BELOTERO BALANCE® (+) Lidocaine DERMAL Filler

(Injectable hyaluronic acid)

Belotero Balance® (+) Lidocaine Dermal Filler (herein Belotero Balance® (+)) is provided as sterile gel packaged in a pre-filled syringe with two sterile needles.

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

Information for the use of Belotero Balance® (+) is provided in this labeling for physicians as well as in the labeling for patients. BEFORE USING BELOTERO BALANCE® (+), PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY. Please direct any questions to Merz North America Inc, Raleigh, NC 27615 at 1-844-469-6379.

DESCRIPTION

Belotero Balance® (+) is a sterile, bioresorbable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel. Belotero Balance® (+) is a bacterially fermented, injectable, hyaluronic-acid-based dermal filler. After extraction and purification, hyaluronic acid manufactured from streptococcal cultures is cross-linked with a binding agent 1,4-butanediol diglycidyl ether (BDDE) in two consecutively executed reactions and reconstituted in a physiologic buffer at pH 7 and concentration of 22.5 mg/mL. Belotero Balance® (+) contains 0.3% lidocaine hydrochloride to reduce pain on injection.

INTENDED USE/INDICATIONS

Belotero Balance® (+) is indicated for injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds.

Belotero Balance® (+) is indicated for volume augmentation for the improvement of the infraorbital hollow in adults over the age of 21.

CONTRAINDICATIONS

- Belotero Balance® (+) is contraindicated in patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Belotero Balance® (+) is not intended to be used in patients with known hypersensitivity to lidocaine or anesthetics of the amide type.
- Belotero Balance® (+) contains trace amounts of gram-positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- Belotero Balance® (+) must not be implanted into blood vessels. Implantation of Belotero Balance® (+) into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

WARNINGS

- Use of Belotero Balance® (+) at specific sites in which an active inflammatory process (skin eruptions such as cold sores, cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled. Health care professionals should review and consider the patient's medical history prior to injection.
- Introduction of Belotero Balance® (+) 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.
- Common treatment responses to Belotero Balance® (+) have been observed, consisting mainly of short-term inflammatory symptoms starting early after treatment and with 17 days duration or less. Refer to the ADVERSE EVENTS section for details.

PRECAUTIONS

- In order to minimize the risks of potential complications, Belotero Balance® (+) 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 practitioners are encouraged to discuss all the potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of the signs and symptoms of potential complications.
- Belotero Balance® (+) is packaged and designed for single use only. Do not re-sterilize. Discard any unused product. Discard any partially used syringes.
- Do not use if the package is opened or damaged or beyond the expiration date cited on the package.
- The safety or effectiveness of Belotero Balance® (+) for the treatment of dermal contour defects other than nasolabial folds and for volume augmentation in infraorbital hollows has not been established in controlled clinical studies. The safety and effectiveness of BELOTERO BALANCE® (+) use in the lips has also not been evaluated.
- As with all transcutaneous procedures, Belotero Balance® (+) injection carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety of Belotero Balance® (+) for use during pregnancy, in breastfeeding females, or in patients under 21 years has not been established.
- The safety of Belotero Balance® (+) in patients with known susceptibility to recurrent sore throat, or Osler Rendu endocarditis has not been studied.

- Injection of Belotero Balance® (+) into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Belotero Balance® (+) should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that reduce coagulation, such as aspirin, non-steroidal anti-inflammatory drugs, and warfarin may, as with any injection, experience increased bruising or bleeding at injection sites.
- As with all invasive procedures, Belotero Balance® (+) 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.
- 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 Balance® (+) 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 and notify Merz North America, Inc. at 1-844-469-6379.
- Laser treatment, chemical peeling, or any other procedure based on active dermal response performed after treatment with Belotero Balance® (+) may increase the risk of an inflammatory reaction at the injection site. Similarly, the administration of BELOTERO BALANCE® (+) before the skin has healed completely after such a procedure may also increase the risk of inflammatory reactions.
- Belotero Balance® (+) is supplied in a syringe ready for use. Belotero Balance® (+) should not be directly mixed with any other products prior to injection of the device. No studies of interactions of Belotero Balance® (+) with drugs or other substances or implants have been made.
- The patient should be informed that he or she 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.
- Care should be taken to determine the risk versus the benefit for patients with congenital methemoglobinemia, with glucose-6-phosphate dehydrogenase deficiencies, and with patients who are receiving concomitant treatment with methemoglobin-inducing agent.
- The long-term safety and effectiveness of Belotero Balance® beyond 96 weeks has not been investigated.
- Based on clinical studies, patients should be limited to 6.0 ml of Belotero Balance® per year. The safety of injecting greater amounts has not been established.

ADVERSE EVENTS

Belotero Balance® and Belotero Balance® (+) have been studied in two anatomical areas, nasolabial folds and the infraorbital hollow region. The only difference between Belotero Balance® and Belotero Balance® (+) is the addition of lidocaine hydrochloride in Belotero Balance® (+) for the purposes of pain reduction.

For the nasolabial fold indication, the main studies evaluating safety and effectiveness were performed with Belotero Balance®. See Section 1A for safety discussion. The safety and effectiveness of lidocaine hydrochloride addition to Belotero Balance®, *referred to as Belotero Balance® (+)*, was assessed in a follow-on study. See Section 1B for the safety discussion.

For the infraorbital hollow region, a pilot study evaluating the safety and effectiveness of Belotero Balance® was performed (see Section 2A for safety discussion) followed by a pivotal study evaluating the safety and effectiveness of Belotero Balance® (+) (see Section 2B).

1. NASOLABIAL FOLDS

A. Belotero Balance®

The safety of Belotero Balance® for injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds, has been evaluated in three studies and 211 patients. These studies are described below.

- **Pivotal Clinical Study Controlled Phase (0 – 24 Weeks):**

In a randomized, controlled clinical trial, 118 subjects at 6 centers were injected with Belotero Balance® in one NLF and bovine collagen dermal filler (Control) in the contralateral NLF to evaluate the safety and effectiveness of Belotero Balance® in comparison with the Control. Pre-printed diary forms were used by subjects to record specific signs and symptoms experienced during each of the first 14 days after initial and touch-up treatments. Subjects were instructed to rate each common treatment response listed on the diary as "Mild", "Moderate", "Severe", or "None." The combined rates of injection site responses reported by >5% of subjects in the pivotal clinical study and the Fitzpatrick Skin Type IV, V, and VI study are summarized by maximum intensity in Table 1 and by duration in Table 2. Adverse events recorded by investigators at study visits are presented in Table 3.

- **Open Label Extension (OLEX) Phase (24 – 96 Weeks):**

95 of 118 subjects who completed the 24 week controlled-phase of the pivotal study received additional treatments with Belotero Balance® from Weeks 24 to 96 after the initial treatment. Follow-up visits occurred at 24, 32, 48, 72, and 96 weeks after the initial treatment. At the Week 24 study visit all enrolled subjects received Belotero Balance® in both NLFs to achieve optimal correction. At the Week 32 visit, subjects were allowed a touch-up treatment on one side to balance any observed differences. Subjects could receive additional treatments to both NLFs at weeks 48, 72, or 96 if their wrinkle severity score met the injection criteria (SRS of 2 or 3). No single AE was reported with more than a 5% rate of incidence during the OLEX phase and the safety profile observed during the OLEX phase was similar to that described above during the controlled-phase.

- **Fitzpatrick Skin Type IV, V and VI Study:**

The safety and effectiveness of Belotero Balance® was evaluated in 93 subjects with Fitzpatrick skin phototype scores of IV, V, and VI at 3 U.S. centers during a 24-week open label study. Subjects received an initial treatment of Belotero Balance® and were eligible to receive an additional touch-up treatment 2 weeks after the initial treatment if necessary. Subject follow-up visits occurred at weeks 2, 4, 8, 12, 16, and 24 weeks. The safety profile observed during this study was similar to that observed in the pivotal controlled clinical study.

Table 1 Maximum Intensity of Symptoms Occurring in >5 % of Subjects, Patient Diary

	BELOTERO BALANCE® Maximum AE Severity (N = 211)				Collagen Control Maximum AE Severity (N = 118)			
Injection Site Response	**Total n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Swelling	145 (68.7)	60 (28.4)	65 (30.8)	20 (9.5)	86 (72.9)	36 (30.5)	38 (32.2)	12 (10.2)
Nodule	92 (43.6)	46 (21.8)	37 (17.5)	9 (4.3)	79 (66.9)	32 (27.1)	35 (29.7)	12 (10.2)
Bruising	115 (54.5)	46 (21.8)	51 (24.2)	18 (8.5)	53 (44.9)	26 (22.0)	21 (17.8)	6 (5.1)
Induration	107 (50.7)	52 (24.6)	45 (21.3)	10 (4.7)	62 (52.5)	28 (23.7)	25 (21.2)	9 (7.6)
Erythema	109 (51.7)	55 (26.1)	48 (22.7)	6 (2.8)	79 (66.9)	37 (31.4)	32 (27.1)	10 (8.5)
Pain	103 (48.8)	68 (32.2)	26 (12.3)	9 (4.3)	63 (53.4)	32 (27.1)	26 (22.0)	5 (4.2)
Discoloration	61 (28.9)	32 (15.2)	25 (11.8)	4 (1.9)	35 (29.7)	22 (18.6)	11 (9.3)	2 (1.7)
Pruritus	46 (21.8)	37 (17.5)	9 (4.3)	0	32 (27.1)	25 (21.2)	7 (5.9)	0

Note 1: Total number of subjects injected with BELOTERO BALANCE® includes 118 subjects from the Pivotal study and 93 subjects from the Fitzpatrick IV, V, and VI study.
Note 2: Each subject is counted only once by maximum severity of injection site response.

Table 2 Duration of Injection Site Responses Occurring in > 5% of Treated Subjects, Patient Diary

	BELOTERO BALANCE® Maximum AE Severity (N = 211)				Collagen Control Maximum AE Severity (N = 118)			
Injection Site Response	**≤ 3 days n (%)**	**4 - 7 days n (%)**	**8 -14 days n (%)**	**> 14 days n (%)**	**≤ 3 days n (%)**	**4 - 7 days n (%)**	**8 -14 days n (%)**	**> 14 days n (%)**
Swelling	66 (31.3)	51 (24.2)	17 (8.1)	11 (5.2)	52 (44.1)	24 (20.3)	6 (5.1)	4 (3.4)
Nodule	27 (12.8)	31 (14.7)	17 (8.1)	17 (8.1)	11 (9.3)	10 (8.5)	19 (16.1)	39 (33.1)
Bruising	29 (13.7)	46 (21.8)	34 (16.1)	6 (2.8)	18 (15.3)	27 (22.9)	6 (5.1)	2 (1.7)
Induration	46 (21.8)	29 (13.7)	20 (9.5)	12 (5.7)	27 (22.9)	13 (11.0)	8 (6.8)	14 (11.9)
Erythema	66 (31.3)	27 (12.8)	10 (4.7)	6 (2.8)	45 (38.1)	13 (11.0)	7 (5.9)	14 (11.9)
Pain	72 (34.1)	22 (10.4)	4 (1.9)	5 (2.4)	36 (30.5)	18 (15.3)	7 (5.9)	2 (1.7)
Discoloration	24 (11.4)	14 (6.6)	17 (8.1)	6 (2.8)	19 (16.1)	6 (5.1)	3 (2.5)	7 (5.9)
Pruritus	32 (15.2)	8 (3.8)	3 (1.4)	3 (1.4)	23 (19.5)	2 (1.7)	4 (3.4)	3 (2.5)

Note 1: Total number of subjects injected with BELOTERO BALANCE® includes 118 subjects from the Pivotal study and 93 subjects from the Fitzpatrick IV, V, and VI study.
Note 2: Each subject is counted only once by maximum severity of injection site response.

Table 3 Adverse Events Occurring in >2% of Subjects, Physician Reported

Description of Adverse Event	BELOTERO BALANCE® Maximum AE Severity (N = 211)				Collagen Control Maximum AE Severity (N = 118)			
	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Any Adverse Event	189 (89.6)				108 (91.5)			
Injection Site Swelling	135 (64.0)	55 (26.1)	60 (28.4)	20 (9.5)	77 (65.3)	31 (26.3)	35 (29.7)	11 (9.3)
Injection Site Induration	104 (49.3)	50 (23.7)	44 (20.9)	10 (4.7)	57 (48.3)	24 (20.3)	25 (21.2)	8 (6.8)
Injection Site Bruising	104 (49.3)	40 (19.0)	49 (23.2)	15 (7.1)	48 (40.7	23 (19.5)	21 (17.8)	4 (3.4)
Injection Site Erythema	102 (48.3)	53 (25.1)	44 (20.9)	5 (2.4)	69 (58.5)	32 (27.1)	27 (22.9)	10 (8.5)
Injection Site Pain	95 (45.0)	63 (29.9)	24 (11.4)	8 (3.8)	57 (48.3)	26 (22.0)	25 (21.2)	6 (5.1)
Injection Site Nodule	91 (43.1)	46 (21.8)	36 (17.1)	9 (4.3)	77 (65.3)	30 (25.4)	35 (29.7)	12 (10.2)
Injection Site Discoloration	61 (28.9)	33 (15.6)	24 (11.4)	4 (1.9)	32 (27.1)	19 (16.1)	11 (9.3)	2 (1.7)
Injection Site Pruritus	44 (20.9)	35 (16.6)	9 (4.3)	0	28 (23.7)	21 (17.8)	7 (5.9)	0
Application Site Exfoliation	6 (2.8)	4 (1.9)	1 (0.5)	1 (0.5)	0	0	0	0
Injection Site Rash	5 (2.4)	3 (1.4)	2 (0.9)	0	0	0	0	0

Note 1: Total number of subjects injected with BELOTERO BALANCE® includes 118 subjects from the Pivotal study and 93 subjects from the Fitzpatrick IV, V, and VI study.
Note 2: A subject is counted only once by maximum severity of the adverse event.
Note 3: Adverse events are sorted in decreasing order of incidence for Total Subjects injected with BELOTERO BALANCE®.

Non-local Adverse Events (All Causality)

Non-local Adverse Events occurred in 7/211 (3.3%) of the study subjects in the combined pivotal and Fitzpatrick IV, V, VI studies. From the pivotal clinical study, 3/118 (2.5%) subjects had at least one non-local adverse event. The non-local AEs included moderate urticaria, mild herpes simplex, and mild headache. Since each patient received Belotero Balance® and Collagen Control, the causality of these events could not be identified. In the Fitzpatrick IV, V, VI study 4/93 (4.3%) subjects experienced 5 non-local Adverse Events. These were moderate headache, moderate swelling on the right side of the nose, moderate cold sore, moderate lip numbness, and mild lip dryness.

Serious Adverse Events

During clinical studies with Belotero Balance®, one subject underwent hip arthroplasty, which was classified as a serious adverse event (SAE). There were no SAEs experienced that were related to treatment with Belotero Balance®.

Post-Approval Study

A post-approval clinical study was conducted to provide additional safety data that would determine if the rate of severe common adverse events after re-treatment with Belotero Balance®

would differ from that reported in the initial treatment session of the Belotero Balance® in the pre-market clinical trial and the Belotero Balance® Fitzpatrick Skin Type IV-VI Study.

Nine study sites and 117 subjects that had participated in the Belotero Balance® pivotal clinical trial and in the Fitzpatrick Skin Type IV-VI clinical study participated in this study to evaluate the rate of severe common adverse events after retreatment with Belotero Balance®.

Subjects received bilateral retreatment of their nasolabial folds with Belotero Balance® and were eligible to receive a touch-up treatment 2 weeks after the initial treatment, if necessary. At 2 weeks, 4 weeks, and 6 weeks (for those that received a touch-up), subjects returned to the treating investigator for assessment. Study participation ended at the completion of the 4 week visit for subjects that did not receive a touch-up, and at the 6 week visit for subjects that had received a touch-up.

Tables 4 through 7 summarize the severe adverse events observed in the initial treatment studies and the retreatment study by type of adverse event, by subjects, and by duration of the adverse events. Each table provides subject data in total and by Fitzpatrick Skin Type.

Table 4 shows the incidence rates of severe common adverse events data evaluated by the type of adverse event.

Table 4 Percent Incidence of Severe Common Adverse Events - by Adverse Event Initial Treatment Studies vs Retreatment Studies

Study	Type of Adverse Event	n / N % Incidence		
		Fitzpatrick Skin Type I-III	Fitzpatrick Skin Type IV-VI	All Subjects
Initial Treatment Studies	Bruising	12/84 (14.3%)	7/82 (8.5%)	19/166 (11.4%)
	Itching	0	0	0
	Redness	5/92 (5.4%)	2/80 (2.5%)	7/172 (4.1%)
	Pain	4/58 (6.9%)	7/79 (8.9%)	11/137 (8.0%)
	Swelling	12/108 (11.1%)	11/141 (7.8%)	23/249 (9.2%)
	Discoloration	1/27 (3.7%)	4/59 (6.8%)	5/86 (5.8%)
	Nodule	8/58 (13.8%)	3/83 (3.6%)	11/141 (7.8%)
	Induration	4/60 (6.7%)	8/121 (6.6%)	12/181 (6.6%)
	Other	6/70 (8.6%)	3/52 (5.8%)	9/122 (7.4%)
	TOTAL	**52/578 (9.0%)**	**45/738 (6.1%**	**97/1316 (7.4%**
		Fitzpatrick Skin Type I-III	**Fitzpatrick Skin Type IV-VI**	**All Subjects**
Retreatment Study	Bruising	10/108 (9.3%)	3/84 (3.6%)	13/192 (6.8%)
	Itching	0	2/45 (4.4%)	2/75 (2.7%)
	Redness	0	2/77 (2.6%)	2/177 (1.7%)
	Pain	0	2/88 (2.3%)	2/119 (1.1%)
	Swelling	0	2/111 (1.8%)	2/211 (0.9%)
	Discoloration	0	2/44 (4.5%)	2/100 (2.0%)
	Nodule	0	4/43 (9.3%)	4/78 (5.1%)
	Induration	0	4/32 (12.5%)	4/47 (8.5%)
	Other	2/13 (15.4%)	0	2/32 (6.3%)
	TOTAL	**12/493 (2.4%**	**21/560 (3.7%**	**33/1053 (3.1%**

Tables 5 and 6 summarize the incidence rates of severe common adverse events observed in the initial treatment studies and in the retreatment study, by Fitzpatrick Skin Type (Grades I-III and Grades IV-VI) and by all subjects.

Table 5 Percent Incidence Rates of Severe Common Adverse Events - Subjects with at Least One Adverse Event Initial Treatment Studies, N = 211 Subjects

Study	Type of Adverse Event	Number of Subjects (%)		
		Fitzpatrick Skin Type I-III N = 100	Fitzpatrick Skin Type IV - VI N = 111	All Subjects N = 211
Initial Treatment Studies	Bruising	12 (12.0%)	6 (5.4%)	18 (8.5%)
	Itching	0	0	0
	Pain	4 (4.0%)	5 (4.5%)	9 (4.3%)
	Redness	4 (4.0%)	2 (1.8%)	6 (2.8%)
	Swelling	12 (12.0%)	8 (7.2%)	20 (9.5%)
	Discoloration	1 (1.0%)	3 (2.7%)	4 (1.9%)
	Nodule	7 (7.0%)	2 (1.8%)	9 (4.3%)
	Induration	4 (4.0%)	6 (5.4%)	10 (4.7%)
	Other	5 (5.0%)	3 (2.7%)	8 (3.8%)
	TOTAL	**27 (27.0%)**	**14 (12.6%)**	**41 (19.4%)**

Table 6 Percent Incidence Rates of Severe Common Adverse Events - by Subject Retreatment Study, N = 117 Subjects

Study	Type of Adverse Event	Number of Subjects (%)		
		Fitzpatrick Skin Type I-III N = 61	Fitzpatrick Skin Type IV - VI N = 56	All Subjects N = 117
Retreatment Study	Bruising	6 (9.8%)	2 (3.6%)	8 (6.8%)
	Itching	0	1 (1.8%)	1 (0.9%)
	Pain	0	1 (1.8%)	1 (0.9%)
	Redness	0	1 (1.8%)	1 (0.9%)
	Swelling	0	1 (1.8%)	1 (0.9%)
	Discoloration	0	1 (1.8%)	1 (0.9%)
	Nodule	0	1 (1.8%)	1 (0.9%)
	Induration	0	1 (1.8%)	1 (0.9%)
	Other	2 (3.3%)	0	2 (1.7%)
	TOTAL	**7 (11.5%)**	**3 (5.4%)**	**10 (8.5%)**

Table 7 summarizes the length of time needed to resolve adverse events as a mean value, measured in days. The statistical analysis demonstrates that there is no difference in the duration of adverse events after initial treatment and after retreatment with Belotero Balance®.

Table 7 Duration of Severe Common Adverse Events - by Days Initial Treatment Studies vs. Retreatment Study

Study	Adverse Event Type	All Subjects 'Severe' Common AEs Mean Duration in Days
Initial Treatment Studies	Bruising	11.74
	Itching	0
	Redness	4.71
	Pain	5.09
	Swelling	9.04
	Discoloration	7.80
	Induration	12.92
	Nodule	13.73
	TOTAL MEAN	**9.83 Days**
Retreatment Study	Bruising	9.0
	Itching	8.0
	Redness	21.5
	Pain	7.0
	Swelling	11.0
	Discoloration	22.0
	Induration	7.5
	Nodule	7.5
	TOTAL MEAN	**10.2 Days**

In patients who received retreatment, there was no increase in severe common adverse events.

B. BELOTERO BALANCE® (+)

- **Belotero Balance® (+) Nasolabial Fold Pre-Market Study (0-6 weeks)**

The safety of the addition of lidocaine hydrochloride to Belotero Balance®, *referred to as Belotero Balance® (+),* in the nasolabial fold was evaluated in the pre-market study described below:

TREATMENT EMERGENT ADVERSE EVENTS

There were five treatment emergent adverse events (TEAE) during the study which were all categorized as mild in intensity. Table 8 provides a summary of the TEAEs.

Table 8 Overall Summary of Treatment Emergent Adverse Events (TEAE), SES

Category	Total (N=52)	
Number (%) of subjects with:	**n**	**%**
Any TEAE	5	9.6
Any TEAE related to treatment	2	3.8
Any serious TEAE	0	--
Any TEAE leading to discontinuation	0	--
Any TEAE leading to discontinuation related to treatment	0	--

Of these TEAEs, two were identified as related to treatment. For the first TEAE, the patient reported a headache which resolved within 1 day; for the second TEAE, the subject experienced skin tightness in the treatment area which resolved within 20 days.

There were no serious adverse events reported during the study. All adverse events resolved within the study period. There were no reports of vascular occlusions or granulomas in this study.

COMMON TREATMENT RESPONSES (CTRs)

Expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (e.g. common treatment responses (CTR)) were individually assessed by subjects in an electronic 30-day diary after each injection. Subjects were asked to rate each CTR as none, mild, moderate or severe, where mild was defined as 'barely noticeable', moderate was defined as 'uncomfortable', and severe was defined as 'severe discomfort.'

CTRs by severity and duration are presented in Table 9 and Table 10, respectively. All CTRs resolved within the duration of the study. There were no CTRs that were considered treatment-related adverse events

Table 9 Common Treatment Site Responses by Incidence of Severity[1]

CTR	Belotero Balance® (+) (Test)				Belotero Balance® (Control)			
	Total n/M (%)	Mild n/N1 (%)	Moderate n/N1 (%)	Severe n/N1 (%)	Total n/M (%)	Mild n/N1 (%)	Moderate n/N1 (%)	Severe n/N1 (%)
Any CTR	41/52 (78.8)	23/41 (56.1)	14/41 (34.1)	4/41 (9.8)	45/52 (86.5)	24/45 (53.3)	18/45 (40.0)	3/45 (6.7)
Swelling	31/52 (59.6)	23/31 (74.2)	6/31 (19.4)	2/31 (6.5)	31/52 (59.6)	20/31 (64.5)	10/31 (32.3)	1/31 (3.2)
Firmness	25/52 (48.1)	18/25 (72.0)	7/25 (28.0)	0/25	25/52 (48.1)	18/25 (72.0)	7/25 (28.0)	0/25
Lumps/Bumps	16/52 (30.8)	9/16 (56.3)	6/16 (37.5)	1/16 (6.3)	22/52 (42.3)	11/22 (50.0)	11/22 (50.0)	0/22
Bruising	22/52 (42.3)	10/22 (45.5)	10/22 (45.5)	2/22 (9.1)	25/52 (48.1)	15/25 (60.0)	8/25 (32.0)	2/25 (8.0)
Pain	15/52 (28.8)	11/15 (73.3)	4/15 (26.7)	0/15	19/52 (36.5)	12/19 (63.2)	7/19 (36.8)	0/19
Tenderness upon pressing	25/52 (48.1)	21/25 (84.0)	4/25 (16.0)	0/25	32/52 (61.5)	25/32 (78.1)	7/32 (21.9)	0/32
Redness	26/52 (50.0)	20/26 (76.9)	6/26 (23.1)	0/26	23/52 (44.2)	16/23 (69.6)	7/23 (30.4)	0/23
Discoloration (not redness or bruising)	10/52 (19.2)	8/10 (80.0)	2/10 (20.0)	0/10	11/52 (21.2)	8/11 (72.7)	3/11 (27.3)	0/11
Itching	11/52 (21.2)	11/11 (100.0)	0/11	0/11	10/52 (19.2)	10/10 (100.0)	0/10	0/10
Stinging/Burning	5/52 (9.6)	3/5 (60.0)	2/5 (40.0)	0/5	8/52 (15.4)	7/8 (87.5)	1/8 (12.5)	0/8
Numbness	15/52 (28.8)	13/15 (86.7)	2/15 (13.3)	0/15	11/52 (21.2)	10/11 (90.9)	1/11 (9.1)	0/11
Other	3/52 (5.8)	1/3 (33.3)	2/3 (66.7)	0/3	3/52 (5.8)	2/3 (66.7)	1/3 (33.3)	0/3

[1] n = number of subjects with a particular CTR of the given maximum severity or longest duration, M = number of subjects with assessment, N1 = number of subjects with a CTR of the given type of any severity or duration

Table 10 Common Treatment Site Responses by Duration[2]

CTR	Belotero Balance® (+) (Test)					Belotero Balance® (Control)				
	1-3 days n/N1 (%)	4-7 days n/N1 (%)	8-17 days n/N1 (%)	15-30 days n/N1 (%)	>30 days n/N1 (%)	1-3 days n/N1 (%)	4-7 days n/N1 (%)	8-17 days n/N1 (%)	15-30 days n/N1 (%)	>30 days n/N1 (%)
Any CTR	16/41 (39.0)	14/41 (34.1)	8/41 (19.5)	3/41 (7.3)	0/41	20/45 (44.4)	14/45 (31.1)	9/45 (20.0)	2/45 (4.4)	0/45
Swelling	23/31 (74.2)	5/31 (16.1)	3/31 (9.7)	0/31	0/31	23/31 (74.2)	6/31 (19.4)	2/31 (6.5)	0/31	0/31
Firmness	16/25 (64.0)	4/25 (16.0)	4/25 (16.0)	1/25 (4.0)	0/25	17/25 (68.0)	6/25 (24.0)	2/25 (8.0)	0/25	0/25
Lumps/Bumps	8/16 (50.0)	6/16 (37.5)	2/16 (12.5)	0/16	0/16	15/22 (68.2)	5/22 (22.7)	1/22 (4.5)	1/22 (4.5)	0/22
Bruising	4/22 (18.2)	12/22 (54.5)	6/22 (27.3)	0/22	0/22	8/25 (32.0)	12/25 (48.0)	5/25 (20.0)	0/25	0/25
Pain	14/15 (93.3)	1/15 (6.7)	0/15	0/15	0/15	19/19 (100.0)	0/19	0/19	0/19	0/19
Tenderness upon pressing	21/25 (84.0)	4/25 (16.0)	0/25	0/25	0/25	27/32 (84.4)	5/32 (15.6)	0/32	0/32	0/32
Redness	24/26 (92.3)	1/26 (3.8)	1/26 (3.8)	0/26	0/26	20/23 (87.0)	1/23 (4.3)	2/23 (8.7)	0/23	0/23
Discoloration (not redness or bruising)	5/10 (50.0)	3/10 (30.0)	0/10	2/10 (20.0)	0/10	6/11 (54.5)	2/11 (18.2)	2/11 (18.2)	1/11 (9.1)	0/11
Itching	8/11 (72.7)	2/11 (18.2)	1/11 (9.1)	0/11	0/11	6/10 (60.0)	3/10 (30.0)	1/10 (10.0)	0/10	0/10
Stinging/Burning	5/5 (100.0)	0/5	0/5	0/5	0/5	7/8 (87.5)	1/8 (12.5)	0/8	0/8	0/8
Numbness	14/15 (93.3)	1/15 (6.7)	0/15	0/15	0/15	10/11 (90.9)	1/11 (9.1)	0/11	0/11	0/11
Other	3/3 (100.0)	0/3	0/3	0/3	0/3	3/3 (100.0)	0/3	0/3	0/3	0/3

[2] n = number of subjects with a particular CTR of the given maximum severity or longest duration, M = number of subjects with assessment, N1 = number of subjects with a CTR of the given type of any severity or duration

2. INFRAORBITAL HOLLOWS

A. Belotero Balance®

- **US Pilot Study of Belotero Balance® for Volume Augmentation of the Infraorbital Hollows**

This prospective, multi-center evaluation was a pilot study to evaluate the safety and effectiveness for Belotero Balance® use in the infraorbital hollow (IOH) in order to utilize the results to inform the design of a future pivotal study, that would utilize Belotero Balance® (+).[3]

There were 43 subjects treated in both (bilateral) infraorbital hollows. Optional touch-up treatments occurred approximately 1 month after initial injection. Subjects were followed for safety via clinic visits for up to 12 months after the last treatment (i.e., initial treatment or touch-up treatment).

Subjects used an electronic diary to record specific signs and symptoms of common treatment responses (CTRs) experienced during the 28 days after initial treatment and touch-up treatment (if performed). Subjects were instructed to rate each CTR listed on the diary as Mild, Moderate, Severe, or None.

The severity and duration of CTRs reported by subjects who completed the post-treatment diary forms after initial treatment are summarized in Table 11. Table 12 shows the maximum severity and duration of all CTRs after the touch-up treatment. The majority of CTRs were mild or moderate in intensity and resolved within 14 days. The incidence, severity, and duration of CTRs after touch-up treatment were generally lower than after initial treatment.

Table 11 Pilot Study: Common Treatment Responses by Maximum Severity & Duration After Initial Treatment, SP

CTR	Severity[b]				Duration[c]			
	None % (n/M[a])	Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1 – 3 Days % (n/M)	4 – 7 Days % (n/M)	8 – 14 Days % (n/M)	≥15 – 28 Days % (n/M)
Any CTR	9.5% (4/42)	31.0% (13/42)	52.4% (22/42)	7.1% (3/42)	14.3% (6/42)	19.0% (8/42)	23.8% (10/42)	33.3% (14/42)
Bruising	35.7% (15/42)	47.6% (20/42)	16.7% (7/42)	0.0% (0/42)	19.0% (8/42)	11.9% (5/42)	23.8% (10/42)	9.5% (4/42)
Bumps you can feel but not see	66.7% (28/42)	21.4% (9/42)	11.9% (5/42)	0.0% (0/42)	14.3% (6/42)	4.8% (2/42)	9.5% (4/42)	4.8% (2/42)
Itching	85.7% (36/42)	11.9% (5/42)	0.0% (0/42)	2.4% (1/42)	7.1% (3/42)	0.0% (0/42)	0.0% (0/42)	7.1% (3/42)
Pain	61.9% (26/42)	35.7% (15/42)	2.4% (1/42)	0.0% (0/42)	23.8% (10/42)	9.5% (4/42)	2.4% (1/42)	2.4% (1/42)

[3] *The only difference between Belotero Balance® and Belotero Balance® (+) is the addition of lidocaine hydrochloride in Belotero Balance® (+) for the purposes of pain reduction.*

CTR	Severity[b]				Duration[c]			
	None % (n/M[a])	Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1 – 3 Days % (n/M)	4 – 7 Days % (n/M)	8 – 14 Days % (n/M)	≥15 – 28 Days % (n/M)
Redness	59.5% (25/42)	31.0% (13/42)	7.1% (3/42)	2.4% (1/42)	21.4% (9/42)	14.3% (6/42)	4.8% (2/42)	0.0% (0/42)
Swelling	16.7% (7/42)	35.7% (15/42)	45.2% (19/42)	2.4% (1/42)	28.6% (12/42)	14.3% (6/42)	19.0% (8/42)	21.4% (9/42)
Visible lumps	40.5% (17/42)	28.6% (12/42)	31.0% (13/42)	0.0% (0/42)	11.9% (5/42)	9.5% (4/42)	23.8% (10/42)	14.3% (6/42)

[a] M = number of subjects who recorded responses in the diaries after initial treatment.
[b] Maximum severity in the patient diary.
[c] Maximum duration in the patient diary.
CTR = common treatment response; SP= Safety Population
Percentages were based on M.

Table 12 Pilot Study: Common Treatment Responses by Maximum Severity & Duration After Touch-Up Treatment, SP

CTR	Severity[b]				Duration[c]			
	None % (n/M[a])	Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1 – 3 Days % (n/M)	4 – 7 Days % (n/M)	8 – 14 Days % (n/M)	≥15 – 28 Days % (n/M)
Any CTR	20.0% (5/25)	68.0% (17/25)	12.0% (3/25)	0.0% (0/25)	20.0% (5/25)	16.0% (4/25)	24.0% (6/25)	20.0% (5/25)
Bruising	60.0% (15/25)	36.0 (9/25)	4.0% (1/25)	0.0% (0/25)	8.0% (2/25)	12.0% (3/25)	16.0% (4/25)	4.0% (1/25)
Bumps you can feel but not see	76.0% (19/25)	20.0% (5/25)	4.0% (1/25)	0.0% (0/25)	16.0% (4/25)	8.0% (2/25)	0.0% (0/25)	0.0% (0/25)
Itching	92.0% (23/25)	8.0% (2/25)	0.0% (0/25)	0.0% (0/25)	8.0% (2/25)	0.0% (0/25)	0.0% (0/25)	0.0% (0/25)
Pain	88.0% (22/25)	8.0% (2/25)	4.0% (1/25)	0.0% (0/25)	12.0% (3/25)	0.0% (0/25)	0.0% (0/25)	0.0% (0/25)
Redness	72.0% (18/25)	28.0% (7/25)	0.0% (0/25)	0.0% (0/25)	16.0% (4/25)	12.0% (3/25)	0.0% (0/25)	0.0% (0/25)
Swelling	28.0% (7/25)	60.0% (15/25)	12.0% (3/25)	0.0% (0/25)	24.0% (6/25)	24.0% (6/25)	20.0% (5/25)	4.0% (1/25)
Visible lumps	52.0% (13/25)	40.0% (10/25)	8.0% (2/25)	0.0% (0/25)	16.0% (4/25)	8.0% (2/25)	8.0% (2/25)	16.0% (4/25)

[a] M = number of subjects who recorded responses in the diaries after touch-up treatment.
[b] Maximum severity in the patient diary.
[c] Maximum duration in the patient diary. CTR = common treatment response, SP= Safety Population
Percentages were based on M.

Subject diaries were used to collect CTR information as well as specific safety concerns. During safety checks, Investigators reviewed subject diaries for potential adverse events (AEs). Among 43 subjects treated with Belotero Balance®, 2 experienced a total of 4 treatment-related AEs. The treatment-related AEs include 2 reports of contusion, 1 of post procedural discomfort, and 1 of injection site swelling. All treatment-related AEs were mild and recovered/resolved in 20 days or less. There were no deaths and other significant AEs that occurred during the study.

There were no treatment-related serious adverse events (SAEs) or unanticipated adverse device effects reported during the pilot study. No subjects were discontinued as a result of AEs. No adverse events were categorized as unexpected or atypical with use of Belotero Balance®. No events associated with retinal artery occlusion or visual disturbance, or the late onset of such events related to Belotero Balance® in the infraorbital hollows were reported.

B. Belotero Balance® **(+)**

- **US Pivotal Study Belotero Balance® (+) for Volume Augmentation of the Infraorbital Hollows**

In the randomized, controlled clinical trial to evaluate the safety and effectiveness of Belotero Balance® (+), a total of 144 subjects (97 initial treatment subjects and 47 delayed-control treatment subjects) were treated in both (bilateral) infraorbital hollows with Belotero Balance® (+).

Subjects who were randomized to the treatment arm were assessed at Week 4 for an optional touch-up treatment in one or both infraorbital hollows. These subjects were eligible for retreatment at 48 weeks post last injection (i.e., baseline injection or touch-up, if applicable) and then followed for an additional 24 weeks, for a total study duration of 72 weeks if no touch-up was performed and 76 weeks if a touch-up was performed.

After the Week 8 effectiveness assessment, the delayed treatment/control subjects received treatment and an optional touch-up at Week 4 post initial treatment.

Subjects used an electronic diary to record specific signs and symptoms of common treatment responses (CTRs) experienced during the 28 days after initial treatment, touch-up treatment (if performed), and retreatment (if performed). Subjects were instructed to rate each CTR listed on the diary as Mild, Moderate, Severe, or None.

The severity and duration of CTRs reported by treatment group subjects who completed the post-treatment diary forms after initial treatment are summarized in Table 13, Table 14 and Table 15. Table 16 shows the severity and duration of CTRs touch-up treatment and Table 17 severity and duration of CTRs after repeat treatment. The majority of CTRs were mild or moderate in intensity, and their duration was less than 14 days. The incidence, severity, and duration of CTRs reported after the touch-up and repeat treatments were generally lower than those reported after initial treatment.

Table 13 Pivotal Study: Common Treatment Responses by Maximum Severity & Duration After Initial Treatment, SP

CTR	Total % (n/M [a])	Severity[b]			Duration[c]			
		Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)
Any CTR	92.3% (132/143)	38.5% (55/143)	44.8% (64/143)	9.1% (13/143)	17.5% (25/143)	21.7% (31/143)	20.3% (29/143)	32.9% (47/143)
Swelling	76.2% 109/143	42.7% (61/143)	30.8% (44/143)	2.8% (4/143)	27.3% (39/143)	22.4% (32/143)	10.5% (15/143)	16.1% (23/143)
Bruising	71.3% (102/143)	42.0% (60/143)	22.4% (32/143)	7.0% (10/143)	18.2% (26/143)	18.2% (26/143)	16.8% (24/143)	18.2% (26/143)
Visible lumps	65.0% (93/143)	32.2% (46/143)	32.2% (46/143)	0.7% (1/143)	23.1% (33/143)	13.3% (19/143)	11.9% (17/143)	16.8% (24/143)
Redness	52.4% (75/143)	37.8 (54/143)	13.3 (19/143)	1.4% (2/143)	32.2% (46/143)	14.7% (21/143)	3.5% (5/143)	2.1% (3/143)
Bumps you can feel but not see	48.3% (69/143)	32.2% (46/143)	15.4% (22/143)	0.7% (1/143)	23.8% (34/143)	15.4% (22/143)	4.9% (7/143)	4.2% (6/143)
Pain/discomfort (including burning/ stinging)	36.4% 52/143	28.7 (41/143)	7.7% (11/143)	0.0% (0/143)	25.2% (36/143)	7.7% (11/143)	2.8% (4/143)	0.7% (1/143)
Itching	18.9% (27/143)	16.1% (23/143)	2.1% (3/143)	0.7% (1/143)	11.9% (17/143)	4.9% (7/143)	1.4% (2/143)	0.7% (1/143)

[a] M = number of subjects who recorded responses in the diaries after initial treatment.

[b] Maximum severity reported as recorded in the patient diary.

[c] Maximum duration reported, as recorded in the patient diary.

CTR = common treatment response; SP= Safety Population

Percentages were based on M.

Table 14 Study M930121002: Common Treatment Responses by, Maximum Severity & Duration After Initial Treatment, SP, Subjects Treated with Needle

CTR	Total % (n/M [a])	Severity[b]			Duration[c]			
		Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)
Any CTR	94.6% (70/74)	39.2% (29/74)	43.2% (32/74)	12.2% (9/74)	14.9% (11/74)	24.3% (18/74)	21.6% (16/74)	33.8% (25/74)
Swelling	78.4% (58/74)	43.2% (32/74)	32.4% (24/74)	2.7% (2/74)	31.1% (23/74)	21.6% (16/74)	8.1% (6/74)	17.6% (13/74)
Bruising	82.4% (61/74)	40.5% (30/74)	31.1% (23/74)	10.8% (8/74)	12.2% (9/74)	23.0% (17/74)	24.3% (18/74)	23.0% (17/74)
Visible lumps	63.5% (47/74)	35.1% (26/74)	28.4% (21/74)	0.0% (0/74)	20.3% (15/74)	18.9% (14/74)	10.8% (8/74)	13.5% (10/74)

CTR	Total % (n/M [a])	Severity[b]			Duration[c]			
		Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)
Redness	58.1% (43/74)	41.9% (31/74)	13.5% (10/74)	2.7% (2/74)	31.1% (23/74)	18.9% (14/74)	6.8% (5/74)	1.4% (1/74)
Bumps you can feel but not see	41.9% (31/74)	28.4% (21/74)	13.5% (10/74)	0.0% (0/74)	21.6% (16/74)	14.9% (11/74)	5.4% (4/74)	0.0% (0/74)
Pain/discomfort (including burning/ stinging)	33.8% (25/74)	27.0% (20/74)	6.8% (5/74)	0.0% (0/74)	25.7% (19/74)	6.8% (5/74)	1.4% (1/74)	0.0% (0/74)
Itching	18.9% (14/74)	16.2% (12/74)	1.4% (1/74)	1.4% (1/74)	12.2% (9/74)	4.1% (3/74)	2.7% (2/74)	0.0% (0/74)

[a] M = number of subjects who recorded responses in the diaries after initial treatment.

[b] Maximum severity reported as recorded in the patient diary.

[c] Maximum duration reported, as recorded in the patient diary.

CTR = common treatment response; SP= Safety Population

Percentages were based on M.

Table 15 Study M930121002: Common Treatment Responses by, Maximum Severity & Duration After Initial Treatment, SP, Subjects Treated with Cannula

CTR	Total % (n/M [a])	Severity[b]			Duration[c]			
		Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)
Any CTR	89.9% (62/69)	37.7% (26/69)	46.4% (32/69)	5.8% (4/69)	20.3% (14/69)	18.8% (13/69)	18.8% (13/69)	31.9% (22/69)
Swelling	73.9% (51/69)	42.0% (29/69)	29.0% (20/69)	2.9% (2/69)	23.2% (16/69)	23.2% (16/69)	13.0% (9/69)	14.5% (10/69)
Bruising	59.4% (41/69)	43.5% (30/69)	13.0% (9/69)	2.9% (2/69)	24.6% (17/69)	13.0% (9/69)	8.7% (6/69)	13.0% (9/69)
Visible lumps	66.7% (46/69)	29.0% (20/69)	36.2% (25/69)	1.4% (1/69)	26.1% (18/69)	7.2% (5/69)	13.0% (9/69)	20.3% (14/69)
Redness	46.4% (32/69)	33.3% (23/69)	13.0% (9/69)	0.0% (0/69)	33.3% (23/69)	10.1% (7/69)	0.0% (0/69)	2.9% (2/69)
Bumps you can feel but not see	55.1% (38/69)	36.2% (25/69)	17.4% (12/69)	1.4% (1/69)	26.1% (18/69)	15.9% (11/69)	4.3% (3/69)	8.7% (6/69)
Pain/discomfort (including burning/ stinging)	39.1% (27/69)	30.4% (21/69)	8.7% (6/69)	0.0% (0/69)	24.6% (17/69)	8.7% (6/69)	4.3% (3/69)	1.4% (1/69)
Itching	18.8% (13/69)	15.9% (11/69)	2.9% (2/69)	0.0% (0/69)	11.6% (8/69)	5.8% (4/69)	0.0% (0/69)	1.4% (1/69)

[a] M = number of subjects who recorded responses in the diaries after initial treatment.

CTR	Total % (n/M [a])	Severity[b]			Duration[c]			
		Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)

[b] Maximum severity reported as recorded in the patient diary.

[c] Maximum duration reported, as recorded in the patient diary.

CTR = common treatment response; SP= Safety Population

Percentages were based on M.

Table 14 Pivotal Study: Common Treatment Responses by Maximum Severity & Duration After Touch-Up Treatment, SP

CTR	Total % (n/M [a])	Severity[b]			Duration[c]			
		Mild % (n/M)	Moderate% (n/M)	Severe % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)
Any CTR	81.0% (64/79)	45.6% (36/79)	27.8% (22/79)	7.6% (6/79)	15.2% (12/79)	20.3% (16/79)	20.3% (16/79)	25.3% (20/79)
Swelling	67.1% (53/79)	50.6% (40/79)	13.9% (11/79)	2.5% (2/79)	20.3% (16/79)	13.9% (11/79)	20.3% (16/79)	12.7% (10/79)
Bruising	73.4% (58/79)	54.4% (43/79)	15.2% (12/79)	3.8% (3/79)	17.7% (14/79)	16.5% (13/79)	26.6% (21/79)	12.7% (10/79)
Visible lumps	54.4% (43/79)	39.2% (31/79)	12.7% (10/79)	2.5% (2/79)	22.8% (18/79)	16.5% (13/79)	7.6% (6/79)	7.6% (6/79)
Redness	44.3% (35/79)	38.0% (30/79)	5.1% (4/79)	1.3% (1/79)	24.1% (19/79)	13.9% (11/79)	5.1% (4/79)	1.3% (1/79)
Bumps you can feel but not see	32.9% (26/79)	29.1% (23/79)	3.8% (3/79)	0.0% (0/79)	21.5% (17/79)	8.9% (7/79)	1.3% (1/79)	1.3% (1/79)
Pain/discomfort (including burning/ stinging)	20.3% (16/79)	16.5% (13/79)	3.8% (3/79)	0% (0/79)	11.4% (9/79)	7.6% (6/79)	0.0% (0/79)	1.3% (1/79)
Itching	8.9% (7/79)	6.3% (5/79)	1.3% (1/79)	1.3% (1/79)	5.1% (4/79)	2.5% (2/79)	0.0% (0/79)	1.3% (1/79)

[a] M = number of subjects who recorded responses in the diaries after touch-up treatment.

[b] Maximum severity reported as recorded in the patient diary.

[c] Maximum duration reported, as recorded in the patient diary.

CTR = common treatment response; SP= Safety Population

Percentages were based on M.

Table 15 Pivotal Study: Common Treatment Responses by Maximum Severity & Duration After Retreatment Treatment, SP

CTR	Total % (n/M [a])	Severity[b]			Duration[c]			
		Mild % (n/M)	Moderate% (n/M)	Severe % (n/M)	1–3 Days % (n/M)	4–7 Days % (n/M)	8–14 Days % (n/M)	≥15–28 Days % (n/M)
Any CTR	68.5% (37/54)	29.6% (16/54)	29.6% (16/54)	9.3% (5/54)	11.1% (6/54)	9.3% (5/54)	29.6% (16/54)	18.5% (10/54)
Swelling	61.1% (33/54)	33.3% (18/54)	25.9% (14/54)	1.9% (1/54)	13.0% (7/54)	13.0% (7/54)	25.9% (14/54)	9.3% (5/54)
Bruising	53.7% (29/54)	29.6% (16/54)	16.7% (9/54)	7.4% (4/54)	7.4% (4/54)	13.0% (7/54)	20.4% (11/54)	13.0% (7/54)
Visible lumps	48.1% (26/54)	24.1% (13/54)	22.2% (12/54)	1.9% (1/54)	11.1% (6/54)	18.5% (10/54)	13.0% (7/54)	5.6% (3/54)
Redness	50.0% (27/54)	33.3% (18/54)	16.7% (9/54)	0.0% (0/54)	27.8% (15/54)	9.3% (5/54)	13.0% (7/54)	0.0% (0/54)
Bumps you can feel but not see	33.3% (18/54)	24.1% (13/54)	9.3% (5/54)	0% (0/54)	16.7% (9/54)	7.4% (4/54)	7.4% (4/54)	1.9% (1/54)
Pain/discomfort (including burning/ stinging)	33.3% (18/54)	24.1% (13/54)	9.3% (5/54)	0.0% (0/54)	16.7% (9/54)	11.1% (6/54)	3.7% (2/54)	1.9% (1/54)
Itching	13.0% (7/54)	9.3% (5/54)	1.9% (1/54)	1.9% (1/54)	7.4% (4/54)	1.9% (1/54)	3.7% (2/54)	0.0% (0/54)

[a] M = number of subjects who recorded responses in the diaries after repeat injection.

[b] Maximum severity reported as recorded in the patient diary.

[c] Maximum duration reported, as recorded in the patient diary.

CTR = common treatment response; SP= Safety Population

Percentages were based on M.

Subject diaries were used to collect CTR information as well as specific safety concerns. Treating investigators reviewed subject diaries for potential AEs. AEs were also reported by the Investigator at follow-up visits. Treatment-related AEs were reported in 13 (9.0%) of 143 treated subjects (Table 18). The most common treatment-related AEs were injection site swelling (n=9, 6.3%). Other treatment-related AEs included: injection site nodule, injection site bruising, injection site pain, injection site dryness, and injection site erythema. Most treatment-related AEs were mild and subjects recovered within 36 days of treatment.

Table 18 Treatment Related TEAEs by PT, SP

MedDRA Preferred Term	Needle (N = 75)			Cannula (N=69)			Total (N=144)		
	N	(%)	m	n	(%)	m	n	(%)	m
Subjects with at least one treatment-related TEAE	6	(8,0)	14	7	(10.1)	15	13	(9.0)	29
Injection Site Swelling	5	(6.7)	5	4	(5.8)	5	9	(6.3)	10
Injection Site Nodule	2	(2.7)	3	2	(2.9)	4	4	(2.8)	7
Injection Site Bruising	2	(2.7)	2	1	(1.4)	2	3	(2.1)	4
Injection Site Pain	1	(1.3)	1	2	(2.9)	2	3	(2.1)	3
Injection Site Dryness	1	(1.3)	2	1	(1.4)	1	2	(1.4)	3
Injection Site Erythema	1	(1.3)	1	1	(1.4)	1	2	(1.4)	2

PT = Preferred term, SP = Safety Population
N = total number of subjects in the corresponding treatment group, n = number of subjects, m = number of treatment-related TEAEs
TEAEs were defined as AEs with onset on or after date of first administration of study treatment; treatment-related TEAEs were defined as any TEAEs related to treatment procedure or related to investigational product.

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

Safety assessments such as visual acuity, confrontational visual fields, ocular motility and retinal imaging were evaluated at the screening visit and throughout the study. Four subjects experienced a temporary and self- resolving greater than one line change in visual acuity at post-injection follow-up safety visits. All changes resolved by their next follow-up visit. None were related to treatment with Belotero Balance® (+) and did not result in an AE.

Safety Subgroup Analyses

Subgroup analyses for CTRs and AEs were performed on baseline Merz Infraorbital Hollow Assessment Scale (MIHAS), injection instrument (cannula or needle), gender, Fitzpatrick skin type, age, race, and ethnicity. Numerical differences were observed between needle and cannula, but no unexpected, clinically relevant trends in CTR or AE incidences were identified between needle and cannula subgroups. In general, clinically relevant differences were not observed among the other subgroups evaluated for CTRs and AEs.

POST MARKETING SURVEILLANCE:

The following adverse events have been identified during post-approval use of Belotero Balance®. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal connection to Belotero Balance®. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Belotero Balance®: Allergic reactions including Quincke's edema, anaphylaxis, rash, hives, necrosis, inflammation, granuloma, indurations, nodules, hematoma, Tyndall effect, bumps, pustule, scarring, swelling, erythema, pain, edema, bruising, lumps, discoloration, infection, migration/displacement, asymmetry, numbness, vascular occlusion, visual disturbance.

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 following interventions have been reported: antibiotics, anti-inflammatories, corticosteroids, anti-histamines, analgesics, hyaluronidase, massage, warm compress, excision, drainage, and surgery. This information does not constitute and is not intended to be medical advice, a recommendation on how to treat an adverse event or an exhaustive list of possible interventions. Physicians should evaluate each case on an individual basis, and independently determine, based on their professional experience, what treatment(s) are appropriate, if any, for their patients.

CLINICAL STUDIES

Belotero Balance® and Belotero Balance® (+) have been studied in two anatomical areas, nasolabial folds and the infraorbital hollow region. The only difference between Belotero Balance® and Belotero Balance® (+) is the addition of lidocaine hydrochloride in Belotero Balance® (+) for the purposes of pain reduction.

For the nasolabial fold indication, the main studies evaluating safety and effectiveness were performed with Belotero Balance®. See Section 1A for study design, population, demographics and effectiveness discussion. The safety and effectiveness of lidocaine hydrochloride addition to Belotero Balance®, *referred to as Belotero Balance® (+)*, was assessed in a follow-on study. See Section 1B for the study design, population, demographics and effectiveness discussion.

For the infraorbital hollow region, a pilot study evaluating the safety and effectiveness of Belotero Balance® was performed (see Section 2A for study design, population, demographics and effectiveness discussion) followed by a pivotal study evaluating the safety and effectiveness of Belotero Balance® (+) (see Section 2B).

1. NASOLABIAL FOLDS

A. BELOTERO BALANCE®

PIVOTAL CLINICAL STUDY

STUDY DESIGN

Controlled Phase (0-24 Weeks):

A blinded, active-controlled, randomized, multicenter trial investigated the effectiveness and safety of BELOTERO BALANCE® in the treatment of nasolabial fold (NLF) wrinkles. Treatment was determined by a random allocation schedule that assigned one NLF of each subject to BELOTERO BALANCE® and the opposite NLF to a bovine collagen control dermal filler.

The initial treatment was first evaluated after 2 weeks, at which time an optional touch-up treatment was administered in order to achieve optimal correction. The follow-up phase of the main trial consisted of visits at 2, 4, 8, 12, 16, and 24 weeks after the last treatment.

OLEX Phase (24-96 Weeks):

Upon completion of the controlled phase, subjects were invited to participate in an open-label extension (OLEX) of the trial in which they received treatment with BELOTERO BALANCE® on both NLFs. The OLEX phase included follow-up visits at 32, 48, 72, and 96 weeks after the initial visit. At each subsequent visit in the OLEX phase, subjects were eligible for retreatment to one or

both NLFs if they met the injection criteria of having an SRS of 2 or 3. The OLEX study was designed to obtain data on repeated treatments with respect to both safety and duration of effectiveness.

STUDY POPULATION

The study enrolled subjects with bilateral nasolabial folds (NLFs) with a 2 or 3 SRS score. Patients were excluded if they had (or were): history of allergic/anaphylactic reactions including hypersensitivity to local anesthetics (e.g., lidocaine), hyaluronic acid preparations and/or gram-positive bacterial proteins; known history of keloids or bleeding disorders; active inflammatory process in the NLF area (skin eruptions such as cysts, pimples, rashes, cancerous/pre-cancerous lesions, psoriasis, neurodermatitis or any other active skin disease) or severe scarring that might interfere with the study assessments; pregnant, planning to become pregnant during the study or breast feeding; planning to undergo major facial surgery during the course of the study; clinically important disease within 3 months of the study (e.g., significant laboratory test abnormalities, MI, stroke, cancer, connective tissue diseases, systemic infection, uncontrolled diabetes, and medical conditions that might require use of immunosuppressive medications during the trial); severe physical, neurological or mental disease; excessive facial hair that might interfere with wrinkle evaluation; any systemic or dermatologic disorder which would interfere with the study results or increase the risk of an adverse event; used exclusionary medications or treatments; or participated in a clinical investigation within 30 days prior to the first planned injection. Entry criteria also required females were post-menopausal for at least 1 year, had a hysterectomy or tubal ligation or agreed to use an approved method of birth control.

STUDY ENDPOINTS

Wrinkle evaluations (Severity Rating Scale [SRS]) were made by a Blinded Evaluator at each study site with the aid of a validated photo-numeric scale. The primary effectiveness comparison between study treatments was made on the difference in SRS rating (assessed by the Blinded Evaluator) at the 12-Week follow-up time point during the controlled phase. Effectiveness of BELOTERO BALANCE® treatment was determined by demonstrating non-inferiority of BELOTERO BALANCE® to the bovine collagen dermal filler control with respect to the primary efficacy endpoint.

NLF correction during the OLEX phase was assessed by the treating investigator at each of the study visits by rating the wrinkle SRS scores. Duration of effectiveness was determined in comparison with the subject's baseline investigator SRS rating from the controlled-phase.

SUBJECT DEMOGRAPHICS

Controlled Phase (0-24 Weeks):

A total of 118 subjects at 6 investigational sites in the United States (US) were enrolled in the study and received at least one injection in each NLF. Entrance to the study required an SRS score of 2 (moderate) or 3 (severe) on each NLF. Of the 118 subjects treated, 106 (89.8%) subjects completed all assessments through Week 24. Subject demographics are summarized in Table 19.

Table 16 Controlled Phase Subject Demographics

	NUMBER OF SUBJECTS (%)
Sex	
Female	109 (92.4)
Male	9 (7.6)
Race	
White	114 (96.6)
Black/African-American	2 (1.7)
Asian	1 (0.8)
Other	1 (0.8)
Age (years)	
MEAN (SD)	52.4 (9.5)

OLEX Phase (24-96 Weeks)

95 of the 106 (89.6%) subjects who completed the controlled phase study elected to receive retreatment with Belotero Balance® on both sides in the OLEX portion of the study. Subject demographics in the OLEX phase were similar to the controlled phase described above.

STUDY TREATMENT

Controlled Phase (0-24 Weeks):

Subjects received an average of 1.16 mL of Belotero Balance® and 1.37 ml of Control implant at the initial injection. 94 of 118 (79.7%) subjects received retreatment 2 weeks later for optimal correction and received an average of 0.81 mL of BELOTERO BALANCE® and 0.94 ml of Control implant at retreatment (touch-up).

OLEX Phase (24-96 Weeks):

During the OLEX phase, 85 of 95 (89.5%) subjects were evaluated through Week 96. The mean cumulative volume of Belotero Balance® received from Week 24 through Week 96 was 1.75 mL in the NLF initially treated with Belotero Balance® and 2.45 mL in the NLF initially treated with Control. The mean number of injections received during the OLEX phase was 2.6 in the NLF initially treated with Belotero Balance® and 2.9 in the NLF initially treated with Control with a mean time between injections of 37 weeks and 31 weeks respectively. The average time between injections following the Week 24 injection (start of OLEX phase) is presented in Table 20.

Table 20 Average Time between Injections during the OLEX Phase

Study Visit	Side Previously Injected with Belotero®	Side Previously Injected with Collagen Control
Number of Injections	85	87
Mean Number of Weeks between Injections (SD)	37.04 (15.62)	30.87 (13.59)
Min, Max (Weeks)	15.4, 73.1	9.7, 71.9

EFFECTIVENESS

Controlled Phase

The results from the controlled phase demonstrate that Belotero Balance® is non-inferior to the Control in the correction of NLFs. The primary effectiveness results from the pivotal clinical study for Belotero Balance® were based on the Blinded Evaluator's assessment of NLF severity (SRS) at Week 12 and are presented in Table 21 .

Table 21 Mean Blinded Evaluator SRS Scores

Time-point	N	BELOTERO BALANCE®	Collagen Control
Initial Treatment	118	2.5	2.5
Week 12	118	1.25	1.51

Immunogenicity

A pre-existing antibody response against Belotero Balance® was not observed in any subjects and 5/116 (4.3%) subjects developed an antibody response after Belotero Balance® injection. None of the subjects with elevated anti-Belotero Balance® titers post-treatment experienced adverse events that were consistent with the clinical symptoms identified in MedDRA as possibly reflecting a local or systemic hypersensitivity reaction. No patient displayed a positive IgE response against the device.

FITZPATRICK SKIN TYPE IV, V, VI STUDY:

STUDY DESIGN

The safety and effectiveness of Belotero Balance® in the treatment of NLFs in subjects with Fitzpatrick Skin Phototype scores of IV, V and VI was investigated in an open label, multi-center trial. Treatment consisted of injection of Belotero Balance® into both nasolabial folds of subjects who were an IV, V or VI on the Fitzpatrick Skin Type Scale and whose nasolabial folds were a 2 or 3 on the Wrinkle Severity Scale (SRS). The initial treatment was evaluated after 2 weeks and if necessary, an optional touch-up treatment was administered in order to achieve optimal correction. The follow-up phase consisted of visits at Weeks 2, 4, 8, 12, 16, and 24 after the last treatment. Wrinkle evaluations (SRS) were made by an Evaluator Investigator at each study site with the aid of a validated, photonumeric scale.

STUDY ENDPOINTS

The primary objective of this study was to evaluate the safety of Belotero Balance® in the treatment of NLFs in individuals with Fitzpatrick Skin Type scores IV and greater. The safety profile of Belotero Balance® in this study population was similar to that observed in the pivotal study (see Adverse Events). Effectiveness of NLF correction (as evaluated by the Evaluator Investigator) was evaluated as a secondary objective. The main effectiveness comparison between baseline rating and after treatment rating was made on the difference in SRS rating (assessed by Evaluator Investigator) at the 12 week follow-up time point. Secondary effectiveness evaluations included investigator/global assessments, investigator visual analogue scale assessments, and Treating Investigator SRS grades.

STUDY DEMOGRAPHICS

A total of 93 subjects with Fitzpatrick skin type IV, V or VI were enrolled at 3 investigational sites in the US. Of 93 subjects treated, 88 subjects completed the study. Subject demographics are summarized in Table 22 .

Table 22 Demographic Summary by Fitzpatrick Skin Type for All Subjects with Skin Types IV, V and VI

	Number of Subjects (%)
Sex	
Female	80 (86.0)
Male	13 (14.0)
Race	
White	1 (1.1)
Black/African-American	90 (96.8)
Asian	1 (1.1)
Other	0 (0.0)
Fitzpatrick Skin Type	
IV	4 (3.7)
V	37 (34.4)
VI	52 (48.4)
Age (years)	
MEAN (SD)	51.5 (10.1)

STUDY TREATMENT

The mean volumes of Belotero Balance® initially injected into the left and right NLFs were 1.46 and 1.47 mLs, respectively. 66 of 93 subjects (70.1%) received touch-up injections. All but 1 subject received touch-up injections in both NLFs. The mean volumes of Belotero Balance® injected for the touch-up procedure were 0.93 mL in the left NLF and 0.90 mL in the right NLF.

Post-approval STUDY

STUDY DESIGN

Nine study sites participated in this post-approval safety study evaluating adverse events after re-treatment of Belotero Balance®. Six of the study sites had previously participated in the Belotero Balance® pivotal clinical trial and 3 of the study sites had previously participated in the Belotero Balance® Fitzpatrick Skin Type IV-VI Study. One hundred seventeen (117) subjects that had participated in the aforementioned studies and had met additional study selection criteria were enrolled in the study.

Subjects received bilateral retreatment of their nasolabial folds with Belotero Balance®. The dermal filler was injected until an optimal cosmetic result was achieved. Subjects were eligible to receive a touch-up treatment 2 weeks after the initial treatment, if necessary. After each re-treatment, each subject received a take-home diary to record any adverse events during the following two weeks. At 2 weeks, 4 weeks, and the last visit, subjects returned to the treating investigator for assessment of their nasolabial folds, collection of completed take-home diaries, assessment of observed adverse events, and recording of concomitant medications. Study participation ended at the completion of the 4 week visit for subjects that did not receive a touch-up, and at the 6 week visit for subjects that had received a touch-up.

STUDY ENDPOINTS

The primary endpoint of this study was to evaluate the safety of retreatment with Belotero Balance® by determining the incidence rate of severe common adverse events and comparing this rate to the incidence rate of severe common adverse events after initial treatment with Belotero Balance®. Investigator assessment of adverse events was performed after bilateral retreatment and touch-up (if needed), of the nasolabial folds. Subjects were assessed for adverse events 2 and 4 weeks after injection. If a touch-up was needed, assessment was performed 2 weeks after the touch-up injection (i.e., 6 weeks after the initial injection).

STUDY DEMOGRAPHICS

Table 23 provides a summary of the demographics of the subjects participating in the study.

Table 23 Subject Demographics, N = 117 Subjects

	Number of Subjects (%)
Gender - N (%)	
Female	104 (88.9%)
Male	13 (11.1%)
Race – N (%)*	
Caucasian	63 (54.3%)
African American	50 (43.1%)
Hispanic	2 (1.7%)
Asian	1 (0.9%)
Fitzpatrick Skin Type – N (%)	
I	4 (3.4%)
II	34 (29.1%)
III	23 (19.7%)
IV	4 (3.4%)
V	20 (17.1%)
VI	32 (27.4%)
Age (years)	
Mean (SD, Range)	57.04 (9.40, 32-81)

* One subject did not specify race.

SUBJECT ACCOUNTABILITY

One hundred seventeen (117) subjects were enrolled in the post-approval study. All 117 subjects were retreated at the two week visit (100% follow-up rate). Of the 117 re-treated subjects, one hundred thirteen (113) subjects completed the final follow-up visit (97% follow-up rate). Four (4) patients withdrew after retreatment but prior to their final study visit.

EFFECTIVENESS

Effectiveness of Belotero Balance® was not an endpoint in this study, and therefore, is not reported in this summary.

SAFETY

The study assessed if the rate of 'severe' common adverse events after retreatment with Belotero Balance® ('Retreatment study') differed from the rate reported in the pivotal clinical trial and the Fitzpatrick Skin Type IV-VI studies ('Initial treatment studies'). Common was defined as adverse

event types occurring in >5% of study subjects and included bruising, itching, pain, redness, swelling, discoloration, nodule and induration.

Tables 4 through 7 summarize 'severe' common adverse event rates in the Initial treatment studies compared to the Retreatment study. The analysis indicates that retreatment with Belotero Balance® does not result in an increase in 'severe' common adverse events. The duration of severe common adverse events in the retreatment study was generally short (mean 10.2 days, SD 5.6, 95% CI = 8.2, 12.2) and none of these events required treatment. See ADVERSE EVENTS, Belotero Balance® POST-APPROVAL STUDY section of the package insert for analysis of the data.

STUDY STRENGTHS

Study evaluated over 100 retreatment patients.

STUDY LIMITATIONS

Belotero Balance® was studied in predominantly female patients.

B. Belotero Balance® **(+)**

- Belotero Balance® **(+) NASOLABIAL FOLD PRE-MARKET STUDY**

STUDY DESIGN

The safety and effectiveness of BELOTERO BALANCE® (+) injectable gel for the treatment of nasolabial folds (NLFs) was evaluated in a multi-center, prospective, randomized clinical trial. The primary objective of the study was to assess pain control when Belotero Balance® (+) was used to treat nasolabial folds.

Subjects were randomized to receive Belotero Balance® (+) gel (Test product) in one fold and the commercially available Belotero Balance® gel (Control product), in the contralateral fold. Pain assessments were performed immediately after treatment, and 30 and 60 minutes post injection. Subjects were eligible for an optional touch-up at the investigator's discretion and to achieve optimal correction, at week 2. All study subjects were followed to week 6 where safety endpoints and other aesthetic endpoints were assessed.

STUDY ENDPOINTS

The primary effectiveness evaluation, mean reduction in pain, was conducted immediately after split-face NLF treatment using a 10 cm visual analog scale (VAS); additionally other effectiveness endpoints evaluating the mean reduction in pain were assessed 30 and 60 minutes after injection using the VAS. Aesthetic outcomes were assessed by the blinded assessing investigator using the validated Merz Nasolabial Fold Scale (MNLFS), the Global Aesthetic Improvement Scale (GAIS), and by the study subject using the GAIS, the FACE-Q appraisal of NLF lines and the FACE-Q age visual analogue scale.

The safety endpoints evaluated were the incidence and nature of device related or injected related adverse events (AEs) and serious adverse events (SAEs) as well as common treatment responses (CTRs).

STUDY DEMOGRAPHICS

Table 24 presents study demographics. 90.4% of the subjects were female. Subjects ranged from 37 to 80 years of age with a mean (standard deviation, SD) age of 58.4 (10.2) years. Fifty-one (51) of the 52 subjects classified themselves as not Hispanic or not Latino. Over two-thirds of the randomized subjects (n=36; 69.2%) were Caucasian and 16 (30.8%) subjects were classified black/African American. In regards to Fitzpatrick Skin Type, 36 (69.2%) of subjects were classified as skin types I, II, or III, and 16 (30.8%) of subjects were classified as skin types IV, V, or VI.

Table 24 Patient Demographics (Safety Evaluation Set)

	Total (N=52)	
Sex (n (%))		
Male	5	(9.6)
Female	47	(90.4)
Age [years]		
Mean (SD)	58.4	(10.2)
Ethnic origin (n (%))*		
Hispanic or Latino	1	(1.9)
Not Hispanic and not Latino	51	(98.1)
Race (n (%))		
Black or African American	16	(30.8)
Caucasian	36	(69.2)
Fitzpatrick Skin Type (n (%))		
Type I	1	(1.9)
Type II	20	(38.5)
Type III	15	(28.8)
Type IV	4	(7.7)
Type V	5	(9.6)
Type VI	7	(13.5)

STUDY TREATMENT

The study protocol allowed a maximum of 3.0 mL in a single NLF per treatment session. The overall total mean volume injected to achieve optimal correction results was 1.59 mL for Belotero Balance® (+), and 1.50 mL for Belotero Balance®. The proportion of subjects who received touch-up treatment at Week 2 with Belotero Balance® (+) was 76.9% and with Belotero Balance® was 75.0%.

At the initial injection, the injection technique included serial puncture (26.9%), linear threading/tunneling (88.5%) and fanning (13.5%) for both Belotero Balance® (+) and Belotero Balance®.

PRIMARY EFFECTIVENESS

The primary endpoint was the demonstration of a statistically significant, mean reduction in pain, measured using a 10-cm VAS, in the test NLF compared to the control NLF immediately after

split face NLF treatment on Day 1. Time zero was defined as the time the last injection needle was removed from each NLF, separately, after a full correction. The mean (95% CI) pain VAS score in the test NLF (Belotero Balance® (+) was 3.07 (2.54 to 3.59), which was lower than the mean (95% CI) pain VAS score of 5.94 (5.27 to 6.61) in the control NLFs. Lower scores in the test NLFs indicated that on average subjects experienced less pain during the injection when treated with Belotero Balance® (+) than when treated with the control. Differences in these scores were found to be statistically significant ($p<0.0001$) indicating that treatment with Belotero Balance® (+) is less painful than BELOTERO BALANCE®.

OTHER PAIN EFFECTIVENESS ENDPOINTS

- **Reduction in Pain VAS Scores in** Belotero Balance® **(+) and** Belotero Balance® **at 30 and 60 minutes post-treatment.**

Mean (95% CI) pain VAS score 30 minutes post-injection in Belotero Balance® (+) was 0.73 (0.43 to 1.03), which was lower than the mean (95% CI) pain VAS score of 2.31 (1.75 to 2.86) in the control Belotero Balance®. Differences in these scores were found to be statistically significant ($p<0.0001$) indicating that treatment with BELOTERO BALANCE® (+) is less painful than Belotero Balance® when pain was assessed 30 minutes post-treatment.

Mean (95% CI) pain VAS score 60 minutes post-injection in Belotero Balance® (+) was 0.28 (0.07 to 0.49), which was lower than the mean (95% CI) pain VAS score of 0.71 (0.43 to 0.99) in the control Belotero Balance®. Differences in these scores were found to be statistically significant ($p<0.0001$) indicating that treatment with Belotero Balance® (+) is less painful than Belotero Balance® when pain was assessed 60 minutes post-treatment.

- **Pain Preference Assessment**

Fifty-one (98.1%) of the fifty-two study subjects self-reported that they noticed a difference in pain between NLFs when comparing one side treated with Belotero Balance® (+) to the other side treated with Belotero Balance®. Of the 51 subjects who reported that there was a difference in pain between the two NLFs, forty-six (90.2%) self-reported that the NLF treated Belotero Balance® (+) was less painful than the NLF treated with Belotero Balance®.

AESTHETIC EFFECTIVENESS ENDPOINTS

- **Merz Nasolabial Fold Scale Assessment**

The secondary effectiveness endpoint was a comparison of responder rates between test and control NLFs, separately at Week 6, assessed live by a blinded evaluator according to the Merz NLF scale. NLFs treated with the test product demonstrated similar Merz NLF scale scores as the control product.

At baseline, all subjects enrolled in the study had symmetrical NLF scores of 2 (moderate folds) or 3 (severe folds). Twenty-five (48.1%) of fifty-two subjects had both right and left NLF scores of 2 (moderate folds) and twenty-seven (51.9%) of fifty-two subjects had both right and left NLF scores of 3 (severe folds) at baseline. At week 6, NLFs treated with Belotero Balance® (+) demonstrated comparable Merz NLF scale scores as Belotero Balance®. For the secondary effectiveness endpoint related to the blinded-evaluator ratings on the Merz NLF Scale, the Belotero

Balance® (+) and Belotero Balance® products demonstrated statistically similar treatment effectiveness (p = 0.6547) when comparing responder rates in both NLF within each subject.

- **Blinded Evaluator GAIS Scores at Week 6**

Blinded evaluator GAIS scores demonstrated similar results in the NLFs treated with Belotero Balance® (+) and Belotero Balance® products. Approximately 63% of subjects NLFs treated with the Belotero Balance® (+) demonstrated level of improvement ('very much improved,' 'much improved,' or 'improved') on the blinded evaluator GAIS at Week 6 . Similarly, approximately 65% of subjects NLFs treated with Belotero Balance® product demonstrated level of improvement. No subjects worsened in either NLF at Week 6 post-treatment when comparing the NLFs treated with Belotero Balance® (+) and Belotero Balance® products.

- **Subject GAIS Scores at Week 6**

Subject GAIS scores demonstrated similar results in the NLFs treated with Belotero Balance® (+) and Belotero Balance® products. Approximately 77% of subjects NLFs treated with the Belotero Balance® (+) and Belotero Balance® products demonstrated level of improvement ('very much improved,' 'much improved,' or 'improved') on the blinded evaluator GAIS at Week 6. No subjects worsened in either NLF at Week 6 post-treatment when comparing the NLFs treated with Belotero Balance® (+) and Belotero Balance® products.

- **Rasch-Transformed FACE-Q Appraisal of NLF Lines**

When subjects assessed the entire face using the FACE-Q appraisal of NLF lines, the Rasch-transformed scores increased from baseline (39.3) to Week 6 (58.8). Increases in the Rasch-transformed scores translate to improved appraisals of NLFs, specifically, subjects were less bothered by: (a) how their NLFs looked compared with other people their age; (b) how their NLFs looked when they smiled; (c) how old their NLFs made them look; (d) how their NLFs looked with their face is relaxed; and (e) how deep their NLFs were. Overall, changes in FACE-Q appraisal scores indicates subjects were satisfied with NLF treatment using both BELOTERO BALANCE® (+) and BELOTERO BALANCE® in a split-face design.

- **FACE-Q Age VAS Scores**

At baseline, subjects reported that they look older than their age prior to NLF treatment with a mean of 0.7 years. The median FACE-Q age VAS scores demonstrated that subjects reported looking approximately 5 years younger after treatment of the NLF. Over three-fourths (78.4%) of the subjects indicated that they looked younger when comparing their looks from baseline to Week 6.

2. INFRAORIBITAL HOLLOWS

A. Belotero Balance®

- **PILOT STUDY FOR VOLUME AUGMENTATION OF THE INFRAORBITAL HOLLOWS**

A prospective, multi-center, evaluator-blinded, randomized-controlled study was conducted to define the safety, effectiveness, and patient-reported outcomes of BELOTERO BALANCE® for

the improvement in the Infraorbital Hollow (IOH) for a future pivotal study, that would utilize Belotero Balance® (+).[4]

Across 3 investigational sites, a total of 66 subjects were randomized to treatment with Belotero Balance® (N=43) or an untreated control (N=23) at the onset of the study. For subjects randomized to the Belotero Balance® treatment group, both right and left IOHs received treatment using a 27G x 40mm blunt-tipped cannula (Figure 1). To achieve symmetrical correction, an optional touch-up injection was performed in one or both IOHs, if deemed necessary, approximately one-month after the initial injection.

Treated subjects had a safety phone call at 72 hours after baseline injection and in-clinic safety visit at Week 2. At Month 1, treated subjects had an in-clinic safety visit and an optional touch-up, if deemed necessary by the treating investigator. Subjects who received a touch-up had an additional safety phone call at 72 hours and Month 1 visit post touch-up injection. For all treated subjects, the follow-up period for safety consisted of visits at Months 2, 3, 6, 9, and 12 post last injection. Effectiveness assessments were performed at baseline, and Month 2 post last injection (baseline or touch-up) for treated subjects or Month 2 post baseline visit for control subjects. After Month 2, control subjects exited the study.

STUDY ENDPOINTS

The primary effectiveness measure for this study was the comparison of the responder rate between the treatment group and the untreated control group at Month 2, according to the Merz Infraorbital Hollow Assessment Scale[5] (MIHAS) as assessed by a blinded evaluator (Figure 1).

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[4] *The only difference between Belotero Balance® and Belotero Balance® (+) is the addition of lidocaine hydrochloride in Belotero Balance® (+) for the purposes of pain reduction.*

[5] MIHAS is a validated 5-point aesthetic assessment scale considered fit-for-use in a clinical setting where qualified healthcare practitioners can accurately rate the aesthetic appearance of a subject pre- and post-treatment infraorbital hollow. See publication: Development and Validation of a Photonumeric Scale for Evaluation of Infraorbital Hollowing. BS Biesman MD, A Verma DrPH MPH, BN Cheng MS, AW Duncan MS PhD. Journal of Drugs in Dermatology 2023. 22(1): 74-81.doi:10.36849/JDD.7191.

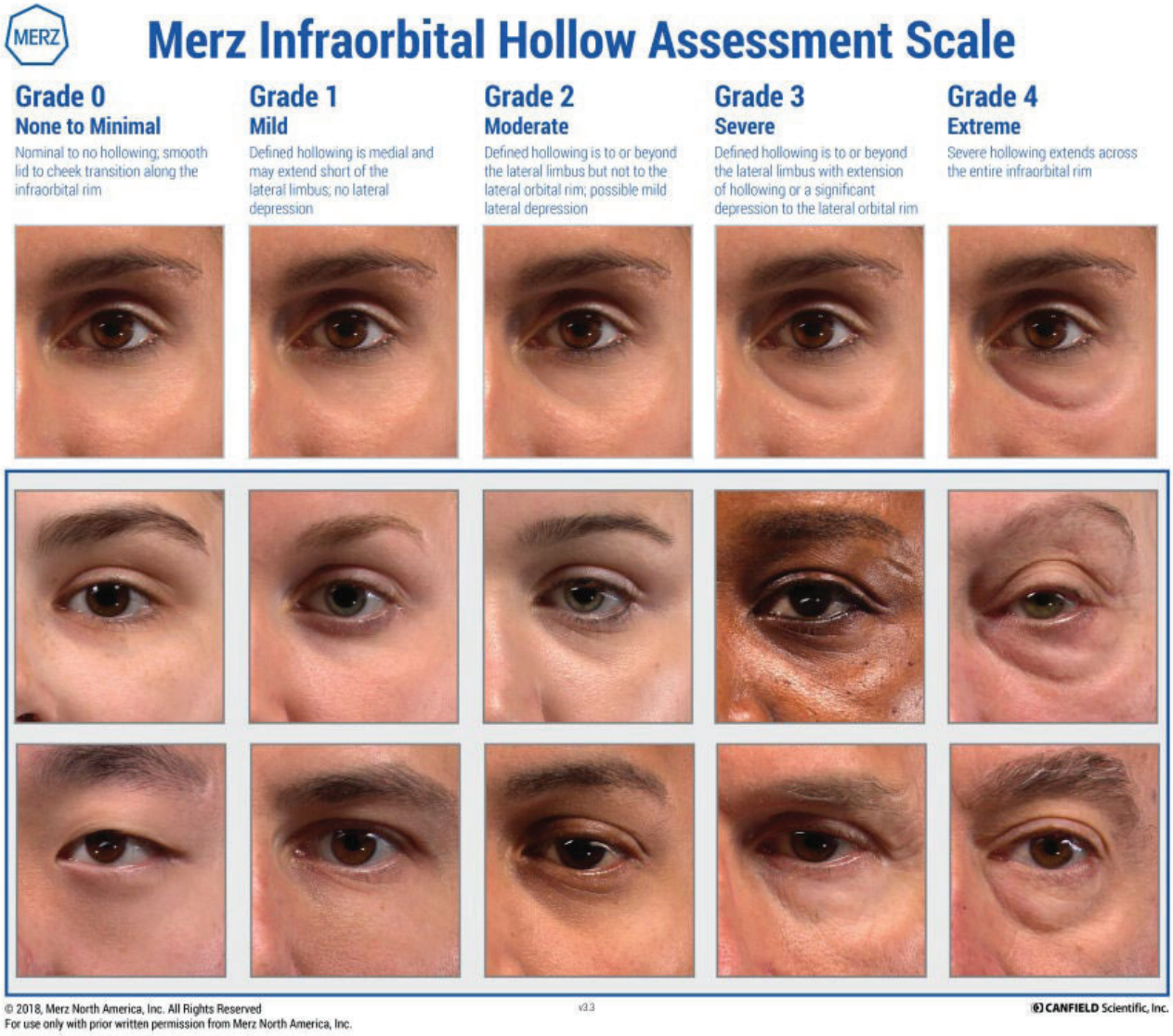


Figure 1 Merz Infraorbital Hollow Assessment Scale (MIHAS)

Responder rate was defined as percentage of participants with treatment response who achieved greater than or equal to (≥) one grade improvement on both IOHs on the MIHAS.

Secondary outcome measures included assessments by the evaluating investigator and the subject for global aesthetic improvement using the GAIS and the subject's self-assessment using the FACE-Q *Satisfaction with Eyes* questionnaire.

Safety measures included evaluation of the incidence and nature of device- and/or injection related AEs and SAEs observed during the study, incidence, severity, and duration of CTRs and AEs, vision assessments including Snellen visual acuity, confrontational visual fields, ocular motility and undilated central retinal fundoscopic exam using an ophthalmoscope.

STUDY DEMOGRAPHICS

Table 25 Belotero Balance® IOH Pilot Study Demographics

	BELOTERO BALANCE® N=43)	Untreated Control (N = 22	Total (N=65)
Sex (n (%))			
Male	37 (86.0)	18 (81.8)	55 (84.6)
Female	6 (14.0)	4 (18.2)	10 (15.4)
Age [years]			
Mean (SD)	45.9 (12.6)	47.3 (11.6)	46.4 (12.2)
Ethnic origin (n (%))			
Hispanic or Latino	5 (11.6)	2 (9.1)	7 (10.8)
Not Hispanic and not Latino	38 (88.4)	20 (90.9)	58 (89.2)
Race (n (%))			
White	38 (88.4)	17 (77.3)	55 (84.6)
Black or African American	3 (7.0)	4 (18.2)	7 (10.8)
American Indian or Alaska Native	1 (2.3)	1 (4.5)	2 (3.1)
Native Hawaiian or Other Pacific Islander	1 (2.3)	0 (0.0)	1 (1.5)
Fitzpatrick Skin Type (n (%))			
Type I – III	29 (67.4)	16 (72.7)	45 (69.2)
Type IV – VI	14 (32.6)	6 (27.3)	20 (30.8)

STUDY TREATMENT

Injections into the infraorbital hollow were in the supraperiosteal plane with a 27G x 40 mm cannula. Insertion sites were at the malar and zygomatic regions. Subjects were injected using a combination of tunneling/threading and fanning injection techniques. The total volume used to achieve optimal improvement for each infraorbital hollow ranged from 0.4 mL to 1.0 mL with a mean total initial volume (SD) injected in both IOHs was 1.71 mL (0.37). A touch-up treatment was performed for 58.1% (25/43) of subjects. The mean total volume (SD) used for touch-up treatment was 0.71 mL (0.30).

EFFECTIVENESS RESULTS

Belotero Balance® provided a clinically and statistically significant improvement in the appearance of the infraorbital hollow compared to the no-treatment control group at Month 2. The primary effectiveness criteria were met as statistically significant differences were demonstrated between the response rates in the treatment group and the control group, based on the Intention to Treat (ITT) Population using observed cases. 81.6% (31/38) subjects in the treatment group and 9.5% (2/21) in the control group were responders. The 95% CI for the difference in response rates was [47.5%, 83.5%].

At Month 2, the GAIS responder rate was at 100% (38/38) based on the Treating Investigator assessment and 92.1% (35/38) based on the subjects' assessment, where the responder rate was the percentage (%) of subjects with a score of improved, much improved, or very much improved compared to baseline.

The overall findings of the FACE-Q satisfaction with eyes demonstrated higher satisfaction with eye appearance (better outcome) post-treatment when comparing baseline to Month 2. In the treatment group, the mean (SD) Rasch-transformed score increased from 42.3 (15.24) at baseline to 71.4 (18.10) at Month 2. The mean (SD) change from baseline to Month 2 was 28.8 (23.24).

B. Belotero Balance ® **(+)**

- **PIVOTAL STUDY OF BELOTERO BALANCE® (+) LIDOCAINE FOR VOLUME AUGMENTATION OF THE INFRAORBITAL HOLLOWS**

PIVOTAL STUDY DESIGN

A prospective, multicenter, randomized, evaluator-blinded, comparative pivotal study was conducted to evaluate the safety and effectiveness of Belotero Balance ® (+) for the improvement of the infraorbital hollow area. Across 9 investigational sites, a total of 150 subjects were randomized at study start into four groups using a 2:2:1:1 randomization as follows: Belotero Balance ® (+) treatment with a needle (N=49), Belotero Balance ® (+) treatment with a cannula (N=48), delayed-treatment control with a needle (N=26) or delayed-treatment control with a cannula (N=21). Subjects randomized to the delayed-treatment control group received treatment with Belotero Balance ® (+) after the Week 8 primary effectiveness assessment.

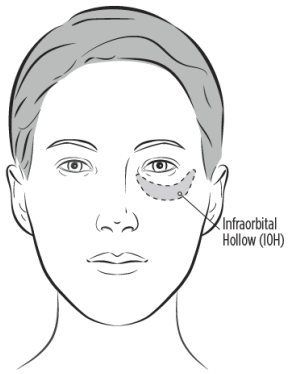


Figure 2 Infraorbital Hollow (IOH)

For all subjects, an optional touch-up injection was performed approximately four weeks after initial injection in one or both IOHs to achieve optimal aesthetic correction. Subjects randomized to treatment arm were given the option for retreatment at 48 weeks post last injection.

All subjects treated with Belotero Balance® (+) had a safety phone call at 72 hours after baseline injection and in-clinic safety visit at Week 2. At Week 4 post initial injection, treated subjects had an in-clinic safety visit and an optional touch-up, if deemed necessary by the treating investigator. Subjects who received a touch-up had an additional safety phone call at 72 hours and Week 4 visit post touch-up injection. The follow-up period for safety consisted of visits at Week 8, 12, 24, 36, 48 post last injection.

For subjects randomized to the treatment arm, an optional retreatment was offered at Week 48 with a post-treatment follow-up at 72 hours (phone call) and 4 weeks after repeat treatment. These

subjects had two additional visits at Week 56 post last injection (or 8 weeks post retreatment) and Week 72 post last injection (or 24 weeks post retreatment).

Effectiveness assessments for subjects randomized to the treatment arm were performed at screening, Week 4 post initial and touch-up (if applicable) injection, and Weeks 8, 12, 24, 36, 48, 56, and 72 post last injection. Effectiveness assessments for subjects randomized to the control/delayed treatment arm were at screening, Week 8 post screening, Week 4 post initial and touch-up (if applicable) injection, and Weeks 8, 12, 24, 36 and 48 post last injection.

STUDY ENDPOINTS

The primary effectiveness measure for this study was the comparison of the responder rate between the treatment group and the untreated control group at Week 8, according to the MIHAS as assessed by a blinded evaluator. Responder rate was defined as percentage of participants with treatment response who achieved greater than or equal to (≥) one grade improvement on both IOHs on the MIHAS.

Secondary outcome measures included assessments by the evaluating investigator and the subject for global aesthetic improvement using the GAIS and the subject's self-assessment using the FACE-Q *Satisfaction with Eyes* questionnaire.

Safety measures included evaluation of the incidence and nature of device- and/or injection related AEs and SAEs observed during the study, incidence, severity, and duration of CTRs and AEs, vision assessments including Snellen visual acuity, confrontational visual fields, ocular motility and retinal imaging.

STUDY DEMOGRAPHICS

Table 26 Belotero Balance® (+) IOH Pivotal Study Demographics

	BELOTERO BALANCE® (+) (N=97)		Control (N = 53)		Total (N=150)	
Sex (n (%))						
Male	17	(17.5)	8	(15.1)	25	(16.7)
Female	80	(82.5)	45	(84.9)	125	(83.3)
Age [years]						
Mean (SD)	44.2	(9.0)	41.6	(10.1)	43.3	(9.5)
Median	43.0		41.0		43.0	
Min, max	24, 64		23, 62		23, 64	
Age category (n (%))						
20 - 29 years	2	(2.1)	7	(13.2)	9	(6.0)
30 - 39 years	32	(33.0)	16	(30.2)	48	(32.0)
40 – 49 years	32	(33.0)	18	(34.0)	50	(33.3)
50 – 59 years	28	(28.9)	9	(17.0)	37	(24.7)
≥ 60 years	3	(3.1)	3	(5.7)	6	(4.0)
Ethnic origin (n (%))						
Hispanic or Latino	36	(37.1)	14	(26.4)	50	(33.3)
Not Hispanic and not Latino	61	(62.9)	39	(73.6)	100	(66.7)
Race (n (%))						
White	73	(75.3)	36	(67.9)	109	(72.7)
Black or African American	9	(9.3)	8	(15.1)	17	(11.3)
Asian	3	(3.1)	1	(1.9)	4	(2.7)
American Indian or Alaska Native	1	(1.0)	1	(1.9)	2	(1.3)
Native Hawaiian or Other Pacific Islander	1	(1.0)	1	(1.9)	2	(1.3)
More than one Race	10	(10.3)	6	(11.3)	16	(10.7)
Fitzpatrick Skin (n (%))						
Type I	1	(1.0)	3	(5.7)	4	(2.7)
Type II	25	(25.8)	14	(26.4)	39	(26.0)
Type III	34	(35.1)	18	(34.0)	52	(34.7)
Type IV	25	(25.8)	11	(20.8)	36	(24.0)
Type V	8	(8.2)	3	(5.7)	11	(7.3)
Type VI	4	(4.1)	4	(7.5)	8	(5.3)
BMI [kg/m2]						
Mean (SD)	26.1	(5.2)	25.5	(4.1)	25.9	(4.8)
Min, max	17.8, 41.4		18.4, 36.7		17.8, 41.4	
Baseline MIHAS severity (n (%))[1]						
Moderate = 2	34	(35.1)	20	(37.7)	54	(36.0)
Severe = 3	63	(64.9)	33	(62.3)	96	(64.0)

BMI = body mass index, Max = maximum, Min minimum, N total number of subjects in the corresponding treatment group, n number of observations, SD = standard deviation

More than one response was allowed for race.

[1]Study protocol required the same MIHAS score for left and right IOHs for all subjects at screening.

Percentages based on total number of subjects in Intention to Treat (ITT) set; subjects analyzed as randomized.

STUDY TREATMENT

Injections into the infraorbital hollow were in the supraperiosteal and/or subcutaneous plane with a Sterimedix® Silkann® 27G x 40 mm cannula or with a 27G x 1/2" needle. Insertion sites were at the malar and zygomatic regions. Subjects were injected using a serial puncture, fanning injection, or a combination of both techniques.

The total volume used to achieve optimal improvement for each infraorbital hollow ranged from 0.15 to 1.0 mL with a mean total initial volume (SD) injected in both IOHs was 1.55 mL (0.49). A touch-up treatment was performed for 55.6% (80/144) of subjects. The mean (SD) total volume used for touch-up treatment was 0.74 (0.27) mL. The mean (SD) total volume injected for repeat treatment was 0.96 (0.44) mL.

EFFECTIVENESS RESULTS

Belotero Balance® (+) provided a clinically and statistically significant improvement in the appearance of the infraorbital hollowing compared to the delayed-treatment control group at Week 8. In the ITT population and using Multiple Imputation, the estimated average MIHAS responder rate at Week 8 was 80.6% [95% CI: 71.4%, 87.4%] among the treatment group (n = 97), demonstrating a statistically significant responder rate of > 50%. In the control group (n = 53), the estimated average responder rate was 1.9% [95% CI: 0.3%, 10.2%]. The difference in estimated response rates between groups was 78.7% [95% CI: 66.3%, 85.6%], demonstrating statistically significant, superior response rate in treated subjects compared to untreated control. Table 27 provides MIHAS Responder Rate at Week 8 by injection instrument.

Table 27 M930121002: MIHAS Responder Rate at Week 8 as Assessed by Blinder Evaluator by Injection Instrument, ITT, Multiple Imputation

	Needle (N=49)	Cannula (N=48)	Control (N=53)
Number of subjects with imputed data	3	5	6
Average responder rate, n (%)[1]	42.8 (87.4)	35.4 (73.7)	1.0 (1.9)
95% CI[2], (%)	(75.0, 94.1)	(59.4, 84.3)	(0.3, 10.2)
Treatment – Control difference (%)	85.4	71.8	
95% CI[2], (%)	(70.5, 92.3)	(55.2, 82.5)	

MIHAS = Merz Infraorbital Hollowing Assessment Scale, N = total number of subjects in the corresponding treatment group, n =number of observations, CI = confidence interval
Responder was defined as a subject with ≥ 1-point improvement from baseline on MIHAS in both IOHs.
Week 8 = Week 8 post last injection in Cycle 1 for treatment-group subjects and Day 1 (pre-injection) for control subjects
Missing Week 8 IOH assessments were imputed 100 times per IOH and treatment group. Baseline MIHAS, Week 4 MIHAS, (pooled) site, and touch-up (yes/no) were included in the multiple-imputation model for treatment-group subjects; baseline MIHAS was included in the multiple-imputation model for control subjects. (Pooled) site was removed from the imputation model for control subjects due to convergence issues
[1] Average number of responders (n) and average responder rate (%) over all imputations
[2] Hierarchical-testing procedure (only if superiority of treatment over control was shown in the primary analysis): Superiority for comparison of treatment with needle versus control was concluded if the lower limit of the 95% Newcombe CI for the responder rate difference was > 0%. Only then was a confirmatory comparison of treatment with cannula versus control performed. Superiority was concluded if the lower limit of the 95%Newcombe CI for the responder rate difference was > 0%.
Subjects analyzed as randomized.

Improvement in appearance of both infraorbital hollows was clinically significant ≥ 1 point) with the majority of treated subjects demonstrating improvement through 48 weeks (see Table 28).

Table 28 Effectiveness Results for all Treated Subjects through 48 Weeks based on the MIHAS Responder Rates Using Observed Cases[a]

	BELOTERO BALANCE® (+) % (n/N)
Week 4	77.1% (108/140)
Week 8	85.4% (111/130)
Week 12	93.0% (120/129)
Week 24	84.4% (108/128)
Week 36	82.9% (102/123)
Week 48	81.4% (96/118)

[a] Week 4 post initial injection; Weeks 8-48 post last injection

Follow-up After Repeat Treatment

Retreatment with BELOTERO BALANCE® (+) was administered to 55 subjects in the BELOTERO BALANCE® (+) randomization groups. The effectiveness profile after repeat treatment was similar to that after initial treatment. At 8 weeks post retreatment, the responder rate was 86.8% (46/53) showing at least a 1-point improvement in the infraorbital hollow compared to baseline, based in the blinded evaluator assessment.

GAIS

At Week 8, the GAIS responder rate was at 98.5% (128/130) based on the Treating Investigator assessment and 97.7% (127/130) based on the subjects' assessment, where the responder rate was the % of subjects with a score of improved, much improved or very much improved compared to baseline. At Week 48, the GAIS responder rate based on the Treating Investigator was 94.9% (112/118) and the GAIS responder rate based on subject was 87.3% (103/118).

FACE-Q Questionnaire

The overall findings of the FACE-Q satisfaction with eyes demonstrated higher satisfaction with eye appearance (better outcome) when comparing baseline to Week 8 post-treatment. The mean (SD) Rasch-transformed score increased from 44.0 (17.15) at baseline to 71.0 (20.46) at Week 8 for all treated subjects. The mean (SD) change from baseline to Week 8 was 26.8 (25.89).

Overall, the improvement in mean scores among subjects treated indicated a better outcome, with subjects reporting being more satisfied with the shape of their eyes, how attractive their eyes looked, how alert (not tired) their eyes looked, how open their eyes looked, how bright eyed their looked, how nice their eyes looked, and how youthful their eyes looked after treatment.

Effectiveness Subgroup Analyses

Subgroup analyses were performed based on baseline MIHAS, primary injection instrument (cannula or needle), gender, race, ethnicity, age, and Fitzpatrick skin type. When stratifying estimated MIHAS responder rates at Week 8 by Baseline MIHAS Score, Gender, Race, Ethnicity,

Age, and FST categories, treatment group subjects demonstrated superior response rates compared to control subjects. Numerical differences were observed when stratifying MIHAS responder rates at Week 8 by Baseline MIHAS, FST categories (I-III versus IV-VI), Gender (males versus females), and Race (white versus non-white). Differences between these groups were not considered clinically relevant as the majority of subjects were satisfied across all secondary and other effectiveness measures.

At Week 8, among the treatment group, estimated average responder rates for needle (87.4%; 95% CI: [75.0%, 94.1%]) and cannula (73.7%; 95% CI: [59.4%, 84.3%]) subgroups were observed. For subgroup comparisons vs. untreated control, the estimated responder rate differences were 85.4%; 95% CI: [70.5%, 92.3%] for needle and 71.8%; 95% CI [55.2%, 82.5%] for cannula. Lower bounds of the CIs were greater than zero, demonstrating statistically significant, superior response rate in the needle and cannula subgroups compared to untreated control. Results between these subgroups were numerically different, but differences were considered not clinically relevant as the majority of subjects were satisfied across all secondary and other effectiveness measures.

HOW SUPPLIED

Belotero Balance® (+) is supplied in a blister pack containing 1-mL of sterile gel prefilled in a glass syringe and packaged with two sterile needles and two patient record labels. The individual treatment syringe is ready for injection.

For single patient use only. Do not re-sterilize the needle or syringe. Do not use if package is opened or damaged. In the event that the package is opened or damaged, do not use the syringe and notify Merz North America, Inc. immediately at 1-844-469-6379 or e-mail complaints2@merz.com.

STORAGE

Belotero Balance® (+) should be stored at room temperature (up to 25°C/77°F), away from heat. DO NOT FREEZE. The product expiry date is located on the syringe and blister labels.

Belotero Balance® (+) has a clear colorless (transparent) appearance. In the event that the syringe contains material that is not clear, do not use the syringe and notify Merz North America, Inc., immediately at 1-844-469-6379 or email complaints2@merz.com.

To place an order, contact Merz North America, Inc. at 1-844-469-6379.

PATIENT TREATMENT

1. Patient Counseling

Belotero Balance® (+) is a monophasic gel with variable density zones that can be injected using 27 – 30 gauge needles when injecting in the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds. Belotero Balance® (+) can also be injected using a 27 – 30 gauge needle or cannula (27G) for volume augmentation in the infraorbital hollow area.

The Sterimedix® Silkann® 27G, 40mm cannula with a 25G pre-hole was used in the clinical trial in the infraorbital hollow area and is the only cannula recommended for use with Belotero Balance® (+).

Prior to treatment with Belotero Balance® (+), the patient's 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.

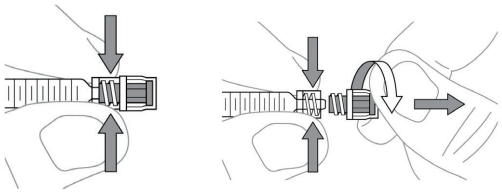
Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing; and to identify a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection.

2. Directions for Attaching Needle or Cannula

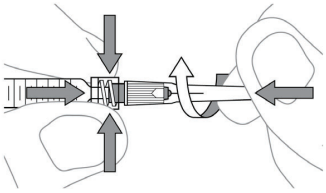
- To ensure proper needle attachment, use needles provided or the Sterimedix® Silkann® 27G, 40mm cannula.

a. To attach the needle or cannula to the syringe, open the needle or cannula packaging to expose the hub. When using cannulas or needles other than the needle(s) provided with Belotero Balance® (+), follow the needle or cannula manufacturer's directions.

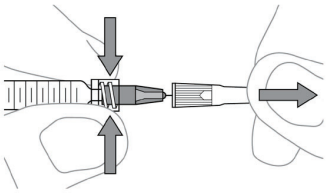
b. Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle or cannula.



c. Holding the Luer lock fitting of the syringe, twist the needle or cannula onto the syringe. The needle or cannula must be tightened securely to the syringe and primed with Belotero Balance® (+). Do not over-tighten as this may break the needle or cannula and/or dislodge the syringe.



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



e. 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 or cannula. If leakage is noted at the Luer fitting, it may be necessary to remove the needle or cannula and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle or cannula.

STERILE NEEDLES

- Follow national, local, or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not re-shield used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.

3 Depth of Injection and Injection Technique

- The injection technique of Belotero Balance® (+) with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered may vary. A linear-threading technique, tunneling technique, fanning technique, serial puncture injections, or a combination of these have been used to achieve optimal results. Care must be used to avoid intravascular injection regardless of technique used. The injection can be performed with a constant low-to-moderate pressure on the plunger while slowly and gradually withdrawing the needle or cannula.
- For treatment in the NLF, the needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle or fold. Belotero Balance® (+) should be injected into the mid-to-deep dermis. The linear threading technique and/or tunneling technique may be used.
- For the serial puncture technique, the needle is inserted at multiple sites along the wrinkle or fold as per the provider's clinical discretion.

- For treatment in the IOH with a cannula, the introductory needle and then cannula are inserted, parallel to the skin at an approximate angle of 30° or less. Insertion sites may be at the malar and zygomatic regions and may be performed in the supraperiosteal or subdermal planes. A tunneling, fanning, or combination injection technique may be used to achieve optimal results.
- For treatment in the IOH with a needle, the depth of injection varies but care should be taken to avoid injection in the superficial dermis. Needle injections will be performed at the junction of the lower eyelid and midface, along the inferior orbital rim in the supraperiosteal plane. Linear threading (fanning) and serial puncture techniques, or a combination thereof, may be used to achieve the desired result. Minimizing the number of injection points may limit the degree of swelling and bruising.
- With all injection techniques, slight elevation of the skin should be observed without significant blanching of the skin. To avoid visible lumps and/or discoloration, avoid injection of Belotero Balance® (+) into the superficial dermis when removing the needle.
- 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. Immediately stop the injection if a patient exhibits any of the following symptoms: 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 healthcare practitioner specialist should an intravascular injection occur. Treat in accordance with the American Society for Dermatologic Surgery guideline, which includes possible hyaluronidase injection.
- Correct to 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.

4 MASSAGE OF INJECTION SITE

When the injection is complete, the site may be gently massaged, if necessary.

5 VOLUME PER INJECTION

In clinical trials, the average volume of Belotero Balance® (+) needed to achieve optimal correction was 1.59 mL per nasolabial fold and approximately 0.77 mL per infraorbital hollow. Correct only to 100% of the volume desired. It is important to avoid overcorrection.

6 POST-TREATMENT CARE

The physician should instruct the patient to promptly report any evidence of adverse outcomes possibly associated with the use of Belotero Balance® (+) such as vascular compromise, or redness and/or visible swelling that lasts more than a few days or any other symptoms that may cause the patient concern.

Patients should also be advised that additional injections may be required to achieve and maintain maximum correction, and that individual results may vary.

PATIENT INSTRUCTIONS

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

- Within the first 12-24 hours, patients should avoid touching/pressing treated parts of the face, applying make-up to treated parts of the face, strenuous exercise, and consuming alcoholic beverages. Patients should also avoid taking anti-coagulation, anti-platelet, or thrombolytic medications, aspirin or non-steroidal anti-inflammatory drugs or other substances known to increase coagulation time for three days after treatment.
- Provide specific after treatment care instructions including steps to care for your skin and what products to use or avoid after treatment.
- To report an adverse reaction, contact Merz North America, Inc. at 1-844-469-6379.

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