SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: BELOTERO® BALANCE

Applicant's Name and Address: Merz Pharmaceuticals, LLC
4215 Tudor Lane
Greensboro, NC 27410

Premarket Approval Application (PMA) Number: P090016

Date of Panel Recommendation: None

Date of FDA Notice of Approval: November 14, 2011

Expedited: Not Applicable

II. INDICATIONS FOR USE

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.

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Belotero Balance physician's Labeling.

V. DEVICE 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) in two consecutively executed reactions and reconstituted in a physiologic buffer at pH 7 and concentration of 22.5 mg/mL.

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VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies for treating moderate to severe nasolabial folds include collagen other hyaluronic acid-based materials, and microparticles of poly-L-lactic acid, synthetic calcium hydroxylapatite or, non-resorbable polymethylmethacrylate dermal fillers and as well as autologous fat transfer. Other methods for treatment of facial rhytides include injection of botulinum toxin, topical creams, chemical peels, laser skin resurfacing, dermabrasion and surgical intervention.

VII. MARKETING HISTORY

Belotero Balance is also marketed as Esthelis®, or IMD1 in Europe and other parts of the world. Belotero Balance /Esthelis® received CE certification clearance in October 2004.

VIII. POTENTIAL ADVERSE EVENTS

The safety of Belotero Balance has been evaluated in three studies and Post Marketing Surveillance. Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Allergic reaction including Quincke's edema, tissues necrosis in the glabellar area after injection, inflammation reaction, injection site granuloma, injection site indurations, hematoma after injection, Tyndall effect, Cordon like effect, bump and pustule at injection site, scarring after injection in the chest
- Application Site Exfoliation
- Bruising
- Discoloration
- Erythema
- Induration
- Injection Site Pruritus
- Injection Site Bruising
- Injection Site Discoloration
- Injection Site Nodule
- Injection Site Pain
- Injection Site Rash
- Injection Site Swelling
- Injection Sit Induration
- Injection Site Erythema
- Mild Headache
- Mild Herpes Simplex
- Mild Lip Dryness
- Moderate Cold Sore
- Moderate Lip Numbness

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- Nodule
- Pain
- Pruritus
- Swelling
- Urticaria

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.

IX. SUMMARY OF PRE-CLINICAL STUDIES

The testing performed in the original application was adequate to support the safety and effectiveness of the device for the correction of moderate-to-severe facial wrinkles and folds (such as nasolabial folds). Because the commercial product will be made at a new facility, the sponsor also performed nonclinical studies to demonstrate that the commercial and investigational devices have equivalent chemical and physical properties.

Biocompatibility Testing

Belotero Balance was tested in accordance with ISO 10993 "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" for devices in contact with tissue and bone for durations of greater than 30 days and in compliance with FDA GLP regulations. Test results are summarized in Table 1.

Table 1. Summary of Biocompatibility Tests

Test	Purpose	Acceptance criteria	Results
Cytotoxicity test	Determine the toxicity of MEM device extracts on L929-mouse fibroblast cells	No signs of cell lysis or toxicity	No evidence of cell lysis or toxicity
Subacute Systemic Toxicity test	Test toxicity of device after single i.d. injection in rats during a 14 day observation	No signs of toxicity	No deaths or signs of toxicity were observed. Necropsy findings were slight erythema and edema (20/20), eschar (9/20), marketed induration (4/20).
Intracutaneous Irritation test	Determine irritation potential in rabbits at 24, 48 and 72 hours after i.c. injection of Belotero Balance and Restylane	No significant signs of irritation	Both products were associated with an increase in erythema and edema at 24, 48 and 72 hours. Both were also more irritating than a negative saline control.
Sensitization test	Determine the sensitization potential of Belotero (5%) and Freund's complete adjuvant in guinea pigs after injection on day 1 followed by laurel sulfate injection on day 7. One day later animals received a second	No signs of a sensitization reaction.	No signs or evidence of dermal sensitization at 24 or 48 hours after the patch application and injection of challenge doses.

	Belotero Balance injection and then a patch soaked in Belotero Balance was applied to the injection site for 48 hours.		
Systemic and Local Tolerance test	Determine local and systemic toxicity of Belotero Balance, Restylane, and 0.9% saline solutions injected once per week for 4 weeks in rats.	No significant signs of local or systemic toxicity during daily observations as well as in blood and urine samples taken after 13 weeks.	No treatment-related deaths observed. All animals were normal throughout the study without signs of toxicity. Gross and histopathological exams yielded no evidence of systemic or local toxicity at the injection sites
AMES test	Determine the mutagenicity of Belotero Balance	Non-mutagenic	No cytotoxicity or mutagenicity was observed in *Salmonella typhimurium* both with and without S9 activation
In vitro Mammalian Cell Gene Mutation test	Determine the mutagenicity of ethanol device extracts with mouse lymphoma cells (containing a heterozygote thymidine kinase) to detect gene mutations.	Non-mutagenic	Non-mutagenic

The results of the submitted biocompatibility tests illustrate that Belotero Balance has an acceptable human safety profile.

Comparison of Belotero Balance from different Manufacturing Facilities

Analyses of Belotero Balance batches manufactured for clinical studies and commercial sale were evaluated for protein content, sterility, bioburden, and detectable low molecular weight hyaluronic acid fragments. The results of these studies indicated that the methods of manufacture and the final product composition for Belotero Balance used in clinical studies is comparable to the proposed commercial product.

Other preclinical studies used to evaluate Belotero Balance are presented in Table 2.

Table 2. Other Preclinical Studies

Test	Purpose	Specification	Results / Conclusions
Cross-link ratio characterization method	To determine the relationship between the degree of device crosslinking and Ejection Force determined as a product release specification.	For information	A linear correlation between Ejection Force and Gel Crosslinking concentration was observed for gels with 6%, 7.5%, 8.5%, 9%, 9.5% and 10.5% crosslinking densities.
Shelf-life tests for: Sterility, Visual appearance,	To determine the stability of the final product during storage.	The specifications for the final product remain	The results of the shelf-life tests indicated that the

Endotoxin, Viscoelastic Properties of Crosslinked Ge (i.e., Storage Modulus G' anc Decrease in G' as a Function of Time Due to Enzyme Digestion), UV Absorbance of the Crosslinked HA, pH, Osmolality, HA Concentration (Gravimetric), Extrusion Force, HA fragments and Lidocaine concentration		within acceptable levels throughout the storage lifetime.	device may be labeled with an 18 month expiration date

X. SUMMARY OF CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness 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 under IDE # G0600170. Data from this clinical study was the basis for the PMA approval decision. A summary of the clinical study is presented below.

The following clinical trial summary includes: 1) the Pivotal Study; (i.e., MUS 90028-00622-1 "A Randomized, Blinded Controlled, Multi-center Study of the Safety and Effectiveness of Dermal Filler, Belotero Balance, After Mid-to-Deep Dermal Implantation for Correction of Moderate to Severe Facial Wrinkles (such as Nasolabial Folds) over 24 Weeks) and 2) the Open-label Extension Study (OLEX); (i.e., "A Randomized Blinded, Controlled Multicenter Study of the Safety and Effectiveness of Dermal Filler, Belotero After Mid- to Deep Dermal Implantation for Correction of Moderate to Severe Facial Wrinkles (Such as Nasolabial Folds) Over 24 Weeks").

A. Study Design

Controlled Phase (0-24 Weeks):
Patients were treated between November 2, 2006 and July 25, 2007

In a randomized, controlled clinical trial, 118 subjects at 6 centers were injected with Belotero Balance in one nasolabial fold (NLF) and bovine collagen control 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 greater than 5% of subjects in the pivotal clinical study and the Fitzpatrick Skin Type IV, V, and VI study are summarized by maximum intensity in Tables 4 and 9, respectively and by duration in Tables 5 and 10, respectively.

The study was a blinded, active-controlled, randomized, multicenter trial that 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.

OLEX Phase (24-96 Weeks):

Upon completion of the Controlled Phase study, subjects were invited to participate in an open-label extension (OLEX) of the trial in which they received treatment with Belotero Balance in 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 Phase was designed to obtain data on repeated treatments with respect to both safety and duration of effectiveness.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in Pivotal Study MUS 90028-00622-1 was limited to patients who met the following inclusion criteria.

Inclusion Criteria:

1. Subjects were 18 to 75 years of age and of any race or sex.
2. Female subjects were postmenopausal for at least 1 year, had a hysterectomy, or had a tubal ligation; or, if of childbearing potential, agreed to use an approved method of birth control throughout the study (i.e., oral/systemic contraceptives, intrauterine device [IUD], or spermicide in combination with a barrier method of contraception), were abstinent, or were in a monogamous relationship with a vasectomized partner; and had a negative urine pregnancy test at the Screening visit.
3. Subjects had bilateral NLFs with a severity score of 2 or 3 on the wrinkle SRS assessed by the Blinded Evaluator.
4. Each subject had an adequate understanding of the language (spoken and written English or Spanish) and was willing to comply with the study requirements.

Exclusion Criteria:

1. A personal history of allergic/anaphylactic reactions including hypersensitivity to local anesthetics (e.g., lidocaine, etc), hyaluronic acid (HA) preparations, and/or gram-positive bacterial protein;
2. A known history of keloids or bleeding disorders;
3. An 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 scanning that might interfere with study assessments;
4. Women who were pregnant, planning to become pregnant during the study, or who were breast feeding;
5. Subjects who planned to undergo major facial surgery during the course of the study (e.g., rhinoplasty [with or without implant], facelift, congenital defect repair, etc);
6. Subjects with a clinically important disease, as judged by the investigator, within 3 months of the study (e.g., significant laboratory test abnormalities, myocardial infarct, stroke, cancer, connective tissue diseases [scleroderma, systemic lupus erythematous],

systemic infection, uncontrolled diabetes, etc.), including those with medical conditions that might require the use of immunosuppressive medications during the trial (e.g., severe, uncontrolled asthma, rheumatoid arthritis, autoimmune diseases, etc);

7. Severe physical, neurological, or mental disease;
8. Excessive facial hair that might interfere with the evaluation of the wrinkle assessments;
9. Any systemic or dermatologic disorder, which, in the opinion of the investigator, would interfere with the study results or increase the risk of adverse events (AEs);
10. Subjects who had used exclusionary medications/treatments as defined in the protocol, IE, medications that would confound interpretation of the results of the study or that might compromise the subject's safety;
11. Participation in a clinical investigation within the 30 days prior to the first planned device administration or during this trial.

2. Follow-up Schedule

The initial treatment was evaluated after 2 weeks and an optional touch-up treatment was permitted at that time to achieve optimal correction. The follow-up during the Controlled Phase consisted of visits at Weeks 2, 4, 8, 12, 16, and 24 after the last treatment. The primary effectiveness endpoint was the mean change from Baseline in the Wrinkle Severity Rating Scale (SRS) score of each NLF (as determined by the Blinded Evaluator) at the 12-week follow-up time point. The Week 12 visit was divided into Weeks 12a and 12b. Any subject who had a touch-up treatment on only one side of the face was evaluated at both Weeks 12a and 12b; Week 12a for the side that was not touched-up and Week 12b for the side that was touched-up. Both sides were evaluated at both time points so as to preserve blinding. Subjects with no touch-up injections or with touch-up injections to both sides of the face only attended a single Week 12 visit. Wrinkle evaluations using the wrinkle SRS were made at each of these visits by a Blinded Evaluator and by the Treating Investigator at each study site with the aid of a validated severity rating scale. Safety-related assessments included reports of adverse events (AEs).

3. Clinical Endpoints

Safety outcomes were determined with a 14 day post-injection subject diary and investigator assessments during clinical visits after treatment and 2, 4, 8, 12, 16 and 24 weeks after the last injection.

The primary effectiveness endpoint was the mean change from baseline to 12 weeks after the last injection measured on the Wrinkle Severity Rating Scale (SRS) by the Blinded Evaluator.

Secondary effectiveness endpoints included: 1) mean change from baseline in the SRS of each nasolabial fold (judged by the Blinded Evaluator) at weeks 2, 4, 8, 16 and 24, 2) the mean change from baseline on the SRS of each nasolabial fold (as determined by the Treating Investigator) at weeks 2, 4, 8, 12, 16 and 24, 3) the Investigators' assessment on a Global Aesthetic Improvement Scale (GAIS) at each visit, 4) patient satisfaction and preference assessment at week 24 and 5) the physician preference at week 24.

To be judged a treatment success, subjects needed to display a one point improvement over baseline at Week 12 on the SRS scale. Patient outcomes were evaluated via both non-inferiority and superiority tests comparing Belotero Balance and a Collagen Control with a 95% 2-sided confidence interval (CI) around the difference between the changes observed with each treatment. The lower limit of the 95% CI for the difference between the two treatments needed to be above -0.25 units on the SRS for Belotero Balance to be judged non-inferior. The lower limit of the 95% CI for the difference between the two treatments needed to be greater than 0 for Belotero Balance to be judged superior.

NLF correction during the OLEX Phase was assessed by the Treating Investigators at each of the study visits by rating the wrinkle SRS scores. Duration of effectiveness was determined in comparison with the subject's baseline SRS rating.

B. Accountability of PMA Cohort

At the time of database lock, 106 of 118 patients (89.9%) enrolled in PMA study completed the Controlled Phase and 85 of 95 (89.5%) patients completed the OLEX Phase of the study and were evaluated for safety and effectiveness as the basis for the PMA submission.

C. Study Population Demographics and Baseline Parameters

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 3.

Table 3 – 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)

Subjects received an average of 1.16 mL of Belotero Balance and 1.37 ml of Collagen Control at the initial injection. 94 of 118 (79.7%) subjects received retreatment 2 weeks later for optimal correction by injection of an average of 0.81 mL of Belotero Balance or 0.94 ml of Control implant.

OLEX Phase (24-96 Weeks)

95 of the 106 (89.6%) subjects who completed the Controlled Phase elected to receive retreatment with Belotero Balance in both NLFs during the OLEX portion of the study. Subject demographics in the OLEX Phase were similar to those in the Controlled Phase described above.

During the OLEX Phase, 85 of 95 (89.5%) subjects were evaluated through Week 96. The mean cumulative volume of Belotero Balance injected 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 Collagen Control. The mean number of injections received during the OLEX Phase was 2.6 mL in the NLF initially treated with Belotero Balance and 2.9 mL in the NLF initially treated with Control with a mean time between injections of 37 weeks and 31 weeks respectively.

D. Safety and Effectiveness Results

1. Safety Results

The safety of Belotero Balance was been evaluated in two 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 Collagen 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 greater than 5% of subjects in the Pivotal Study and the Fitzpatrick Skin Type IV, V, and VI study are summarized by maximum intensity in Tables 4 and 9 and by duration in Tables 5 and 10, respectively. Adverse events recorded by investigators at study visits for the Controlled Study and the Fitzpatrick Skin Type IV, V, and VI study are combined and presented in Table 6.

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 Safety and 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 4 - Maximum Intensity of Symptoms Occurring in >5 % of Controlled Study 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 5 - Duration of Injection Site Responses Occurring in >5% of Controlled Study 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 on 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 6 – Adverse Events Occurring in >2% of Controlled Study and Fitzpatrick Skin Type IV, V and VI Study Subjects, Physician Reported

	Belotero Balance Maximum AE Severity [N = 211]				Collagen Control Maximum AE Severity [N = 118]			
Description of Adverse Event	**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 on 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)
A total of non-local adverse events (AEs) occurred in 7/211 (3.3%) of the study subjects in the Controlled and Fitzpatrick IV, V, VI Skin Type Studies. In the Controlled Study 3/118 (2.5%) of the 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 injections, the causality of AEs could not be identified. In the Fitzpatrick IV, V, VI Study 4/93 (4.3%) subjects experienced 5 non-local AEs. These events 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 that were judged related to Belotero Balance or Collagen Control injections.

Post Marketing Surveillance
The following adverse events were observed during post-marketing surveillance of Belotero Balance used outside the US, that were not reported in the US clinical trials with Belotero Balance. Suspicion of allergic reaction including Quincke's edema, tissues necrosis in the glabellar area after injection, inflammation reaction, injection site granuloma, injection site indurations, hematoma after injection, Tyndall effect, Cordon like effect, bump and pustule at injection site, scarring after injection in the chest. Time to onset for these AEs ranged from a few hours to 24 months post-injection and the patient outcomes ranged from 'improved' to 'on-going' at last contact.

No serious AEs were reported more than five times for any one specific type of event during post-marketing surveillance.

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 titer post-treatment experienced AEs that were consistent with the clinical symptoms identified in MedDRA for a possible local or systemic hypersensitivity reaction. No patient displayed a positive IgE response against the device.

2. Effectiveness Results

The analysis of effectiveness was based on the 118 evaluable patients at the 12 Week time point. Key effectiveness outcome is presented in Table 7.

Table 7 – Mean Blinded Evaluator SRS Scores

Time point	N	Belotero	Collagen Control
Initial Treatment	118	2.5	2.5
Week 12	118	1.25	1.51

The results from the controlled phase demonstrate that Belotero Balance is non-inferior to the Control in the correction of NLFs.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

FITZPATRICK SKIN TYPE IV, V, VI STUDY: A Multicenter Study of the Safety and Effectiveness of Dermal Filler, BELOTERO, After Mid-to-Deep Dermal Implantation for Correction of Moderate to Severe Facial Wrinkles (such as Nasolabial Folds) Over 24 weeks in Subjects with Fitzpatrick Phototype Scores IV, V and VI."

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 Safety and 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.

STUDY DESIGN

Treatment consisted of injection of Belotero Balance into both nasolabial folds of subjects who were a 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 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, photo numeric 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 was evaluated as a secondary objective. The main effectiveness assessment was a comparison of baseline and after treatment ratings on the SRS scale as assessed by an Evaluator Investigator at the 12 weeks after the last treatment. 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. 88/93 subjects completed the study. Subject demographics are summarized in Table 8.

Table 8: 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-	90 (96.8)

American	
Asian	1 (1.1)
Other	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 mLs and 1.47 mLs, respectively. 66 of 93 subjects (70.1%) received touch-up injections. All but one subject received a touch-up injection 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.

The safety profile observed during this study was similar to that observed in the Controlled Study.

Table 9 - 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 10 - 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 on 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.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

Because the data submitted in this PMA substantially duplicates information previously reviewed by the General and Plastic Surgery Devices Advisory Panel, this PMA was not referred to the Advisory Panel for review and recommendation.

XIII. CONCLUSIONS DRAWN FROM THE STUDIES

a. Safety Conclusions

The adverse effects of the device are based on data collected in two clinical studies conducted to support PMA approval as described above. From these studies and evaluation of Post Market Surveillance reports from patients treated outside the U.S. one can conclude:

The incidence, severity and duration of adverse outcomes collected in patient diaries and the adverse events reported by treating physicians were similar for both Belotero Balance and the approved Collagen Control.

Non-local adverse events occurred in 7/211 (3.3%) of the subjects in both the Controlled and Fitzpatrick Skin Type IV, V, and VI studies. 3/118 (2.5%) subjects in the Controlled Study had at least one non-local adverse event (i.e., moderate urticaria, mild herpes simplex, and mild headache). Since each patient received both Belotero Balance and Collagen Control injections, the causality of these AEs could not be identified. In the Fitzpatrick IV, V, VI Skin Type Study 4/93 (4.3%) subjects experienced 5 non-local adverse events (i.e., moderate headache, moderate swelling on the right side of the nose, moderate cold sore, moderate lip numbness, and mild lip dryness).

No severe adverse event (SAE) related to Belotero Balance treatment was reported in the U.S. clinical studies. The only SAE reported during the U.S. study was a subject that underwent hip arthroplasty.

No serious adverse events were reported more than five times during post-marketing surveillance and the adverse events reported during post market surveillance, (that were not observed in U.S. studies), were: suspicion of allergic reaction including Quincke's edema, tissues necrosis in the glabellar area after injection, inflammation reaction, injection site granuloma, injection site indurations, hematoma after injection, Tyndall effect, Cordon like effect, bump and pustule at injection site, scarring after injection in the chest.

While 5/116 (4.3%) subjects in the Controlled Study developed an antibody response after Belotero Balance injection, none of the subjects displayed clinical symptoms consistent with a possibly local or systemic hypersensitivity reaction. No patients displayed a positive IgE response against Belotero Balance.

b. Effectiveness Conclusions

In the Controlled Study, Belotero Balance was non-inferior to an approved Collagen Control in the correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds.

c. Overall Conclusions

Based on the blinded evaluator, treating investigator and subject assessments during the Controlled Study, Belotero Balance was effective and not inferior to an FDA-approved bovine collagen dermal filler. Masked evaluators judged that 55.1% of the Belotero Balance-treated NLF had better then a one point improvement on the SRS scale at 24 weeks after injection.

The *in vitro* and *in vivo* studies performed with Belotero Balance: 1) the device was biocompatible; 2) the commercial and investigational device forms were equivalent in specification and characteristic; and 3) the Final product, when manufactured in accordance with the approved design outputs, meets all user requirements and design inputs.

Therefore it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risks of illness or injury when used as indicated in accordance with the direction for use.

XI. CDRH DECISION

CDRH issued an approval order on November 9, 2011. The final conditions of approval cited in the approval order are described below.

XII. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XI. CDRH DECISION

CDRH issued an approval order on November 14, 2011. The final conditions of approval cited in the approval order are described below.

XII. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.