	(85.9, 95.2)

*Derived from 95% Clopper-Pearson exact confidence interval.

Table 10: Primary: Change from Baseline to Week 8 Post-Last Treatment in MLFAS as Assessed by the Blinded Evaluator

	PPS		ITT (Observed Cases)	
	Belotero® Intense (+) (N=158)	Comparator (N=52)	Belotero® Intense (+) (N=162)	Comparator (N=52)

Observed means	1.31	1.23	1.31	1.23
Between group difference, 95% CI*	0.1 (0.0, 0.3)		0.1 (0.0, 0.3)	

*A baseline adjusted analysis of covariance (ANCOVA) with baseline value, fixed effects treatment, site, and Fitzpatrick skin type groups (I – III & IV – VI) is used to derive a two-sided 95% confidence interval.

Throughout the follow-up period, Belotero® Intense (+) continued to provide a clinically significant improvement in lip fullness, with the majority of participants demonstrating improvement up to 48 weeks after treatment. The proportion MLFAS responders (≥ 1 point mean change on MLFAS as assessed by blinded evaluator) by time point is presented in Table 11. Up to Week 48 in the Belotero® Intense (+) group, improvements in upper and lower lip fullness were similar to the improvements observed in overall lip fullness.

Table 11: Effectiveness Results through Week 48 (PPS) By Blinded Evaluator

	Belotero® Intense (+) % (n/N)	Comparator % (n/N)
Week 4	84.2% (133/158)	67.3% (35/52)
Week 8	91.1% (144/158)	90.4% (47/52)
Week 16	89.6% (138/154)	78.4% (40/51)
Week 24	78.8% (119/151)	72.9% (35/48)
Week 36	69.8% (104/149)	63.8% (30/47)
Week 48	48.7% (73/150)	47.8% (22/46)

When evaluated by IPR, 92/158 (58.2%) participants randomized to Belotero® Intense (+) participants and 31/52 (59.6%) randomized to the comparator participants showed a treatment response at Week 8 post-last treatment, according to MLFAS.

According to the GAIS, at Week 8, all (100%) participants treated with Belotero® Intense (+) showed some level of aesthetic improvement when assessed by the investigator, with 92.4% (146/158) scoring 'much improved' or 'very much improved' in appearance. By Week 48, 92% (138/150) of treated participants continued to show some level of aesthetic improvement (i.e., 'improved', 'much improved', or 'very much improved').

Similarly, at Week 8, all (100%) participants treated with Belotero® Intense (+) reported some level of aesthetic improvement according to the GAIS, with 91.1% (144/158) of treated participants scoring themselves as 'much improved' or 'very much improved' in appearance. By Week 48, 90% (135/150) of treated participants continued to report some level of aesthetic improvement (i.e., 'improved', 'much improved', or 'very much improved').

At Week 8, participants treated with Belotero® Intense (+) reported improvement in satisfaction with their lips, based on the *Satisfaction with Lips* module of the FACE Q questionnaire. The mean score increased from 37.9 at baseline to 88.7 eight weeks post-last treatment, corroborating the GAIS findings that indicate participants were satisfied with the appearance of their lips. Similarly, participants reported being satisfied with the outcome of Belotero® Intense (+) treatment up to 48 weeks, based on the *Satisfaction with Outcomes* module of the FACE Q questionnaire. Participants treated with Belotero® Intense (+) also self-reported improvements on the FACE-Q *Psychological*

Function module, with an increase of mean scores from 72.9 at baseline to 88.5 at Week 8 post-last treatment. These improvements were maintained to Week 48 post-last treatment, with participants self-reporting a mean score of 84.9. This validated quality-of-life scale asks respondents to answer 10 questions with their facial appearance in mind measuring concepts such as feeling happy, positive, confidence, self-acceptance, etc. which evaluated how confident, attractive or happy the participants felt after treatment.

According to responses to the lip hydration and appearance questionnaire, improvements were maintained through Week 48 in the Belotero® Intense (+) treatment group, with mean scores increasing from 14.3 at baseline to 26.0 at Week 8, 26.1 at week 16 and reaching 23.3 at Week 48 post last treatment.

The majority (92.4%, 133/144) of participants treated with Belotero® Intense (+) were satisfied with treatment and most (66.7%) reported being extremely likely to receive future treatment.

No differences in overall lip volume responder rates at week 8 were observed based on the following subgroup analyses: baseline lip fullness, sex, race, ethnicity, investigational site, and Fitzpatrick Skin Phototype. The results of these subgroup analyses were consistent with the co-primary and the primary endpoint analyses in the overall population.

Follow-Up After Repeat Treatment

At Week 48, repeat treatment with Belotero® Intense (+) was administered to 116 participants. In the subgroup for retreated participants, 79.1% of retreated participants with evaluable data showed at least a 1-point improvement in treated lip fullness, based on the blinded evaluator assessment at 12 weeks after repeat treatment, i.e. at week 60 after initial treatment or touch-up, if applicable. In the subgroup for not retreated participants, 60 weeks post last Belotero® Intense (+) treatment, 45.7% of participants with evaluable data showed at least a 1-point improvement in treated lip fullness, based on the blinded evaluator assessment.

GAIS improvement, as determined by the investigator and the participant, remained after repeat treatment, with investigators rating 96.6% of participants with any improvement and 95.2% of participants self-reporting any improvement 12 weeks after repeat treatment, or 60 weeks post-last treatment (i.e., without repeat treatment). These findings further demonstrate that treatment with Belotero® Intense (+) resulted in overall aesthetic improvement of the lips.

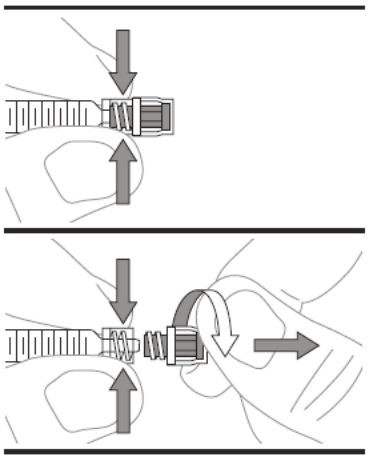
INSTRUCTIONS FOR USE

B. Attach Needle to Syringe

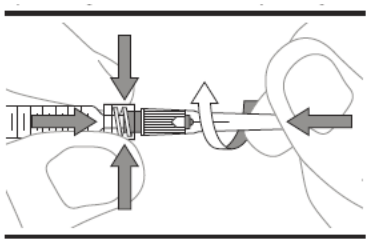
To ensure proper attachment, use needles provided.

a. Open the needle packaging to expose the needle hub. When using needles other than those provided with Belotero® Intense (+), follow the needle 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.



c. Holding the Luer lock fitting of the syringe, twist the needle onto the syringe. The needle must be tightened securely to the syringe. Do not over-tighten as this may break the needle and/or dislodge the syringe.



d. Pull off the needle guard to expose the needle.

e. Prime the needle with Belotero® Intense (+) 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. If leakage is noted at the Luer fitting, it may be necessary to remove the needle and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle.

C. Health Care Professional Instructions

1. Belotero® Intense (+) injectable gel is a crosslinked, injectable gel formulation, injected using a thin-gauge needle 27 G ½″ needle to add volume in the lips.

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 touch-up treatments may be required to achieve and maintain maximum correction.

7. For lip augmentation, the patient's treatment goals should be characterized with regard to proper proportion of upper and lower lip, vertical height, horizontal length, vermilion fullness, contouring of the vermilion border, Cupid's bow, and philtral columns. Pretreatment photographs are recommended.

8. Topical anesthetic may be used to manage pain during and after injection.

9. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be prepped with alcohol or other antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle.

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

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 may vary with regard to angle and orientation of the needle bevel, injection depth (submucosal or subcutaneous plane), and the quantity administered. Tunneling and fanning, or a combination of these techniques may be used for lip augmentation. Injection of Belotero® Intense (+) injectable gel too superficially, or in large volumes over a small area, may result in visible and persistent lumps and/or discoloration.

14. The typical volume injected into the lips to achieve optimal correction for lip augmentation is approximately 1.6 mL which may vary depending on the goals the patient wishes to achieve. Injection volumes into the lips after repeat treatment tended to be lower, with the typical total injection volume to achieve optimal correction being approximately 0.9 mL. The maximum volume evaluated in the clinical study was 3.0 mL total per treatment session/day (1.5 mL per lip). Repeat treatments may be performed based on individual participant needs; however, the total annual treatment volume should not exceed 6.0 mL.

15. 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.

16. 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]

17. When injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.

18. 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® Intense (+) injectable gel for each return visit; do not save and reuse unfinished Belotero® Intense (+) injectable gel syringes.

19. 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 treatment goals, lip fullness, skin elasticity and dermal thickness at the treatment site.

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

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

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® Intense (+) dermal filler is supplied in individual syringes co-packaged with sterile 27 G ½″ needles for single patient use. 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® Intense (+) 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® Intense (+) 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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Distributed by:

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Various features of BELOTERO® INTENSE (+) 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.

IN00262-00/July 2026

[1] Bloom J, Kaplan J, Verma A, Duncan A. Development and Validation of a Photonumeric Scale for Evaluation of Lip Fullness. *J Drugs Dermatol.* 2023;22(3):274-281. doi:10.36849/JDD.7309.

[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