BELOTERO BALANCE®

BELOTERO BALANCE®
(Injectable hyaluronic acid)
BELOTERO BALANCE® is provided as a 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 and the Instructions for Use, as well as in 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 device. **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.

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.

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®** 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.
- Injection site responses to **BELOTERO BALANCE®** have been observed, consisting mainly of short-term inflammatory symptoms starting early after treatment and with 7 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 resterilize. 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 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 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.

- 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, and extreme cold weather until any initial swelling and redness have resolved and puncture sites have healed.

ADVERSE EVENTS

The safety of **BELOTERO BALANCE®** 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 control dermal fi (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 fi 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 Duration of Event [N = 211]				Collagen Control Maximum Duration of Event [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: A subject is counted only once by maximum duration 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 (0.0)	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 Study

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 Incident 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 Subjects 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
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.

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.

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

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 fi .

The initial treatment was fi 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 fi 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 filer 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 8.

Table 8 – 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)
	MEAN (SD)
Age	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 9.

Table 9 – Average Time between Injections During the OLEX Phase

Study Visit	Side Previously Injected with BELOTERO BALANCE®	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 10.

Table 10 – Mean Blinded Evaluator SRS Scores

Timepoint	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 11.

Table 11 – 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)
	MEAN (SD)
Age	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 fi 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 12 provides a summary of the demographics of the subjects participating in the study.

Table 12 – 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 fi follow-up visit (97% follow-up rate). Four (4) patients withdrew after retreatment but prior to their fi 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, 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.

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. 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@merzaesthetics.com.

STORAGE

BELOTERO BALANCE® should be stored at room temperature (up to 30°C/86°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@merzaesthetics.com.

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

Patient Treatment

1. Patient Counseling.

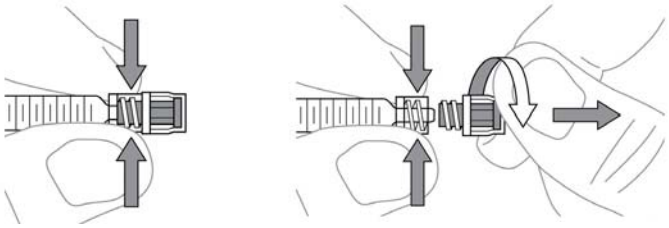
- **BELOTERO BALANCE®** is a monophasic gel with variable density zones that can be injected using 27 – 30 gauge needles. Prior to treatment with **BELOTERO BALANCE®**, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration.

2. Injection Needle.

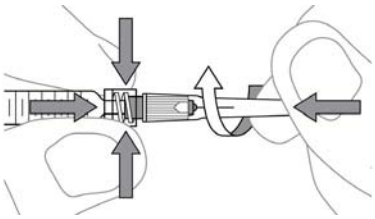
- To assure proper needle attachment, use needles provided.

a. To attach needle to syringe, open the needle packaging to expose the needle hub. For use of needles other than the needle(s) provided with this package, follow the directions provided with the needle(s).

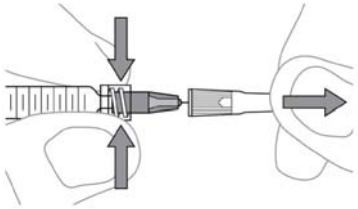
b. Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle.



c. Holding the luer lock fitting of the syringe, twist the needle onto the syringe. **The needle must be tightened securely to the syringe and primed with BELOTERO BALANCE®. Do not over-tighten as this may break the needle and/or dislodge the syringe.**



d. Pull off the needle guard to expose needle



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

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 reshield 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, 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.
- For the linear threading technique and/or tunneling technique, 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 injection can be performed with a constant low-to-moderate pressure on the plunger while slowly and gradually withdrawing the needle.
- For the serial puncture technique, the needle is inserted at multiple sites along the wrinkle or fold as per the provider's clinical discretion.
- With both 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. Volume per Injection.

In clinical trials, the average volume of **BELOTERO BALANCE®** needed to achieve optimal correction was 1.5 mL per nasolabial fold. Correct only to 100% of the volume desired. It is important to avoid overcorrection.

5. Massage During Injection Site.

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

6. Post Treatment Care.

The physician should instruct the patient to promptly report to her/him any evidence of problems possibly associated with the use of **BELOTERO BALANCE®**, such as vascular compromise, or redness and/or visible swelling that lasts for 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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