SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: Belotero Balance® (+)

Device Procode: LMH

Applicant's Name and Address: Merz North America Inc.
6501 Six Forks Road
Raleigh, NC 27615

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P090016/S050

Date of FDA Notice of Approval: September 27, 2023

Priority Review: No

Breakthrough Device: N/A

The original PMA (PMA #P090016/S028) was approved on August 29, 2019 and is indicated for injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds. The SSED to support the indication is available on the CDRH website and is incorporated by reference here.

The current supplement was submitted to expand the indication for the device. Two clinical studies were performed in the U.S. under IDE G170211 to establish a reasonable assurance of safety and effectiveness for the use of Belotero Balance® (+) for volume augmentation for the improvement of infraorbital hollowing in adults over the age of 21.

II. INDICATIONS FOR USE

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

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® (+) 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Belotero Balance® (+) labeling.

V. DEVICE DESCRIPTION

Belotero Balance® (+) is a sterile, bioresorbable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel. Belotero Balance® (+) is 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.

Belotero Balance® (+) is supplied sterile in a pre-filled 1cc syringe in a blister pack unit with two sterile needles (27G ½" and 30G ½") and two patient record labels.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative therapies to treat infraorbital hollowing include another hyaluronic acid dermal filler product, autologous fat injection or transposition, plasma gel injection, surgery, and acellular dermal graft treatment. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with their physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Belotero Balance® (+) received FDA Approval under P090016/S028 on 29 August 2019 for correction of moderate to severe wrinkles and folds, such as nasolabial folds.

Belotero Balance® (+) is currently marketed globally in eighty countries, including Australia, Brazil, Canada, China, the European Union, India, Japan, Mexico, Russia, Singapore, South Korea, Switzerland, Taiwan, Ukraine, and the United Kingdom. The device has not been withdrawn from the market for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g. complications) associated with the use of the device as reported in the pivotal clinical study at a frequency less than 3% of subjects include injection site nodule, injection site bruising, injection site pain, injection site dryness and injection site erythema; and at a frequency of 6.3% of subjects include injection site swelling.

The following adverse events have been identified during post-approval use of Belotero Balance® or Belotero Balance® (+) through post-marketing surveillance (from voluntary reporting and published literature). These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Belotero Balance® or 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.

Although rare, serious adverse events (SAEs) 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; abscesses; granulomas; eyelid muscle degeneration; eyelid ptosis; and damage to the underlying facial structures. Implantation of soft-tissue filler into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction.

The following interventions have been reported: antibiotics, anti-inflammatories, corticosteroids, anti-histamines, analgesics, hyaluronidase, massage, warm compress, excision, drainage, and surgery. Some adverse events resolved without treatment.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

This supplement presented clinical data to support approval of a new indication for the improvement of infraorbital hollowing. There was no change in product manufacturing or specifications. Therefore, the non-clinical data was previously presented in support of PMA P090016/S028.

A. Laboratory Studies

Additional laboratory studies were performed to evaluate the extrusion force of the product through a 27G x 40 mm cannula.

Table 1. Summary of Laboratory Studies

Test	Purpose	Acceptance Criteria	Results
Extrusion force Testing	The purpose of this study is to evaluate the ejectability of Belotero Balance® (+) Lidocaine through a 27G x 40mm cannula.	Mean ejection Force $\leq$ 30N	All results below acceptance criterion

B. Animal Studies

This supplement presented clinical data to support approval of a new indication for use. Because no change in product manufactured or specification was proposed, the biocompatibility studies previously submitted in PMA P090016/S028 and subsequent supplements support the new proposed indications for use.

C. Additional Studies

This supplement presented clinical data to support approval of a new indication for use. Because no change in product manufactured or specifications were proposed, the studies previously submitted in PMA P090016/S028 and subsequent supplements support the new proposed indications for use.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Two clinical studies were performed in the United States to establish a reasonable assurance of safety and effectiveness of the Belotero Balance® (+) dermal filler product family for volume augmentation for the improvement of the infraorbital hollow (hereafter IOH) in adults over the age of 21 under IDE G170211. Note that the pilot study was conducted on Belotero Balance®, which does not contain lidocaine, while the pivotal study was conducted on Belotero Balance® (+). Data from these two studies were the basis of the PMA approval decision. A summary of the clinical studies is presented below.

Table 2 Summary of Clinical Studies Supporting the Safety and Effectiveness of Belotero Balance® **Product Family for the Improvement of the IOHs**

Study #	Objective	Primary Endpoint
M930121001	The pilot study aimed to define safety, effectiveness, and patient-reported outcomes for Belotero Balance® use in the IOH in order to utilize the results to inform the design of the pivotal study	The primary endpoint established effectiveness by using the Merz Infraorbital Hollow Assessment Scale (MIHAS) to demonstrate that clinically relevant changes of ≥ 1-point on both IOHs can be detected 2-months post-treatment
M930121002	The pivotal study aimed to evaluate the safety and effectiveness of Belotero Balance® (+) for volume augmentation for the improvement of the infraorbital hollow area.	The primary endpoint established effectiveness by using the Merz Infraorbital Hollow Assessment Scale (MIHAS) to demonstrate that clinically relevant changes of ≥ 1-point on both IOHs can be detected 2-months post-treatment

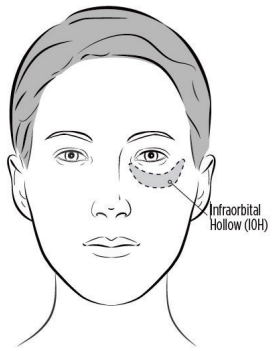
Study # M930121001 A Pilot Study to Assess the Effectiveness and Safety of Belotero Balance® Injection for Volume Augmentation of the Infraorbital Hollow

A. Study Design

Subjects were treated between December 27, 2018 and April 17, 2019. The database for this Panel Track Supplement reflected data collected through March 11, 2020 and included 66 subjects (Treatment: n=43; Untreated Control: n=23). There were three investigational sites located in the United States. The clinical study was a thirteen-month study (from baseline visit to end of study). Data presented is through Month 12 post last injection.

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® (+). Subjects were randomized to either a treatment group or an untreated control group using a 2:1 (treatment:control) allocation ratio. For subjects randomized to the treatment group, both right and left IOHs received treatment with Belotero Balance® using a 27G x 40 mm cannula. The Treating Investigator (TI) determined the appropriate volume of Belotero Balance® (see **Figure 1**). To achieve symmetrical correction a touch-up injection was given 4 weeks post-initial injection, with the subject's consent, in one or both IOHs if the treating investigator determined a treated subject had asymmetrical IOHs based on a visual assessment.

Figure 1 Treatment Region for the Infraorbital Hollowing



1. Main Clinical Inclusion and Exclusion Criteria

Enrollment in the Study # M930121001 was limited to patients who met the following key inclusion criteria:

- Had right and left IOH volume deficit with a rating of 2 or 3 (moderate or severe) on the MIHAS, as determined by the blinded evaluator. The treating investigator had to agree that the subject met this criterion of a 2 or 3 rating on the MIHAS.

- Had the same MIHAS score on both IOHs (i.e., IOHs were symmetrical).
- Was at least 22 years of age.

Patients were not permitted to enroll in the Study # M930121001 if they met any of the following key exclusion criteria:

- Had prior lower-eyelid surgery, including orbital or midface surgery, or had a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments or planned to have it during the study.
- Had gained or lost ≥ 2 body mass index BMI) units within the previous 90 days or had the intention to gain or lose a significant amount of weight during the first 90 days of the study.
- Had ever been treated with fat injections or permanent and/or semi-permanent dermal fillers in the midfacial region or planned to receive such treatments during participation in the study.
- Received lower eyelid and/or malar region treatments with any absorbable or temporary fillers such as porcine-based collagen fillers, hyaluronic acid (HA) products, RADIESSE®, poly L-lactic acid (PLLA) or received mesotherapy treatment to the area within the past 24 months or planned to receive such treatments during participation in the study.
- Had any current or history of uncontrolled retinal disease or detached retina or any other condition with the potential to cause a decline of visual acuity (e.g., uncontrolled diabetes).
- Received deep facial dermal therapies (i.e., facial ablative or fractional laser, deep chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage]) to the periorbital or malar region within the past 12 months or planned to receive such treatment during participation in the study.
- Received superficial facial dermal therapies (i.e., microdermabrasion, superficial chemical peels) to the periorbital or malar region within the past six months or planned to receive such treatment during participation in the study.
- Received toxin treatment to the periorbital region within the past six months or planned to receive such treatment during participation in the study.
- Received immunosuppressive medications or systemic steroids (except intranasal/inhaled steroids) in the past two months or planned to receive them during participation in the study.
- Had tendency to accumulate fluid in the lower eyelids, had developed festoons, or had large and/or herniating infraorbital fat pads.
- Had lower eyelid retraction, significant prominent eyes, or severe negative facial vector.
- Had dark circles under the eyes due to pigmentation changes and not from IOH shadowing.
- Had ectropium, entropion, or trichiasis of the lower eyelid or eye diseases that could lead to reddening and tendency of watering of the eye.

- Had active or a history of recurrent or chronic infraorbital edema or rosacea or uncontrolled severe seasonal allergies.
- Had a history of allergic/anaphylactic reactions, including hypersensitivity to lidocaine or anesthetics of the amide type, HA preparations, gram positive bacterial proteins, or any of the device components.
- Had a known bleeding disorder or had received or was planning to receive anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., Vitamin E, garlic, gingko), from 10 days before to 3 days after injection.
- Had any other medical condition with the potential to interfere with the study outcome assessments or compromise subject safety (e.g., increase the risk of adverse events [AEs]).

2. Follow-up Schedule

The treated subjects had a safety phone call 72 hours after baseline treatment and in-clinic safety visit at Week 2. If a subject were to report a safety concern during the 72-hour phone call, an unscheduled visit was to be organized to bring the subject into the clinic to address safety concerns. All treated subjects were assessed one month after baseline injection for asymmetry and safety.

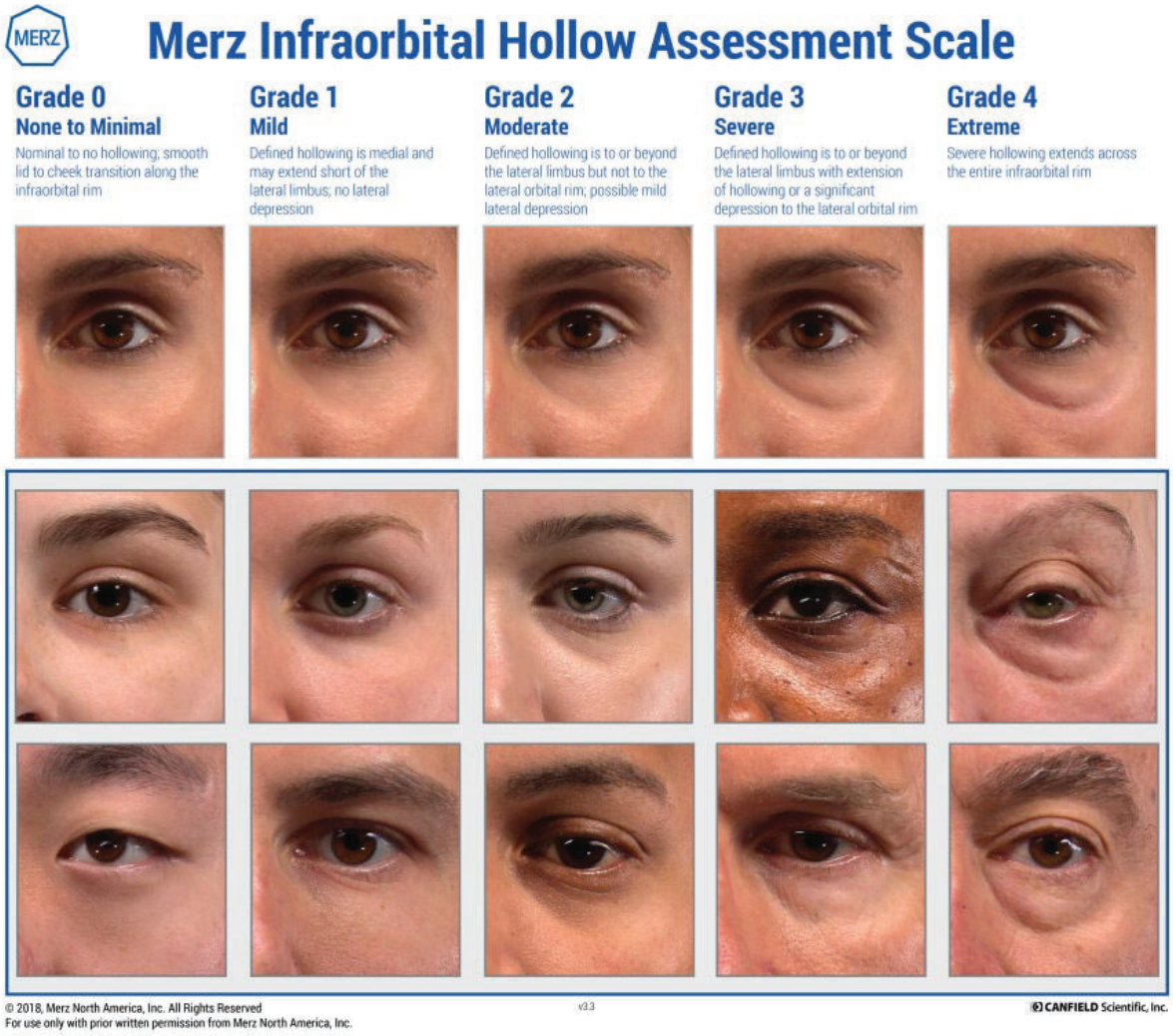
- Subjects who did not require touch-up injection returned for Months 2, 3, 6, 9, and 12 post baseline injection visit;
- Subjects who required a touch-up injection for asymmetric correction received a revised visit schedule: 72-hour phone call post touch-up injection, Week 2 visit post touch-up injection, Months 2, 3, 6, 9 and 12 post touch up injection visit.

Treated subjects completed a patient diary for one month after injection [baseline, touch-up (if applicable)], to collect common treatment responses (CTRs).

At all in-clinic visits, visual assessments (i.e. Snellen visual acuity, confrontational visual fields, and ocular motility) were performed on study participants. Adverse events and complications were recorded at all visits.

The objective parameters measured during the study included the blinded evaluator live assessment of participants' infraorbital hollowing using a validated 5-point photo numeric Merz Infraorbital Hollow Assessment Scale (MIHAS) assessment (**Figure 2**) of all study participants.

Figure 2 Merz Infraorbital Hollow Assessment Scale (MIHAS)[1]



For treated subjects, effectiveness assessments were performed in clinic at baseline and Month 2 post last injection. Effectiveness assessments consisted of the blinded evaluator MIHAS assessment and treating investigator Global Aesthetic Improvement Scale (GAIS) (**Table 3**). Treated study participants performed self-

[1] MIHAS is a validated 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.*

assessments on the GAIS, and the FACE-Q instruments (a patient-reported assessment).[2,3]

Table 3. Global Aesthetic Improvemente Scale (GAIS)

Score	Rating
+3	Very much improved
+2	Much improved
+1	Improved
0	No change
-1	Worse
-2	Much worse
-3	Very much worse

The Control-group subjects were evaluated at enrollment and Month 2 in the clinic. Adverse events and complications were recorded at all visits. The only effectiveness assessment that was performed in the control group was the blinded-evaluator MIHAS and control subject self-assessment on the FACE-Q instruments. No investigator GAIS was performed with control subjects, nor did these subjects self-report on the GAIS.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

- **Safety**

With regards to safety, treated study participants received an electronic diary after treatment to record specific signs and symptoms experienced for one month after initial and touch-up (if applicable) treatments. Participants were instructed to rate each common treatment response (CTRs) listed on the diary as "Mild, (easily tolerate)," "Moderate (affecting daily activity)," "Severe (unable to do daily activity)," or "None".

Adverse Events (AEs) were reported by the treating investigator at all follow-up visits for all study participants.

[2] FACE-Q instruments included: FACE-Q Satisfaction with Eyes, FACE-Q Appraisal of the Lower Eye Lids. *AF Klassen, et al. FACE-Q Eye Module for Measuring Patient-Reported Outcomes Following Cosmetic Eye Treatments. JAMA Facial Plast Surg 2017 ; 19(1):7-14 doi:10.1001/jamafacial.2016.1018.*

[3] FACE-Q instrument included: FACE-Q Patient Perceived Age Visual Analog Scale. *V Panchapakesan, et al. Development and psychometric evaluation of the FACE-Q Aging Appraisal Scale and Patient-Perceived Age Visual Analog Scale. Aesthet Surg J 2013; 33(8):1099-109*

- **Effectiveness**

With regards to effectiveness, the primary effectiveness measure was the blinded rater assessment of the participant's infraorbital hollowing in a live assessment using the validated 5-point MIHAS two months post-last treatment. This assessment was performed separately for each infraorbital hollow area. Treatment response was defined as ≥ 1-point improvement on both IOHs compared to baseline.

Secondary effectiveness measurements included:

- Treated Subjects: GAIS assessment by the treating investigator and subject self-assessment GAIS and FACE-Q satisfaction with eyes.
- Control Subjects: FACE-Q satisfaction with eyes.

The investigator and subject GAIS scores at Month 2 post last injection were utilized to demonstrate the level of improvement, when compared to baseline photographs, resulting from treatment in the IOHs. Improvements in the FACE-Q satisfaction with eyes scores from baseline to two months post-treatment indicated that subjects were satisfied with treatment effects observed on their IOHs and such changes were considered to be clinically relevant from the subject's perspective. Responses for FACE-Q satisfaction with eye scores in the control group were compared to that of the treatment group in order to show that changes in satisfaction post-treatment are clinically relevant to the subject.

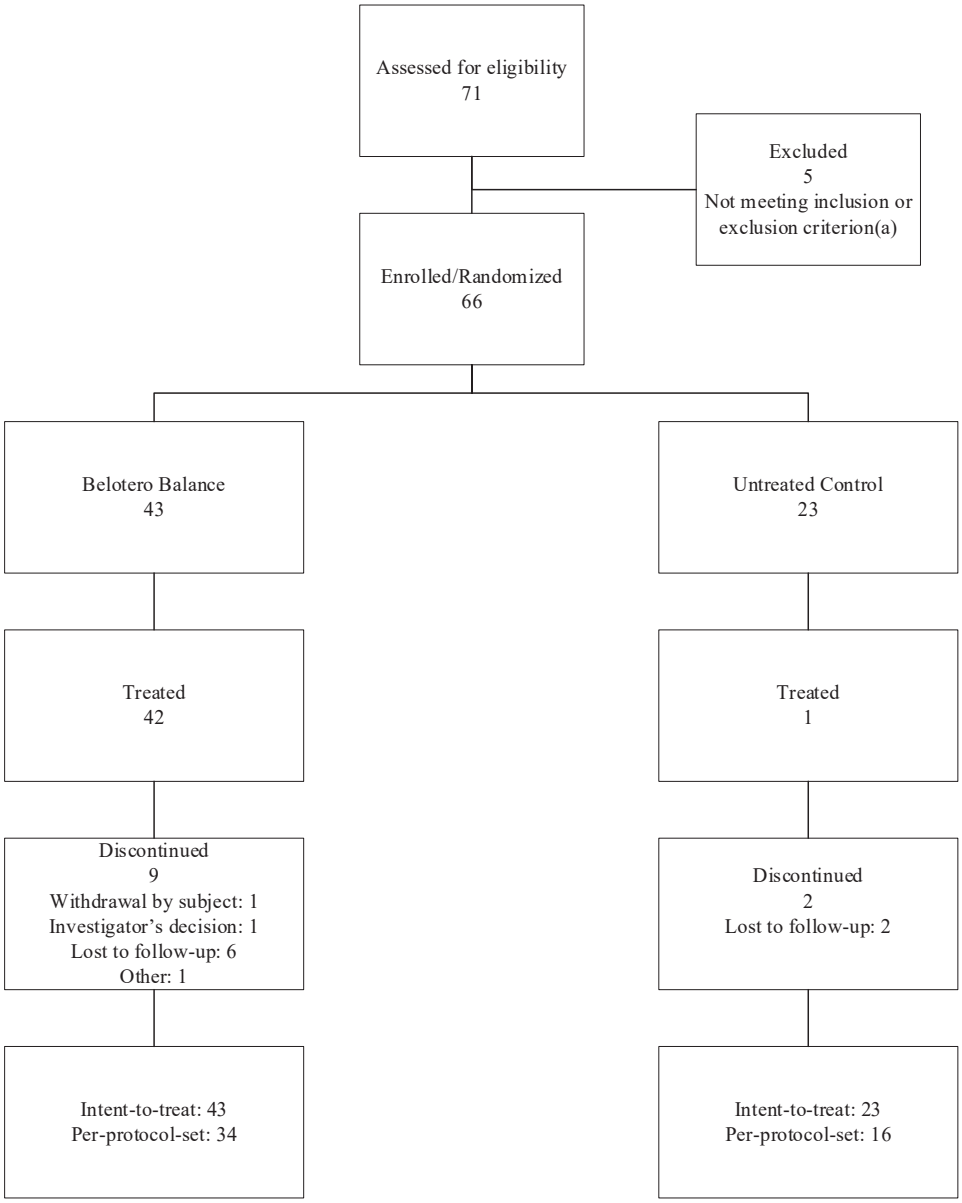
- **Success/Failure Criteria**

With regard to success/failure criteria, the responder rate was defined as the percentage of subjects with ≥ 1-grade improvement of both infraorbital hollows on the MIHAS from baseline to Month 2. Effectiveness of Belotero Balance® was demonstrated if the responder rate at Month 2 for the treatment group was statistically significantly greater than that for the no-treatment control group.

B. Accountability of the Pilot Study Cohort

Figure 3 provides an overview of the subject disposition in Study M930121001.

Figure 3 Study M930121001 Subject Disposition



Among subjects in the treatment group, 34 (79.1%) of 43 subjects completed the study, while 9 (20.9%) subjects in this group prematurely discontinued the study (lost to follow-up: n = 6; withdrawal by subject: n = 1; investigator's decision: n = 1; other: n = 1). Twenty-one (91.3%) of 23 subjects in untreated control group completed the study, while 2 (8.7%) subjects prematurely discontinued (both subjects were lost to follow-up). One subject, who was randomized to the untreated control group but treated, was followed for long-term safety monitoring until Month 12 and was considered to have completed the study.

In regard to the analysis populations, 43 (100%) subjects in the treatment group and 23 (100%) subjects in the control group were included in the intent to treat (ITT) population. Thirty-four (79.1%) subjects in the treatment group and 16 (69.6%) subjects in the control group were included in the per protocol (PP) population. All subjects randomized and treated (65) were included in the safety population (SP). One subject that was randomized to the treatment group did not receive treatment and one subject randomized to the control group accidentally received treatment.

C. Study Population Demographics and Baseline Parameters

Table 4 provides an overview of Study M930121001 demographics.

Table 4 Study M930121001 Demographics

	Belotero Balance® (N=43)	**Untreated Control** (N=22)	**Total** (N=65)
Sex (n (%))			
Female	37 (86.0)	18 (81.8)	55 (84.6)
Male	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)
Median	49.0	48.5	49.0
Min, Max	22, 73	25, 63	22, 73
Ethnicity (n (%))			
Hispanic or Latino	5 (11.6)	2 (9.1)	7 (10.8)
Not Hispanic or Latino	38 (88.4)	20 (90.9)	58 (89.2)
Race			
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 Alaskan 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			
I – III	29 (67.4)	16 (72.7)	45 (69.2)
IV - VI	14 (32.6)	6 (27.3)	20 (30.8)

Max = maximum; Min = minimum; n = number of observations; N = number of subjects in respective group, as actually treated; SD = Standard Deviation; SP = safety population

The majority of subjects (84.6%) were female. Age ranged from 22 to 73 years with a mean of 46.4 years. Majority of the subjects (84.6%) were classified as White, 10.8% as Black/African American, 3.1% as American Indian/Alaskan Native, and 1.5% as Native Hawaiian/Other Pacific Islander. Regarding Fitzpatrick Skin Type categories, 69.2% subjects were classified as Skin

Types I, II, or III, and 30.8% were Skin Types IV, V, or VI. The demographics of the study population are typical for an aesthetic study performed in the US.

With regard to baseline severity, all subjects randomized had the same MIHAS severity score on both their left and right IOHs according to the assessment performed by the blinded evaluator at each of the sites. Of the 43 subjects in the treatment group (ITT population, Observed Cases (OCs)), 17 (39.5%) had a score of a 2 (moderate) on both IOHs, and 26 (60.5%) had a score of a 3 (severe) on both IOHs. Of the 23 subjects in the control group, 4 (17.4%) had a score of a 2 on both IOHs and 19 (82.6%) had a score of a 3 on both IOHs.

Table 5 provides injection information for all treated subjects. 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).

Table 5 Study M930121001 Injection Information for Treated Subjects (SP)

	Right IOH (N = 43)	Left IOH (N = 43)	Any IOH (N = 43)
Initial Injection Information			
Total number of subjects receiving initial injection, n	43	43	43
Total initial injection volume (mL)			
Mean (SD)	0.85 (0.21)	0.86 (0.18)	1.71 (0.37)
Median	1.00	1.00	1.90
Min, Max	0.08, 1.00	0.40, 1.00	0.80, 2.00
Initial injection technique, n (%)[1,2]			
Tunneling/Threading	43 (100.0)	42 (97.7)	43 (100.0)
Fanning	43 (100.0)	43 (100)	43 (100.0)
Number of initial injection points, n (%)[2]			
1 injection point	42 (97.7)	42 (97.7)	42 (97.7)
2 injection points	1 (2.3)	1 (2.3)	1 (2.3)
Ice and topical anesthetic applied, n (%)[1,2]			
Ice used pre-injection	13 (30.2)	12 (27.9)	13 (30.2)
Ice used post-injection	23 (53.5)	23 (53.5)	23 (53.5)
Topical anesthetic applied	27 (62.8)	27 (62.8)	27 (62.8)
Touch-up injection information			
Total number of subjects receiving touch-up injection, n[3,4]	18	22	25
Total initial injection volume (mL)			
Mean (SD)	0.44 (0.11)	0.44 (0.15)	0.71 (0.30)
Median	0.50	0.50	0.70
Min, Max	0.30, 0.75	0.10, 0.70	0.10, 1.25
Initial injection technique, n (%)[1,4]			
Tunneling/Threading	16 (88.9)	21 (95.5)	23 (92.0)
Fanning	17 (94.4)	21 (95.5)	24 (96.0)
Number of initial injection points, n (%)[4]			
1 injection point	18 (100.0)	22 (100.0)	25 (100.0)
2 injection points	0 (0.0)	0 (0.0)	0 (0.0)
Ice and topical anesthetic applied, n (%)[1,4]			
Ice used pre-injection	3 (16.7)	4 (18.2)	5 (20.0)
Ice used post-injection	7 (38.9)	11 (50.0)	12 (48.0)
Topical anesthetic applied	14 (77.8)	13 (59.1)	16 (64.0)

[1] Multiple entries possible; [2] Percentages based on total number of subjects receiving initial injection; [3] Touch-up was administered at the discretion of the treating investigator; [4] Percentages are based on the total number of subjects receiving a touch-up.
IOH = infraorbital hollow; max = maximum; min = minimum; n = number of observations; N = number of subjects in the treatment group and analysis set; SD = standard deviation; SP = safety population

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety population cohort of 66 participants. The safety population included participants who were randomized to the study treatment and received at least one study device treatment and participants randomized to the control group.

Safety assessments such as visual acuity, confrontational visual fields, and ocular motility were evaluated at the screening visit and throughout the study. None of the safety assessments were remarkable or presented safety concerns after treatment with Belotero Balance®.

- **Common Treatment Responses (CTR) Reported in Study M930121001**

Electronic diaries were used by subjects who received treatment to record specific signs and symptoms experienced during the month after treatment. Subjects were instructed to rate each CTR listed in the diary as 'mild', 'moderate', 'severe' or 'none'. **Table 6** summarizes the incidences of CTRs by maximum severity and longest duration after initial baseline treatment.

Table 6 Study M930121001: CTRs by Maximum Severity and Longest Duration after Initial Treatment for Treated Participants

CTR – initial injection	Maximum Severity (N=43)				Longest Duration (N=43)			
	None % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % (n/M)	1-3 Day % (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)
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)

Note: One subject had no subject diary data, subject was lost to follow-up after baseline. CTR = common treatment response; eDiary = electronic diary; N= number of subjects in the respective group, as actually treated; n = number of subjects with particular CTR of the given severity / duration; M = number of subjects with assessment; SAP = statistical analysis plan; SP = safety population.

For the initial injection, 38 (90.5%) of 42 subjects self-reported experiencing at least one CTR. Overall, a majority (35;83.4%)) of subjects reported CTRs for the initial injection that were mild to moderate in severity. For the majority of these reported events (24 of 42, 57.1%), the longest duration was within 14 days of treatment. Fourteen (14) of 42 subjects (33.3%) had ongoing CTR events for ≥ 15 days after initial injection. All CTRs resolved in 28 day reporting period. The events were evaluated by the treating investigator and determined to not require additional reporting as adverse events.

- **Adverse Effects that Occurred in Study M930121001**

Adverse events (AEs) were reported by Treating Investigators at all follow-up visits, where applicable. **Table 7** provides an overall summary of Treatment Emergent Adverse Events (TEAEs).

Table 7. Study M930121001: Overall Summary of TEAEs (SP)

	Belotero Balance (N = 43)	
	n	**(%)**
Number (%) of subjects with:		
Any TEAE	9	(20.9)
Any TEAE related to treatment	2	(4.7)
Any serious TEAE	1	(2.3)
Any serious TEAE related to treatment	0	(0.0)
Any TEAE leading to discontinuation	0	(0.0)
Any fatal TEAE	0	(0.0)

Note: TEAEs were defined as adverse events (AEs) with onset on or after the first administration of study treatment. MedDRA version 22.1
N = number of subjects in respective group, as actually treated; n = number of observations; MedDRA = Medical Dictionary of Regulatory Activities; SP = safety population; TEAE = treatment emergent adverse event

Two treated subjects (4.7%) experienced TEAEs related to treatment accounting for four events in the following system organ classes (*SOCs*):

- *Injury, poisoning, and procedural complication:* contusion (bruising) (one subject reported two events, duration = 6 days, each) and post procedural discomfort (one subject, duration = 2 days).
- *General disorders and administration site conditions:* injection site swelling (one subject, duration = 20 days).

The four events occurring in two subjects summarized above were reported to be mild in intensity and recovered/resolved.

There were no serious adverse events related to treatment. There were no unanticipated adverse device effects and there were no deaths that occurred during the study.

2. Effectiveness Results

○ Primary Effectiveness Results

Table 8 summarizes the results for the primary effectiveness endpoint and shows the proportion of subjects that achieved a response in both the treated and control groups.

Table 8 Study M930121001: Primary Effectiveness Results: Summary of Responders showing a ≥ 1 point improvement on the MIHAS (ITT, Observed Cases)

Visit	Belotero Balance®		Untreated Control		Difference in Response Rates	95% CI for Difference in Response Rates[1]	Left-sided p=value[2]
	n/Nobs	%	n/Nobs	%	%		
Month 2	31/38	81.6	2/21	9.5	72.1	[47.5, 83.5]	<0.0001

[1] Two-sided Newcombe confidence interval;

[2] From Fisher's exact test

Note: Month 2 was defined as time from last injection (e.g. either initial treatment or touch-up, if applicable) for the treatment group and for the control group Month 2 was defined as time from the baseline visit.

Note: N = number of subjects in the respective group, as randomized.

Note: Nobs = total number of subjects with available data per group.

Note: Treatment response was defined as a ≥ 1 point improvement on the MIHAS scale for both IOHs compared to baseline as assessed by the blinded evaluator.

CI = confidence interval; IOH = infraorbital hollow; ITT = intent-to-treat; MIHAS = Merz Infraorbital Hollow Assessment Scale

Statistically significant differences ($p < 0.0001$; Fisher's Exact Test) were demonstrated between the response rates in the treatment group and the control group. Thirty-one (81.6%) of 38 subjects in the treatment group and 2 (9.5%) in the control group were responders. The 95% CI for the difference in response rates was [47.5%, 83.5%]. Hence, the analysis of primary analysis demonstrated a statistically significant superiority of Belotero Balance® over control.

Table 9 summarizes the primary effectiveness results and shows the proportion of subjects that achieved a response by Fitzpatrick Skin Type (FST).

Table 9 Study M930121001: Primary Effectiveness Results: Responders by Fitzpatrick Skin Types, ITT (observed cases)

Visit	FST	Belotero Balance® (N=43) % (n/Nobs)	Untreated Control (N=23) % (n/Nobs)	Difference in Response Rates	95% CI for difference in response rates[1]
Month 2	Type I-III	72.0 (18/25)	6.3 (1/16)	65.8	[36.2, 80.4]
	Type IV-VI	100.0 (13/13)	20.0 (1/5)	80	[31.8, 96.4]

[1] Two-sided Newcombe confidence interval based on Wilson´s scores
N = number of subjects in the respective group, as randomized, Nobs = total number of subjects with available data per group, CI = confidence interval
Treatment response is defined as >= 1-point improvement on the MIHAS scale for both IOHs compared to baseline as assessed by a blinded evaluator

When stratified by Fitzpatrick Skin Type, 18 (72.0%) of 25 subjects of Skin Types I-III and all 13 (100%) subjects of skin types IV-VI in the treatment group were responders. In comparison, of the 16 control subjects of Fitzpatrick Skin Types I-III and 5 control subjects of Fitzpatrick Skin Types IV-VI, 1 (6.3%) subject of Skin Type I-III and 1 (20.0%) subject of Skin Type IV-VI responded.

- **Secondary Effectiveness Results**

FACE-Q Satisfaction with Eyes Assessment

Table 10 summarizes the Rasch-Transformed FACE-Q satisfaction with eyes assessment for the treatment and control subjects at baseline and Month 2.

- In the treatment group, the mean Rasch-transformed score increased from 42.3 at baseline to 71.4 at Month 2. The mean change from baseline to Month 2 was 28.8 and the respective 95% CI of [21.2, 36.5] excluded zero.
- In the control group, the Rasch-transformed scores essentially stayed the same from baseline (mean = 36.0) to Month 2 (mean = 37.4). The 95% CI [-3.9, 8.1] of the change from baseline included zero.

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 eyes looked, how nice their eyes looked, and how youthful their eyes looked after treatment.

Table 10 Study M930121001: Summary of the Rasch-Transformed Scores for the FACE-Q Satisfaction with Eyes (ITT, Observed Cases)

Statistics	Belotero Balance® (N = 43)			Untreated Control (N = 23)		
	Baseline	Month 2	Change from Baseline to Month 2	Baseline	Month 2	Change from Baseline to Month 2
N	42	38	38	23	21	21
Mean (SD)	42.3 (15.2)	71.4 (18.1)	28.8 (23.2)	36.0 (16.5)	37.4 (17.2)	2.1 (13.1)
95% CI	[37.5, 47.0]	[65.5, 77.4]	[21.2, 36.5]	[28.9, 43.2]	[29.6, 45.3]	[-3.9, 8.1]
Median	43.0	72.0	24.5	35.0	39.0	4.0
Min, Max	0, 86	39, 100	-16, 82	0, 59	0, 63	-23, 31

Note: N = number of subjects in the respective group, as randomized.
Note: Month 2 was defined as time from last injection (e.g. either initial treatment or touch-up, if applicable.
Note: Higher scores indicated greater satisfaction
CI = confidence interval for the mean; ITT = intent-to-treat; max = maximum; min = minimum; SD = standard deviation

Treating Investigator GAIS

Table 11 summarizes the treating investigator GAIS scores when comparing Month 2 photographs to baseline photographs. This assessment was only performed on subjects in the treatment group. Investigator GAIS data collected at Month 2 was available for 38 subjects. All (n = 38; 100%) of these subjects were reported to show a level of improvement on the GAIS as judged by the treating investigator. More specifically, 23 (60.5%) subjects were reported to be very much improved, 4 (10.5%) were reported to have shown much improvement, and 11 (28.9%) were reported improved on the GAIS when comparing post-treatment photographs to baseline photographs. Treating investigators did not report any subjects to have no change or any level of worsening post-treatment. Overall, the investigator GAIS scores demonstrated that treatment with Belotero Balance® resulted in overall aesthetic improvement of the IOHs.

Table 11 Study M930121001: Summary of Treating Investigator GAIS at Month 2, Treatment Group Only (ITT, Observed Cases)

Investigator GAIS Scores at Month 2	Belotero Balance® (N = 43)		
	n/Nobs	(%)	95% CI*
+3 = Very much improved	23/38	(60.5)	
+2 = Much improved	4/38	(10.5)	
+1 = Improved	11/38	(28.9)	
0 = No change	0/38	(0.0)	
-1 = Worse	0/38	(0.0)	
-2 = Much worse	0/38	(0.0)	
-3= Very much worse	0/38	(0.0)	
Any Improvement	38/38	(100.0)	(90.82, 100.00)
No Change	0/38	(0.0)	
Any worsening	0/38	(0.0)	

Note: Month 2 was defined as time from last injection (e.g. either initial treatment or touch-up, if applicable.
Note: N = number of subjects in the respective group, as randomized.
Nobs = total number of subjects with available data
*95% Wilson CI
GAIS = Global Aesthetic Improvement Scale; ITT = intent-to-treat, CI = Confidence Interval

Subject Self-Reported GAIS

Table 12 summarizes the subject self-reported GAIS scores when comparing Month 2 photographs to baseline photographs. This assessment was only performed on subjects in the treatment group. Subject GAIS data collected at Month 2 was available for 38 subjects. The majority of the treated subjects (n = 35; 92.1%) self-reported to show a level of improvement on the GAIS. More specifically, 11 (28.9%) treated subjects reported to be very much improved, 9 (23.7%) reported to have shown much improvement, and 15 (39.5%) reported to improve on the subject GAIS when comparing post-treatment photographs to baseline photographs.

Table 12 Study M930121001: Summary of Subject GAIS at Month 2, Treatment Group Only (ITT, Observed Cases)

Subject GAIS Scores at Month 2	Belotero Balance® (N = 43)		
	n/Nobs	(%)	95% CI*
+3 = Very much improved	11/38	(28.9)	
+2 = Much improved	9/38	(23.7)	
+1 = Improved	15/38	(39.5)	
0 = No change	2/38	(5.3)	
-1 = Worse	1/38	(2.6)	
-2 = Much worse	0/38	(0.0)	
-3= Very much worse	0/38	(0.0)	
Any Improvement	35/38	(92.1)	(79.20, 97.28)
No Change	2/38	(5.3)	
Any worsening	1/38	(2.6)	

Note: Month 2 was defined as time from last injection (e.g. either initial treatment or touch-up, if applicable.
Note: N = number of subjects in the respective group, as randomized.
Nobs = total number of subjects with available data
*95% Wilson CI
GAIS = Global Aesthetic Improvement Scale; ITT = intent-to-treat, CI = Confidence Interval

- **Other Effectiveness Results**

Cross-Tabulation of MIHAS Scores with Treating Investigator GAIS Scores, ITT, Observed Cases

Table 13 summarizes the outcome for a cross-tabulation between treated subjects that achieved a ≥ 1-point improvement on both IOHs using the MIHAS (assessed by a live blinded evaluator) versus treating investigator GAIS scores at Month 2.

Month 2 data for the blinded evaluator MIHAS and the treating investigator GAIS was available for 38 subjects. Thirty-one (81.6%) of these subjects achieved a ≥ 1-point improvement on both IOHs according to the blinded evaluator MIHAS rating and had a level of improvement on the GAIS when the treating investigator compared the subject's baseline photographs to post-treatment photographs.

The cross-tabulation analysis demonstrated that the objective clinical outcome from the MIHAS as assessed by live blinded evaluators were consistent with the treating investigator's perspective of aesthetic improvements post-treatment on the GAIS, thus supporting that the MIHAS outcomes from the live blinded evaluator were clinically relevant by means of the GAIS assessment from the treating investigator.

Table 13 Summary of Cross-Tabulation of the MIHAS Results for Changes from Baseline to Month 2 versus Treating Investigator GAIS Results at Month 2, Treatment Group Only (ITT, Observed Cases)

Investigator GAIS	Belotero Balance® (N = 43) ≥ 1-point improvement on both IOHs					
	Yes		No		Total	
	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)
Improvement[1]	31/38	(81.6)	7/38	(18.4)	38/38	(100.0)
No change from baseline	0/38	(0.0)	0/38	(0.0)	0/38	(0.0)
Worsening[2]	0/38	(0.0)	0/38	(0.0)	0/38	(0.0)
Total	31/38	(81.6)	7/38	(18.4)	38/38	(100.0)

GAIS = Global Aesthetic Improvement Scale; IOH = infraorbital hollow; ITT = intent-to-treat.
% = (n/Nobs)*100.
[1] Included 'improved', 'much improved' and 'very much improved' in GAIS
[2] Included 'worse', 'much worse', and 'very much worse' in GAIS.
Note: Month 2 was defined as time from last injection (e.g. either initial treatment or touch-up, if applicable.
Note: N = number of subjects in the respective group, as randomized.
Note: Nobs = total number of subjects with available data per group.

Cross-Tabulation of MIHAS Scores with Subject GAIS Scores, ITT, Observed Cases

Table 14 summarizes the outcome for a cross-tabulation between treated subjects that achieved a ≥ 1-point improvement on both IOHs using the MIHAS (assessed by a live blinded evaluator) versus subject GAIS responses at Month 2.

Month 2 data for the live blinded evaluator MIHAS and the subject GAIS was available for 38 subjects. Thirty 78.9%) of these subjects achieved a ≥ 1-point improvement on both IOHs according to the live blinded evaluator MIHAS rating and had a level of improvement on the GAIS when the subject compared baseline photographs to post-treatment photographs.

One (2.6%) subject that achieved a ≥ 1-point improvement on both IOHs according to the live blinded evaluator MIHAS rating self-reported that no change was observed when comparing baseline photographs to Month 2 post-treatment photographs. This subject indicated that the pre- and post-treatment photographs looked the same and no improvement was observed.

There were a total of 7 (18.4%) of 38 treated subjects that did not achieve a ≥ 1-point improvement on both IOHs according to the live blinded evaluator MIHAS rating at Month 2. Five (13.2%) of these subjects self-reported a level of improvement on the GAIS; 1 (2.6%) subject self-reported no change from baseline; and 1 (2.6%) subject self-reported a level of worsening. No follow-up information was provided as to why these subjects answered no change or worsening on the GAIS assessment.

The cross-tabulation analysis demonstrated that the objective clinical outcome from the MIHAS as assessed by blinded evaluators was consistent with the subject's

perspective of aesthetic improvement post-treatment on the GAIS; thus supporting that the MIHAS outcomes from the live blinded evaluator were clinically relevant by means of the GAIS assessment from the subject.

Table 14 Summary of Cross-Tabulation of the MIHAS Results for Changes from Baseline to Month 2 versus Subject GAIS Results at Month 2, Treatment Group Only (ITT, Observed Cases)

	Belotero Balance® (N = 43) ≥ 1-point improvement on both IOHs					
Investigator GAIS	Yes		No		Total	
	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)
Improvement[1]	30/38	(78.9)	5/38	(13.2)	35/38	(92.1)
No change from baseline	1/38	(2.6)	1/38	(2.6)	2/38	(5.3)
Worsening[2]	0/38	(0.0)	1/38	(2.6)	1/38	(2.6)
Total	31/38	(81.6)	7/38	(18.4)	38/38	(100.0)

GAIS = Global Aesthetic Improvement Scale; IOH = infraorbital hollow; ITT = intent-to-treat.
% = (n/Nobs)*100.
[1] Included 'improved', 'much improved' and 'very much improved' in GAIS
[2] Included 'worse', 'much worse', and 'very much worse' in GAIS.
Note: Month 2 was defined as time from last injection (e.g. either initial treatment or touch-up, if applicable.
Note: N = number of subjects in the respective group, as randomized.
Note: Nobs = total number of subjects with available data per group.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR Part 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pilot clinical study # M930121001 included three investigators who all executed a financial disclosure/certification form and verified that they have no applicable financial arrangements with Merz North America Inc. as defined in sections 54.2(a), (b), (c) and (f). The information provided does not raise any questions about the reliability of the data. There were no investigators who had financial arrangements with Merz North America Inc. to be disclosed under 21 CFR Part 54.2(b).

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators.

Study M930121002 Evaluation of Effectiveness and Safety of Belotero Balance® (+) for Volume Augmentation of the Infraorbital Hollow (PIVOTAL STUDY)

The Sponsor performed a clinical study M930121002 to establish a reasonable assurance of safety and effectiveness of Belotero Balance® (+) for volume augmentation for the improvement of infraorbital hollows under IDE G170211/S004. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients received treatment between September 14, 2020 and January 11, 2022.[4] The database for this Panel Track Supplement reflected data collected through June 21, 2022 and included 150 patients who were randomized and underwent treatment with Belotero Balance® (+) (N= 97) or delayed treatment control (N=53) at the outset of the study. There were nine investigational sites.

The study was a prospective, multi-center, randomized, comparative, evaluator-blinded pivotal study. Subjects eligible for study enrollment were to have symmetrical right and left IOHs with the same MIHAS score of 2 or 3 (moderate or severe), as assessed live by a blinded evaluator. All blinded evaluators were qualified healthcare practitioners, delegated by the treating investigator (TI), and trained by the sponsor. At screening, eligible subjects were randomized to four groups, using a 2:2:1:1 ratio as follows: Belotero Balance® (+) with needle (TN), Belotero Balance® (+) with cannula (TC), control/delayed treatment Belotero Balance® (+) with needle (CDTN), and control/delayed-treatment Belotero Balance® (+) with cannula (CDTC). The TI determined the appropriate volume of Belotero Balance® (+) to be injected into the orbital rim (**Figure 1**). Injections into the infraorbital hollow were in the supraperiosteal and/or subcutaneous plane with a Sterimedix® Silkann® 27G x 40 mm cannula with or 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 control participants had treatment delayed for eight weeks after the primary effectiveness assessment.

1. Main Clinical Inclusion and Exclusion Criteria

Enrollment in the Study # M930121002 was limited to patients who met the following inclusion criteria:

- Subject is a candidate for bilateral IOH treatment.
- Subject has symmetrical right and left IOHs with the same MIHAS score of 2 or 3 (moderate or severe), as assessed live by a blinded evaluator.
- Female or male ≥ 22 and ≤ 65 years old.

[4] Patients in the treatment arm received initial treatment, optional touch-up, and optional retreatment. These dates reflect the first subject who received initial treatment and the last subject who received optional retreatment.

Patients were not permitted to enroll in Study # M930121002 if they met any of the following exclusion criteria:

- Prior lower-eyelid surgery, including orbital or midface surgery, or a permanent implant or graft in the midfacial region that could interfere with effectiveness assessments.
- Previous treatment with fat injections or permanent and/or semi-permanent dermal fillers in the midfacial region.
- Previous lower-eyelid and/or malar-region treatments with any dermal fillers (e.g., collagen, hyaluronic acid (HA), calcium hydroxyapatite, poly L-lactic acid (PLLA)) within the past 24 months.
- Tendency to accumulate fluid in the lower eyelids, has developed festoons, or has large and/or herniating infraorbital fat pads.

2. Follow-up Schedule

Participants randomized to the treatment arm were scheduled to return for the follow-up examinations at 4, 8, 12, 24, 36, and 48 weeks after the last treatment (initial or touch-up). Participants in the treatment arm were eligible for an optional touch-up treatment with Belotero Balance® (+), 4 weeks after the initial treatment. An optional repeat treatment was offered to the treatment arm after completion of the 48 week follow-up visits, with a 4 week follow-up after repeat treatment. All participants in the treatment arm were scheduled for follow-up examinations at 56 and 72 weeks after the last treatment (initial or touch-up).

Participants randomized to the control/delayed treatment arm were scheduled for primary effectiveness assessment 8 weeks post screening visit. After completion of the primary effectiveness assessment, participants in the control/delayed treatment arm received their treatment and were scheduled to return for follow-up examinations at 8, 12, 24, 36 and 48 weeks after the last treatment (initial or touch-up). Participants in the control/delayed treatment arm were eligible for an optional touch-up treatment with Belotero Balance® (+), 4 weeks after the initial treatment), but not eligible for retreatment.

3. Clinical 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.

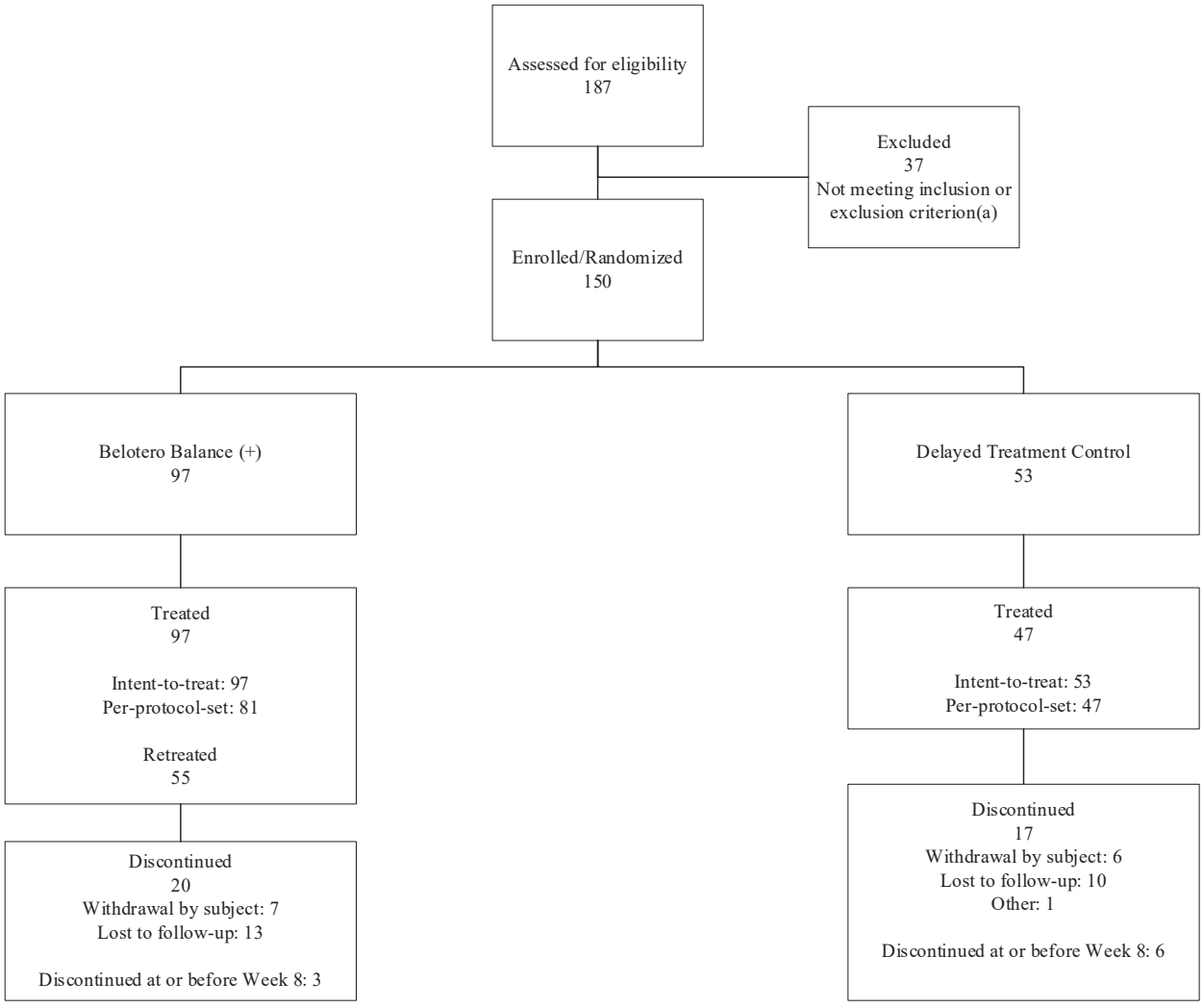
Other effectiveness subject self-assessments included the FACE-Q *Appraisal of Lower Eyelids* questionnaire, FACE-Q *Patient-Perceived Age VAS,* subject reported pain VAS assessment and the likelihood of retreatment.

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.

B. Accountability of PMA Cohort

Figure 4 provides an overview of the subject disposition in Study M930121002.

Figure 4 Study M930121002 Subject Disposition



Among subjects in the treatment group, 77 (79.4%) of 97 patients completed the study, while 20 (20.6%) subjects in this group prematurely discontinued the study (lost to follow-up: n =

13; withdrawal by subject: n = 7). 36 (67.9%) of 53 subjects in the untreated control group completed the study, while 17 (32.1%) subjects prematurely discontinued (lost to follow-up: n = 10; withdrawal by patient: n = 6; other: n = 1).

In regard to the analysis populations, 97 (100%) subjects in the treatment group and 53 (100%) subjects in the control group were included in the ITT population. 81 (83.5%) subjects in the treatment group and 47 (88.7%) subjects in the control group were included in the per-protocol (PP) population. All subjects randomized and treated were included in the safety population (SP).

C. Study Population Demographics and Baseline Parameters

Table 15 provides an overview of Study M930121002 demographics. Overall, demographic and baseline characteristics were similar between the treatment and control/delayed-treatment groups. All minimum criteria for enrollment of males and Fitzpatrick skin types were met.

Most subjects were female (125/150, 83.3%) and self-identified as White (109/150, 72.7%). Mean age of subjects was 43.3 years. Regarding Fitzpatrick skin type categories, 95/150 (63.3%) subjects had skin types I, II, or III and 55/150 (36.7%) subjects had skin types IV, V, or VI.

All subjects randomized had the same MIHAS baseline severity score on both their left and right IOH according to the assessment performed by the blinded evaluator. In the treatment group, 34/97 (35.1%) subjects had a baseline MIHAS score of 2 (moderate) and 63/97 (64.9%) had a score of 3 (severe). In the control/delayed-treatment group, 20/53 (37.7%) subjects had a baseline MIHAS score of 2 and 33/53 (62.3%) had a score of 3.

Table 15 Study M930121002: 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	0 (0.0) 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.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety population cohort of 144 participants. The safety population included participants who received at least one study device treatment.

Safety assessments such as visual acuity, confrontational visual fields, ocular motility and retinal screening were evaluated at the screening visit and throughout the study. None of these safety assessments were remarkable or presented safety concerns with treatment with Belotero Balance® (+).

An electronic diary was used by participants after treatment to record specific signs and symptoms (Common Treatment Responses; CTRs) experienced during the first 28 days after initial treatment, and touch-up and retreatment, if applicable as well as any specific safety concerns. A total of 144 participants underwent treatment; and 143 subjects completed the electronic diary (both from the treatment and delayed-control groups). Participants 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 16, Table 19 and Table 20**; **Table 17** shows the severity and duration of CTRs after touch-up treatment; and **Table 18** 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. Fifteen treatment related TEAEs lasted > 28 days and were experienced by 6 (4.2%) patients. Fourteen events were mild and 1 event was of moderate intensity. 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 16 Study M930121002: 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 17 Study M930121002: 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 18 Study M930121002: 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.

Table 19 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)

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)
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)
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 20 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)

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	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.

[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.

Treating Investigators reviewed subject diaries for potential adverse events (AEs). AEs were also reported by the Treating Investigator at follow-up visits. Treatment-related AEs were reported in 13 (9.0%) of 144 treated subjects.

Table 21. 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 Stie 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.

The most common treatment-related AE was injection site swelling (9/144 subjects, 6.3%). Other treatment-related AEs included: injection site nodule (4/144 subjects, 2.8%), injection site bruising (3/144 subjects, 2.1%), injection site pain (3/144 subjects, 2.1%), injection site dryness (2/144 subjects, 1.4%), and injection site erythema (2/144 subjects, 1.4%). Most treatment-related AEs were mild and subjects recovered within 36 days of treatment. The percentage of subjects with treatment-related TEAEs were comparable between needle (6/75 subjects, 8.0%) and cannula (7/69 subjects, 10.1%)

There were no treatment-related serious adverse events reported during the study. There were no reports of Tyndall Effect.

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 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.

2. 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 22 provides MIHAS Responder Rate at Week 8 by injection instrument.

Table 22 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 =numberof 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 23**).

Table 23 Study M930121002: 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

Optional retreatment with Belotero Balance® (+) was requested and administered to 55 subjects of 97 in the treatment arm randomization group. 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 on 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 assessment was 94.9% (112/118) and the GAIS responder rate based on subject assessment was 87.3% (103/118).

FACE-Q Satisfaction with Eyes 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.

Independent Photographic Rater (IPR) Assessment

Responder rates at Week 8, according to MIHAS were assessed by three blinded IPRs using available baseline and Week 8 photographs. IPRs assessed that 40/89 (44.9%) subjects in the treatment group and 1/6 (16.7%) subjects in the control group showed a treatment response. When considering subjects with a baseline MIHAS score of at least moderate (MIHAS = 2, as assessed by all three IPRs), responder rates exceeded 60% for the treatment group. IPRs assessed that 34/54 (63.0%) subjects in the treatment group, with at least a baseline MIHAS score of moderate, showed a treatment response, compared to 1/4 (25%) subjects in the control group.

Other Subject-Reported Effectiveness Results

- **FACE-Q Appraisal of Lower Eyelids**: Rasch-transformed scores improved post treatment and remained above baseline scores, indicating better outcomes, demonstrating subject satisfaction with how their eyelids looked.

- **FACE-Q Patient-Perceived Age VAS**: Subjects reported looking younger by 2.5 years on average at 8 weeks after treatment.

- 89% of subjects would be likely to have future treatment with Belotero Balance® (+)

- **Subject reported pain VAS** results from 5 minutes after initial treatment of both IOHs: The mean (SD) score, on a 0 to 10 scale, with 0 being "no pain" and 10 being "very severe pain," was 1.6 (1.7), indicating that Belotero Balance® (+) -treatment procedure resulted in minimal pain.

3. Subgroup Analyses

Primary Injection Instrument

52% (75/144) subjects received their injection(s) via a needle; 48% (69/144) received their injection(s) via a cannula.

Study Injection Volume

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.

While injection volumes were similar at the initial-treatment visit for needle and cannula treatment groups, more subjects randomized to needle (75/144, 52.1%) received a touch-up injection compared to those randomized to cannula who received a touch -up injection (69/144, 47.9%). As a result, subjects treated with needle received a slightly higher injection volume than subjects treated with cannula when considering total volume of initial and touch-up injections. No clinically relevant trends were identified between groups.

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.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR Part 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included eight investigators who all executed a financial disclosure/certification form and verified that they had no applicable financial arrangements with Merz North America Inc. as defined in sections 54.2(a), (b), (c) and (f). The information provided does not raise any questions about the reliability of the data. One of the nine investigators had financial arrangements with Merz North America Inc. to be disclosed under 21 CFR Part 54.2(b), not affecting the outcome of the Study M930121002.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation

because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The study demonstrated significant improvement in the infraorbital hollows following treatment with Belotero Balance® (+). The data was robust and showed significant improvement in the treatment group vs. the control group (80.6% vs. 1.9% responder rates). Similar improvement was seen in subjects treated with needles (87.4%) vs. cannula (73.7%). Additional subgroup analyses by baseline MIHAS severity, gender, Fitzpatrick Skin Type, age, and race showed acceptable responder rates for the various subgroups. Secondary and other effectiveness endpoints, which included evaluations via investigator GAIS, subject GAIS, and FACE-Q Satisfaction with Eyes, were also favorable. While the responder rate appeared low per the IPR, the results from the other endpoints support the overall effectiveness of the device for the proposed indication. Belotero Balance® (+) met the pre-specified primary endpoint, and the secondary endpoints to support product effectiveness. The data confirms that Belotero Balance® (+) is effective for volume augmentation for the improvement of the infraorbital hollow in adults over the age of 21. See data above.

B. Safety Conclusions

The potential risks and adverse effects of the device are based on pre-clinical studies and the data collected in the clinical studies conducted to support the indication expansion as described above as well as evaluation of device use in the Post-Marketing setting. The data submitted provide a reasonable assurance that the device is safe for injections in the supraperiosteal and/or subcutaneous planes for volume augmentation for the improvement of the infraorbital hollow in adults over the age of 21. The specific conclusions are:

- Safety assessments such as visual acuity, confrontational visual fields, ocular motility and retinal imaging were evaluated at the screening visit and throughout the study. None of the safety assessments were remarkable or presented safety concerns after treatment with Belotero Balance (+). Treatment with Belotero Balance® (+) did not lead to serious vision-related adverse events in the study.
- For initial, touch-up and repeat treatments, the most common CTRs were swelling, bruising, visible lumps and redness. Most CTRs were mild to moderate in severity (initial treatment 83.3%; touch-up 73.4% and repeat treatment 59.2%), resolved within 14 days (initial treatment 59.5%; touch-up 55.8% and repeat treatment 50.0%) and were as expected for soft tissue filler treatments.
- The percentage of subjects with treatment-related TEAEs were comparable between needle (6/75 subjects, 8.0%) and cannula (7/69 subjects, 10.1%).

- The most common treatment related TEAEs after initial/touch-up treatment were injection site swelling, injection site nodule, injection site bruising, and injection site pain. All other treatment related TEAEs occurred in less than 2% of patients.
- There were 29 treatment related TEAEs experienced by 13 patients. Fifteen treatment related TEAEs lasted > 28 days and were experienced by only 6 (4.2%) patients. Fourteen events were mild and 1 event was of moderate intensity.
- There were no deaths or treatment related serious adverse events (TESAEs) reported in the study.
- Participants assessed procedural pain during injection as minimal.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The pivotal study was a prospective, delayed-treatment control study using a validated scale and blinded, live evaluations. In the Belotero Balance® (+) group at Week 8, the average MIHAS response rate was 80.6% [95% CI: 71.4%, 87.4%] exceeding the targeted margin of 50% and demonstrating statistical significance. In contrast, an average response rate of 1.9% [95% CI: 0.3%, 10.2%] was seen for the untreated control group. The difference in response rates was 78.7% [95% CI: 66.3%, 85.6%], demonstrating a statistically significant, superior response rate in treated subjects compared to the untreated control. Moreover, the majority of responders at Week 8 retained treatment response up to 48 weeks after treatment (88/97 subjects, 90.7%). These findings support the effect of Belotero Balance® (+) treatment for up to 48 weeks when used for volume augmentation for the improvement of the infraorbital hollow. Additionally, in the subset of subjects who did not receive retreatment, treatment response was retained up to 72 weeks post treatment (20/22 subjects, 90.9%). The results from the secondary endpoints related to the subject- and investigator-reported assessments (e.g., FACE-Q Satisfaction with Eyes, and the investigator and subject GAIS) all support the primary endpoint indicating that BBL is an effective treatment for volume augmentation for the improvement of the infraorbital hollow in adults over the age of 21.

The probable risks of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. Most (92.3%) of the patients experienced common treatment responses which included swelling, bruising, lumps/bumps, redness, pain/discomfort and itching. These were predominantly mild in severity with the majority resolving within 14 days. Six patients (4.2%) had mild treatment related TEAEs that lasted over 28 days. No serious treatment-related TEAEs were reported, and no subject withdrew from the study because of a treatment-related TEAE.

Patient perspectives considered during the review included several patient reported outcome tools and questionnaires:

- Subject GAIS

- FACE-Q *Satisfaction With Eyes*
- FACE-Q *Appraisal of Lower Eyelids*
- FACE-Q *Patient Perceived Age* VAS
- Subject Reported Pain VAS
- Likelihood of retreatment survey

In conclusion, given the available information above, the data support the use of Belotero Balance® (+) for volume augmentation for the improvement of the infraorbital hollow in adults over the age of 21, and the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on September 27, 2023.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. 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.