SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	Belotero® Intense (+) Lidocaine
Device Procode:	LMH
Applicant's Name and Address:	Merz North America Inc. 6501 Six Forks Road, Raleigh, NC 27615 United States of America
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P250016
Date of FDA Notice of Approval:	July 9, 2026

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

- Belotero® Intense (+) Lidocaine is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history of multiple severe allergies.
- Belotero® Intense (+) Lidocaine contains lidocaine and is contraindicated for patients with known hypersensitivity to lidocaine or anesthetics of the amide type.
- Belotero® Intense (+) Lidocaine contains trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTION

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

V. DEVICE DESCRIPTION

Belotero® Intense (+) Lidocaine is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenous gel implant. It consists of hyaluronic acid (HA) of non-animal origin, which is crosslinked with BDDE (1,4-butanediol diglycidyl ether) and formulated to a

concentration of 25.5 mg/mL with 3.0 mg/mL lidocaine in a physiological phosphate buffer. Belotero® Intense (+) Lidocaine is supplied in a prefilled syringe co-packaged with two sterile 27G 1/2" needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives to achieve lip volume and lip fullness such as other dermal filler products, surgical procedures, implants, or fat injections. 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® Intense (+) Lidocaine was first approved for commercial distribution in October 2013 in the European Union (EU). The product was subsequently approved in several countries worldwide and is currently registered and sold in seventy-eight countries outside of the US. Belotero® Intense (+) Lidocaine has not been removed from any marketplace 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 ≤ 5% of the study participants after initial and touch-up treatment included injection site swelling, induration, pain, discoloration, bruising, erythema, edema, and oral herpes; and after repeat treatment included injection site pain, swelling, bruising, discoloration, and erythema. The common potential adverse effect as reported in the pivotal clinical study at a frequency > 5% of the study participants included injection site mass.

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

Additionally, the following rare but serious adverse events that are associated with intravascular injection of other dermal filler material in the face have been reported in the literature: vision impairment (acute or permanent), blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

The following additional adverse events were observed with similar dermal filler implants and are considered as potential risks for this device: abscess, angioedema, infection, dizziness, fever, hypoesthesia, induration, nausea, numbness, peeling, presyncope, rash, burning sensation, syncope, inflammation, pruritus/itching, swelling, and skin discoloration.

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

IX. SUMMARY OF NONCLINICAL STUDIES

Belotero® Intense (+) Lidocaine was extensively tested and characterized through physical and chemical testing (Table 1), and biocompatibility studies (Table 2). Preclinical testing results were adequate to support initiation of human clinical studies as a dermal filler.

A. Laboratory Studies

The results of non-clinical laboratory studies for Belotero® Intense (+) Lidocaine are summarized in Table 1.

Table 1: Physical and Chemical Analyses

Test	Results
Appearance	Pass
pH	Pass
Osmolarity	Pass
Mean of Ejection Force	Pass
Rheological properties: Elastic modulus G'	Pass
Rheological properties: Tan δ	Pass
Extractable Volume	Pass
NaHA Content	Pass
Lidocaine hydrochloride content	Pass
2,6 DMA content	Pass
Residual BDDE content	Pass
Endotoxin content	Pass
Protein content	Pass

Sterilization – Pre-filled syringes are sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle is validated according to ISO 17665-1 sterilization standard. The validated sterilization cycle provides a Sterility Assurance Level (SAL) of 10^{-6}.

Stability/Shelf life - Packaged product data has been collected at 25°C/60% relative humidity and was evaluated for conformance to microbiological, physical, and chemical properties. Conformance with all specifications was confirmed.

B. Biocompatibility Studies

Belotero® Intense (+) Lidocaine was tested in accordance with ISO 10993 and FDA's biocompatibility guidance "Use of International Standard ISO 10993-1, Biological

evaluation of medical devices – Part 1: Evaluation and testing within a risk management" and in compliance with FDA GLP regulations (21 CFR § 58).

Test results are summarized in Table 2

Table 2: Summary of Biocompatibility Results

Biological Endpoint	Method	ISO Standard	Results
Cytotoxicity	ISO MEM Elution Assay	ISO 10993-5	Extracts (at 37 °C for 72h in EMEM10 at 0.2 g/mL ratio) gel showed no evidence of cell lysis or cytotoxicity
Sensitization	ISO Guinea Pig Maximization Sensitization Test	ISO 10993-10	Non-sensitizing
Intracutaneous Reactivity/Irritation	ISO Intracutaneous Reactivity / Irritation in rabbits	ISO 10993-23	Non-irritant Further mitigated using long-term implantation study (minipig) study results which demonstrated no evidence of long-term local intolerance.
Pyrogenicity	Material Mediated; Bacterial Endotoxin Mediated	USP <151> USP <85>	Non-pyrogenic
Systemic Toxicity (acute, subacute, subchronic, chronic) & Genotoxicity	Exhaustive Extractable Study Toxicological Risk Assessment	ISO 10993-18 ISO 10993-17	Chemical characterization of BIL was conducted under exhaustive condition in accordance with the current ISO 10993-18:2020/A1:2022. All reported compounds were assessed as confirmed/ confident/tentative (being the only tentative a hyaluronic acid degradation compound). Toxicological evaluation was performed according to ISO 10993-17:2023 requirements, the latter being recognized by the FDA in December 2023. Under highly conservative worst-case exposure assumptions, all reported compounds demonstrated a Margin of Safety (MOS) greater than 1. Systemic toxicity and genotoxicity risks are considered adequately covered.

			None of the extractables potentially leaching out of the product is considered to pose an undue risk to the patient under intended clinical use
Implantation/ Chronic Local Tissue and Degradation Effects	167-Week Implantation study in a mini-pig model	ISO 10993-6	Local Tissue Effects: Non-irritant In vivo Degradation: These advanced levels of article degradation, together with the minimal local tissue reaction observed at the last time point of 167 weeks (steady-state) are compatible with the late time frame as per the ISO 10993-6 standard

Carcinogenicity risks: The excess cancer risks for Belotero® Intense (+) Lidocaine are in the same range of acceptable cancer risks as other previously approved dermal filler products.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of Belotero® Intense (+) Lidocaine dermal filler for lip augmentation in adults over the age of 21 in the US under IDE G220271. Data from this clinical study was the basis for the PMA approval decision.

A summary of the clinical study is presented below.

A. Study Design

Participants were treated between 07-MAR-2023 and 08-JUL-2024. The database for this PMA reflected data collected through 26-SEP-2024 and included 220 treated participants (165 treated with Belotero® Intense (+) Lidocaine and 55 treated with an FDA-approved comparator product). There were 14 investigational sites and 13 of these 14 investigational sites enrolled participants.

The study was a multicenter, evaluator-blinded, randomized, comparator-controlled pivotal clinical study to evaluate the safety and effectiveness of Belotero® Intense (+) Lidocaine versus an FDA-approved comparator product for injection into the lips.

The control group was a legally marketed alternative with similar indications for use.

A total of 220 participants were randomized and received treatment with either Belotero® Intense (+) Lidocaine (n=165) or comparator (n=55) at the outset of the study. An optional touch-up treatment was performed approximately 4 weeks after the initial treatment, if deemed necessary, to achieve optimal correction.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the clinical study was limited to participants who met the following **inclusion criteria**.

- A) Participant of FST I to IV who desired lip augmentation to correct volume deficit and had upper and lower lip deficit with a rating of 0 (very thin), 1 (thin), or 2 (medium) on the Merz Lip Fullness Assessment Scale (MLFAS), as determined independently by the treating investigator and the blinded evaluator.

  B) Participant of FST V or VI who desired lip augmentation to correct volume deficit and had upper and/or lower lip deficit with a rating of 0 (very thin), 1 (thin), or 2 (medium) on the MLFAS, as determined independently by the treating investigator and the blinded evaluator.

- Female or male who was ≥21 and ≤65 years of age at screening.

- Had an adequate understanding (reading, speaking, and writing) of the English language.

Participants were not permitted to enroll in the clinical study if they met any of the following **exclusion criteria**:

- Received treatments with porcine-based collagen fillers or with Juvéderm® Voluma XC, Restylane® Lyft Lidocaine, or calcium hydroxylapatite (CaHA), within the past 24 months and/or with other dermal HA fillers within the past 12 months in the lips, in the lower third of the face, and/or the nose or planned to receive such treatments in the face during the study.

- Prior treatment with dermal therapies (e.g., facial ablative or fractional laser, microdermabrasion, chemical peels, noninvasive skin tightening) within the past three months in the lower third of the face, including the nose, that could interfere with effectiveness assessments.

- Undergone oral surgery (e.g., orthodontia, extraction, implants) in the past 30 days or planned to undergo oral surgery during the study.

- Lip volume deficit due to a medical condition, such as a congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated disease, such as generalized lipodystrophy (i.e., juvenile dermatomyositis), partial lipodystrophy (i.e., Barraquer-Simons Syndrome), inherited disease, or human immunodeficiency virus (HIV)-related disease.

- Abnormal lip function, with inability to effectively suck water through a straw.

- Abnormal lip sensation, with inability to feel a 0.4 g monofilament or a cotton wisp at any site on the lip.

- Moderate or severe abnormal lip asymmetry.

- Acute inflammatory process or active infection at the injection site (e.g., skin eruptions, such as cold scores, cysts, pimples, acne, eczema, rashes, hives, abscess, or Streptococcus infection) or had a history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of AEs.

2. Follow-up Schedule

All participants were scheduled to return for follow-up in-clinic examinations at 2, 4, 8, 16, 24, 36 and 48 weeks after the last treatment (initial or touch-up) postoperatively. Participants who received a touch-up treatment at Week 4 also had a safety follow up visit at Week 6 and Week 8.

At 48 weeks after last treatment, participants randomized to initial treatment with Belotero® Intense (+) Lidocaine treatment were eligible for an optional repeat treatment, with post repeat treatment follow-up period of additional 12 weeks, for a total study duration of up to 64 weeks. If repeat treatment was performed, in-person safety assessments were scheduled 2 and 4 weeks post repeat treatment. Participants treated with comparator were followed for 48 weeks post-last treatment (i.e., initial or applicable touchup), for a total study duration of up to 52 weeks.

Preoperatively, the following evaluations were performed: pregnancy test (for females of childbearing potential), height and weight measurements for body mass index (BMI), FACE-Q assessments (satisfaction with lips, psychological function), blinded evaluator MLFAS assessment, treating investigator MLFAS assessment, lip function / sensation assessments, lip symmetry and movement questionnaire, lip hydration and appearance questionnaire, and visual safety assessments (visual acuity test, confrontation visual field test, ocular motility test and retinal photography).

Table 3 provides the objective parameters that were assessed during the study. Adverse events and complications were recorded at all visits during the study.

Table 3: Objective Assessments Performed During the Study

	Visit Timepoint	Safety Assessments	Effectiveness Assessments
Day 1 / Baseline	**Initial treatment**	Visual safety assessments CTR diary AEs	N/A
	Up to 72h after treatment	CTR diary AEs	N/A
	2 weeks after treatment	Visual safety assessments Lip function / sensation assessments CTR diary AEs	N/A

Optional touch-up treatment	**Week 4** post-initial treatment	Visual safety assessments Lip function / sensation assessments CTR diary AEs	Merz Lip Fullness Assessment Scale (MLFAS)
	Up to 72h after treatment[1]	CTR diary AEs	N/A
	2 weeks after treatment[1]	Visual safety assessments Lip function / sensation assessments CTR diary AEs	N/A
	4 weeks after treatment[1]	Visual safety assessments Lip function / sensation assessments CTR diary AEs	N/A
Primary Endpoint assessment	**Week 8** post-last treatment	Visual safety assessments Lip function / sensation assessments AEs	MLFAS, investigator Global Aesthetic Improvement Scale (iGAIS), subject Global Aesthetic Improvement Scale (sGAIS), and Face-Q questionnaires
Maintenance Phase	**Week 16** post-last treatment	Visual safety assessments Lip function / sensation assessments AEs	MLFAS, iGAIS, sGAIS, and Face-Q
Maintenance Phase	**Week 24** post-last treatment	Lip function / sensation assessments AEs	MLFAS, iGAIS, sGAIS, and Face-Q
Maintenance Phase	**Week 36** post-last treatment	Lip function / sensation assessments AEs	MLFAS, iGAIS, sGAIS, and Face-Q
Optional retreatment[2]	**Week 48** post-last treatment	Visual safety assessments Lip function / sensation assessments AEs	MLFAS, iGAIS, sGAIS, and Face-Q
	Up to 72h after retreatment[3]	CTR diary AEs	N/A
	2 weeks after retreatment[3]	Visual safety assessments Lip function / sensation assessments CTR diary AEs	N/A
	4 weeks after retreatment[3]	Visual safety assessments Lip function / sensation assessments CTR diary AEs	N/A

Retreatment Phase	**Week 60** post-initial treatment / touch-up or 12 weeks post retreatment	Visual safety assessments Lip function / sensation assessments CTR diary AEs	MLFAS, iGAIS, sGAIS, Face-Q and likelihood of retreatment survey

[1] Safety follow up assessments were only for participants who received a touch-up at Week 4.
[2] Optional retreatment was only offered to participants in the Belotero® Intense (+) Lidocaine treatment groups.
[3] Safety follow up assessments were only for participants who received optional retreatment at Week 48 post-initial treatment.

All participants received a safety follow-up phone call 72 hours after each treatment (i.e., initial, touch up, optional retreatment).The treating investigator determined the appropriate volume of Belotero® Intense (+) Lidocaine or comparator product to be injected in the lips (injection volumes did not exceed 6 mL (3 mL per lip) for initial and touch-up treatment combined, and another 3 mL for Belotero® Intense (+) Lidocaine repeat treatment. Participants were in the Belotero® Intense (+) Lidocaine group received treatment in the lips with the co-packaged 27G ½" needles.

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

3. Clinical Endpoints

Belotero® Intense (+) Lidocaine was injected into the subcutaneous and/or submucosal plane. A tunneling technique, fanning technique, or a combination was used to achieve optimal results. The overall total median volume of Belotero® Intense (+) Lidocaine injected to achieve optimal aesthetic outcome was 1.6 mL during initial/touch-up treatment. Participants received a median volume of 0.8 mL in the upper lip, 0.8 mL in the lower lip. Injection volumes into the lips after repeat treatment tended to be lower, with the typical total median injection volume to achieve optimal correction after repeat treatment being approximately 0.9 mL. Similar injection volumes were used in participants treated with the comparator device.

With regards to safety, the following endpoints were evaluated:

- Incidence of related serious adverse events (SAEs) or related delayed-onset AEs (> 21 days after last treatment) following the first treatment including touch-up until Week 48,
- Incidence of any AEs, SAEs, related AEs, and AEs leading to discontinuation,
- Incidence of related serious adverse events (SAEs) or related delayed-onset AEs (> 21 days after last treatment) following repeat treatment from Week 48 to Week 60 for participants retreated with Belotero® Intense (+) Lidocaine and not retreated,
- Incidence, severity, and duration of common treatment responses (CTRs) reported in participant diaries for 28 days following each injection.

With regards to effectiveness, the primary effectiveness endpoint was the mean change from baseline to Week 8 post last injection in mean lip fullness as assessed live by the blinded evaluator using the validated 5-point MLFAS. The co-primary effectiveness endpoint was the responder rate at Week 8 post last injection according to the MLFAS, as assessed live by blinded evaluator. Responders were defined as participants with ≥ 1-point MLFAS improvement compared to baseline on treated lip(s). For participants with both lips treated, each lip was required to demonstrate ≥1-point MLFAS improvement from baseline for the participant to qualify as a responder.

The primary objective of the study was to demonstrate that the response rate in the Belotero® Intense (+) Lidocaine group is statistically significantly larger than 50% and to demonstrate noninferiority of Belotero® Intense (+) Lidocaine over comparator control in mean change from baseline in MLFAS with a pre-specified non-inferiority margin of -0.5 and a significance level of one-sided 0.025.

With regard to success/failure criteria, effectiveness of Belotero® Intense (+) Lidocaine at Week 8 (post-initial or touch-up injection) was demonstrated if the change from baseline in the treatment group was statistically non-inferior to that of the comparator group. The analysis was based on the average MLFAS scores of both lips for each participant, if both lips were treated. A baseline-adjusted analysis of covariance (ANCOVA) model was applied, including treatment group, study site, and Fitzpatrick Skin Type as fixed effects and baseline MLFAS as a covariate, to estimate the treatment difference and its corresponding confidence interval. Non-inferiority was assessed at a one-sided significance level of 2.5%, corresponding to a two-sided 95% confidence interval. The null hypothesis of inferiority was rejected if the lower bound of the 95% confidence interval for the difference in mean change from baseline (treatment minus comparator) exceeded the non-inferiority margin of −0.5.

Success for the co-primary effectiveness endpoint was achieved if the proportion of responders at Week 8 (after the initial and/or touch-up injection) was statistically greater than 50%. The null hypothesis of a responder rate ≤ 50% was rejected if the lower bound of the exact two-sided 95% confidence interval for the responder rate, based on a binomial distribution, exceeded the pre-defined threshold of 50%.

Both success criteria for the primary and co-primary effectiveness endpoints had to be met to conclude overall effectiveness of Belotero® Intense (+) Lidocaine. Hypotheses and analysis methods were pre-specified for both endpoints. The one-sided family-wise type I error rate ($\alpha = 2.5\%$) was controlled using a hierarchical testing procedure. Specifically, the primary endpoint was tested only if the co-primary endpoint demonstrated statistical significance. The analyses were conducted in the Per Protocol Set (PPS), defined as the

subset of all randomized participants without major protocol deviations, with the Intent-to-Treat Set (ITT), defined as all randomized subjects, serving as a supportive analysis set. .

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

Additional effectiveness measures included the blinded evaluator's assessments of participants' average of treated lip fullness using MLFAS, and upper and lower lip fullness. Time course of participants' satisfaction with lip treatment using the Satisfaction with Outcomes and Psychological Function modules of the FACE-Q. Participants' self-perception of lip hydration and appearance using, as well as the par assessments of willingness to undergo treatment again. Responder rates at Week 8 using MLFAS as assessed by 3 blinded independent panel raters (IPR) using participant photographs were also evaluated as a secondary effectiveness endpoint.

Secondary and additional endpoints were analyzed descriptively using summary statistics for continuous variables and frequency tables for categorical variables.

The Merz Lips Fullness Assessment Scale (MLFAS) has been published in Journal of Drugs in Dermatology (JDD) – "doi:10.36849/JDD.7309 Citation: Bloom J, Kaplan J, Verma A, et al. Development and validation of a photonumeric scale for evaluation of lip fullness. J Drugs Dermatol. 2023;22(3):274-281. doi:10.36849/JDD.7309"

https://jddonline.com/articles/development-and-validation-of-a-photonumeric-scale-for-evaluation-of-lip-fullness-S1545961623P0274X/

B. Accountability of Study Cohort

At the time of database lock, of 220 participants enrolled in the PMA study, 195 (88.6%) participants were available for analysis at the completion of the study (up to Week 64 for participants randomized to Belotero® Intense (+) Lidocaine participants and up to Week 52 for participants randomized to the comparator).

A total of 250 participants were screened, and 220 participants were enrolled and randomized. Of these, 165 participants were randomized to Belotero® Intense (+) Lidocaine, and 55 participants were randomized to comparator.

All randomized participants received the initial treatment, and 158/220 (71.8%) participants received a touch-up – 117/165 (70.9%) participants randomized to Belotero® Intense (+) Lidocaine and 41/55 (74.5%) participants randomized to the comparator. In addition, 116/165 (70.3%) Belotero® Intense (+) Lidocaine participants received retreatment.

One-hundred ninety-five (195/220, 88.6%) participants completed the study: 149/165 (90.3%) Belotero® Intense (+) Lidocaine participants and 46/55 (83.6%) comparator participants. Of the 116 retreated participants, 113 (97.4%) completed the follow-up period after optional retreatment.

Figure 1 provides an overview of the participant disposition for the pivotal study.

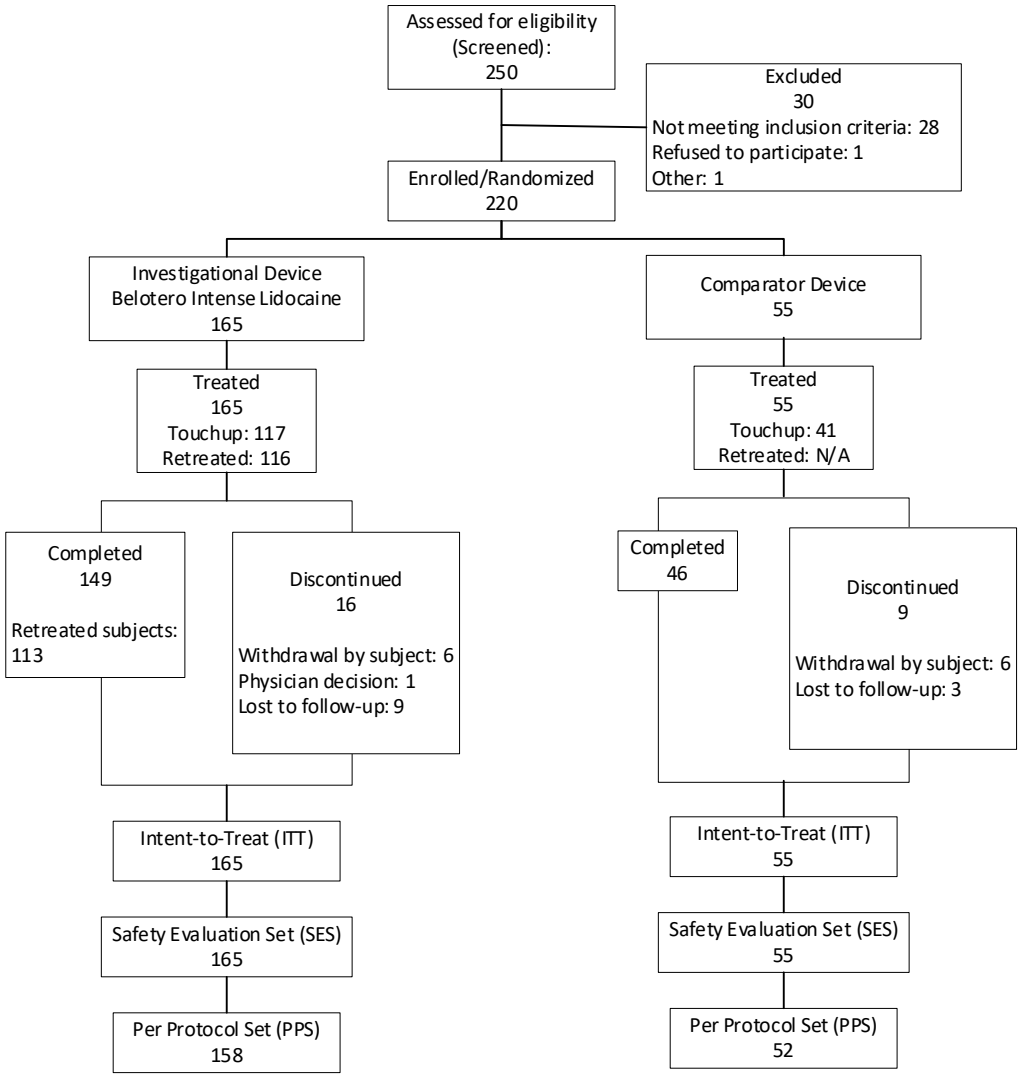

Figure 1: Participant Disposition

The Safety Evaluation Set (SES) is the subset of all participants who were exposed to Belotero® Intense (+) Lidocaine or comparator device at least once. Participants in the SES analyses are analyzed as treated. The Intent-to-treat (ITT) includes all randomized participants. Participants in the ITT analyses are analyzed as randomized. The Per Protocol Set (PPS) is a subset of participants in the ITT without major protocol deviations.

The analyses of the primary, co-primary and secondary effectiveness endpoints are based primarily on the PPS and additionally, for sensitivity purposes, on the ITT. All the remaining effectiveness endpoints are analyzed based on the PPS.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal dermal filler study for similar indications performed in the US.

The majority of participants were female and White and identified themselves as Not Hispanic or Latino and White. In general, demographic data was comparable between Belotero® Intense (+) Lidocaine and comparator.

Table 4 provides an overview of pivotal study demographics.

Table 4: Demographics

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

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

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Safety Evaluation Set (SES) of 220 participants available up to the final evaluation at Week 60. The key safety outcomes for this study are presented below in Table 5 through Table 10. Adverse effects are reported in Table 11.

Adverse effects that occurred in the PMA clinical study:

- **Common Treatment Responses (CTRs)**

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

The severity and duration of CTRs reported by >5% of participants in either treatment group who completed post-treatment eDiaries after initial treatment, touch-up treatment (if performed), and repeat treatment (if performed) are summarized in Table 5 through Table 10. The majority of CTRs were mild or moderate in intensity and resolved within 15-28 days. The incidences, severity and duration of CTRs reported after the touch-up and repeat treatments with Belotero® Intense (+) Lidocaine were generally similar to the initial treatment.

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

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 165 / M = 164)				Comparator (N = 55 / M = 55)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Overall	88.4% (145/164)	24.4% (40/164)	59.1% (97/164)	4.9% (8/164)	80.0% (44/55)	23.6% (13/55)	45.5% (25/55)	10.9% (6/55)
Upper Lip								
Swelling	83.5% (137/164)	37.2% (61/164)	43.9% (72/164)	2.4% (4/164)	76.4% (42/55)	30.9% (17/55)	36.4% (20/55)	9.1% (5/55)
Lumps / Bumps	72.6% (119/164)	47.6% (78/164)	24.4% (40/164)	0.6% (1/164)	56.4% (31/55)	34.5% (19/55)	20.0% (11/55)	1.8% (1/55)
Bruising	72.0% (118/164)	40.2% (66/164)	29.3% (48/164)	2.4% (4/164)	49.1% (27/55)	32.7% (18/55)	14.5% (8/55)	1.8% (1/55)
Soreness	70.1% (115/164)	54.3% (89/164)	15.2% (25/164)	0.6% (1/164)	61.8% (34/55)	38.2% (21/55)	21.8% (12/55)	1.8% (1/55)
Redness	67.7% (111/164)	52.4% (86/164)	14.0% (23/164)	1.2% (2/164)	58.2% (32/55)	41.8% (23/55)	16.4% (9/55)	0.0% (0/55)
Pain / Tenderness	67.1% (110/164)	49.4% (81/164)	16.5% (27/164)	1.2% (2/164)	61.8% (34/55)	36.4% (20/55)	23.6% (13/55)	1.8% (1/55)
Firmness / Hardness	65.2%	42.7%	22.0%	0.6%	60.0%	38.2%	18.2%	3.6%

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 165 / M = 164)				Comparator (N = 55 / M = 55)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
	(107/164)	(70/164)	(36/164)	(1/164)	(33/55)	(21/55)	(10/55)	(2/55)
Discoloration	28.7% (47/164)	22.6% (37/164)	5.5% (9/164)	0.6% (1/164)	18.2% (10/55)	16.4% (9/55)	1.8% (1/55)	0.0% (0/55)
Burning / Stinging	23.8% (39/164)	20.7% (34/164)	3.0% (5/164)	0.0% (0/164)	27.3% (15/55)	18.2% (10/55)	9.1% (5/55)	0.0% (0/55)
Itching	14.0% (23/164)	14.0% (23/164)	0.0% (0/164)	0.0% (0/164)	20.0% (11/55)	16.4% (9/55)	3.6% (2/55)	0.0% (0/55)
Lower Lip								
Swelling	77.4% (127/164)	37.8% (62/164)	37.8% (62/164)	1.8% (3/164)	76.4% (42/55)	38.2% (21/55)	36.4% (20/55)	1.8% (1/55)
Lumps / Bumps	70.1% (115/164)	47.6% (78/164)	21.3% (35/164)	1.2% (2/164)	58.2% (32/55)	40.0% (22/55)	18.2% (10/55)	0.0% (0/55)
Bruising	67.7% (111/164)	38.4% (63/164)	26.8% (44/164)	2.4% (4/164)	56.4% (31/55)	38.2% (21/55)	18.2% (10/55)	0.0% (0/55)
Pain / Tenderness	65.9% (108/164)	50.0% (82/164)	15.2% (25/164)	0.6% (1/164)	61.8% (34/55)	34.5% (19/55)	25.5% (14/55)	1.8% (1/55)
Firmness / Hardness	65.2% (107/164)	46.3.% (76/164)	18.3% (30/164)	0.6% (1/164)	58.2% (32/55)	36.4% (20/55)	20.0% (11/55)	1.8% (1/55)
Soreness	61.6% (101/164)	47.6% (78/164)	13.4% (22/164)	0.6% (1/164)	63.6% (35/55)	40.0% (22/55)	21.8% (12/55)	1.8% (1/55)
Redness	59.1% (97/164)	44.5% (73/164)	12.8% (21/164)	1.8% (3/164)	54.5% (30/55)	32.7% (18/55)	21.8% (12/55)	0.0% (0/55)
Discoloration	29.9% (49/164)	25.6% (42/164)	3.7% (6/164)	0.6% (1/164)	20.0% (11/55)	16.4% (9/55)	3.6% (2/55)	0.0% (0/55)
Burning / Stinging	22.0% (36/164)	18.3% (30/164)	3.7% (6/164)	0.0% (0/164)	34.5% (19/55)	23.6% (13/55)	10.9% (6/55)	0.0% (0/55)
Itching	12.8% (21/164)	12.8% (21/164)	0.0% (0/164)	0.0% (0/164)	21.8% (12/55)	18.2% (10/55)	3.6% (2/55)	0.0% (0/55)

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

Table 6: Common Treatment Site Responses by Maximum Severity After Applicable Touch-up Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 117 / M = 117)				Comparator (N = 41 / M = 41)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Overall	82.9% (97/117)	39.3% (46/117)	40.2% (47/117)	3.4% (4/117)	78.0% (32/41)	17.1% (7/41)	53.7% (22/41)	7.3% (3/41)
Upper Lip								
Swelling	71.8% (84/117)	47.9% (56/117)	20.5% (24/117)	3.4% (4/117)	75.6% (31/41)	29.3% (12/41)	39.0% (16/41)	7.3% (3/41)
Lumps / Bumps	57.3% (67/117)	38.5% (45/117)	18.8% (22/117)	0.0% (0/117)	58.5% (24/41)	43.9% (18/41)	14.6% (6/41)	0.0% (0/41)
Bruising	57.3% (67/117)	45.3% (53/117)	12.0% (14/117)	0.0% (0/117)	46.3% (19/41)	31.7% (13/41)	14.6% (6/41)	0.0% (0/41)
Pain / Tenderness	57.3% (67/117)	47.0% (55/117)	10.3% (12/117)	0.0% (0/117)	73.2% (30/41)	56.1% (23/41)	17.1% (7/41)	0.0% (0/41)

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 117 / M = 117)				Comparator (N = 41 / M = 41)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Firmness / Hardness	54.7% (64/117)	41.9% (49/117)	12.8% (15/117)	0.0% (0/117)	68.3% (28/41)	48.8% (20/41)	19.5% (8/41)	0.0% (0/41)
Soreness	53.0% (62/117)	42.7% (50/117)	10.3% (12/117)	0.0% (0/117)	70.7% (29/41)	56.1% (23/41)	14.6% (6/41)	0.0% (0/41)
Redness	43.6% (51/117)	29.9% (35/117)	13.7% (16/117)	0.0% (0/117)	58.5% (24/41)	39.0% (16/41)	19.5% (8/41)	0.0% (0/41)
Discoloration	17.9% (21/117)	17.1% (20/117)	0.9% (1/117)	0.0% (0/117)	17.1% (7/41)	12.2% (5/41)	4.9% (2/41)	0.0% (0/41)
Burning / Stinging	16.2% (19/117)	11.1% (13/117)	5.1% (6/117)	0.0% (0/117)	31.2% (13/41)	29.3% (12/41)	2.4% (1/41)	0.0% (0/41)
Itching	7.7% (9/117)	6.0% (7/117)	1.7% (2/117)	0.0% (0/117)	12.2% (5/41)	12.2% (5/41)	0.0% (0/41)	0.0% (0/41)
Lower Lip								
Firmness / Hardness	48.7% (57/117)	35.9% (42/117)	12.8% (15/117)	0.0% (0/117)	65.9% (27/41)	39.0% (16/41)	26.8% (11/41)	0.0% (0/41)
Lumps / Bumps	47.9% (56/117)	32.5% (38/117)	15.4% (18/117)	0.0% (0/117)	48.8% (20/41)	24.4% (10/41)	24.4% (10/41)	0.0% (0/41)
Pain / Tenderness	47.9% (56/117)	38.5% (45/117)	9.4% (11/117)	0.0% (0/117)	73.2% (30/41)	56.1% (23/41)	17.1% (7/41)	0.0% (0/41)
Bruising	47.0% (55/117)	35.0% (41/117)	12.0% (14/117)	0.0% (0/117)	53.7% (22/41)	29.3% (12/41)	24.4% (10/41)	0.0% (0/41)
Soreness	46.2% (54/117)	36.8% (43/117)	9.4% (11/117)	0.0% (0/117)	65.9% (27/41)	43.9% (18/41)	22.0% (9/41)	0.0% (0/41)
Swelling	39.3% (71/117)	39.3% (46/117)	20.5% (24/117)	0.9% (1/117)	75.6% (31/41)	34.1% (14/41)	36.6% (15/41)	4.9% (2/41)
Redness	39.3% (46/117)	30.8% (36/117)	8.5% (10/117)	0.0% (0/117)	53.7% (22/41)	41.5% (17/41)	12.2% (5/41)	0.0% (0/41)
Discoloration	14.5% (17/117)	12.8% (15/117)	1.7% (2/117)	0.0% (0/117)	17.1% (7/41)	14.6% (6/41)	2.4% (1/41)	0.0% (0/41)
Burning / Stinging	14.5% (17/117)	12.0% (14/117)	2.6% (3/117)	0.0% (0/117)	26.2% (11/41)	22.0% (9/41)	4.9% (2/41)	0.0% (0/41)
Itching	4.3% (5/117)	2.6% (3/117)	1.7% (2/117)	0.0% (0/117)	9.8% (4/41)	9.8% (4/41)	0.0% (0/41)	0.0% (0/41)

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

Table 7: Common Treatment Site Responses by Maximum Severity After Optional Retreatment Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 116 / M = 114)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Overall	71.9% (82/114)	29.8% (34/114)	38.6% (44/114)	3.5% (4/114)
Upper Lip				
Swelling	67.5% (77/114)	40.4% (46/114)	36.3% (30/114)	0.9% (1/114)

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 116 / M = 114)			
	Total % (n/M)	Mild % (n/M)	Moderate % (n/M)	Severe % % (n/M)
Firmness / Hardness	60.5% (69/114)	42.1% (48/114)	17.5% (20/114)	0.9% (1/114)
Pain / Tenderness	56.1% (64/114)	44.7% (51/114)	11.4% (13/114)	0.0% (0/114)
Soreness	55.3% (63/114)	45.6% (52/114)	9.6% (11/114)	0.0% (0/114)
Bruising	54.4% (62/114)	30.7% (35/114)	22.8% (26/114)	0.9% (1/114)
Lumps / Bumps	54.4% (62/114)	43.0% (49/114)	11.4% (13/114)	0.0% (0/114)
Redness	52.6% (60/114)	37.7% (43/114)	14.9% (17/114)	0.0% (0/114)
Burning / Stinging	17.5% (20/114)	13.2% (15/114)	3.5% (4/114)	0.9% (1/114)
Discoloration	15.8% (18/114)	13.2% (15/114)	2.6% (3/114)	0.0% (0/114)
Itching	10.5% (12/114)	8.8% (10/114)	1.8% (2/114)	0.0% (0/114)
Lower Lip				
Swelling	60.5% (69/114)	41.2% (47/114)	18.4% (21/114)	0.9% (1/114)
Firmness / Hardness	53.5% (61/114)	41.2% (47/114)	11.4% (13/114)	0.9% (1/114)
Pain / Tenderness	50.9% (58/114)	41.2% (47/114)	9.6% (11/114)	0.0% (0/114)
Soreness	50.9% (58/114)	43.0% (49/114)	7.9% (9/114)	0.0% (0/114)
Bruising	50.0% (57/114)	32.5% (37/114)	17.5% (20/114)	0.0% (0/114)
Lumps / Bumps	49.1% (56/114)	36.8% (42/114)	12.3% (14/114)	0.0% (0/114)
Redness	43.0% (49/114)	34.2% (39/114)	8.8% (10/114)	0.0% (0/114)
Burning / Stinging	18.4% (21/114)	15.8% (18/114)	2.6% (3/114)	0.0% (0/114)
Discoloration	14.0% (16/114)	10.5% (12/114)	2.6% (3/114)	0.9% (1/114)
Itching	6.1% (7/114)	5.3% (6/114)	0.9% (1/114)	0.0% (0/114)

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

Table 8: Common Treatment Site Responses by Maximum Duration After Initial Treatment Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 165 / M = 164)					Comparator (N = 55 / M = 55)				
	Total % (n/M)	1-3 Days % (n/M)	4-7 Days % (n/M)	8-14 Days % (n/M)	15-28 Days % (n/M)	Total % (n/M)	1-3 Days % (n/M)	4-7 Days % (n/M)	8-14 Days % (n/M)	15-28 Days % (n/M)
Overall	88.4% (145/164)	0.0% (0/164)	1.8% (3/164)	2.4% (4/164)	84.1% (138/164)	80.0% (44/55)	0.0% (0/55)	1.8% (1/55)	0.0% (0/55)	78.2% (43/55)
Upper Lip										
Swelling	83.5% (137/164)	13.4% (22/164)	28.0% (46/164)	13.4% (22/164)	28.7% (47/164)	76.4% (42/55)	14.5% (8/55)	25.5% (14/55)	1.8% (1/55)	34.5% (19/55)
Lumps / Bumps	72.6% (119/164)	9.1% (15/164)	4.9% (8/164)	5.5% (9/164)	53.0% (87/164)	56.4% (31/55)	10.9% (6/55)	9.1% (5/55)	0.0% (0/55)	36.4% (20/55)
Bruising	72.0% (118/164)	6.7% (11/164)	28.0% (46/164)	20.1% (33/164)	17.1% (28/164)	49.1% (27/55)	14.5% (8/55)	16.4% (9/55)	1.8% (1/55)	16.4% (9/55)
Soreness	70.1% (115/164)	23.2% (38/164)	12.8% (21/164)	15.2% (25/164)	18.9% (31/164)	61.8% (34/55)	21.8% (12/55)	18.2% (10/55)	3.6% (2/55)	18.2% (10/55)
Redness	67.7% (111/164)	27.4% (45/164)	16.5% (27/164)	11.0% (18/164)	12.8% (21/164)	58.2% (32/55)	20.0% (11/55)	18.2% (10/55)	1.8% (1/55)	18.2% (10/55)
Pain / Tenderness	67.1% (110/164)	15.2% (25/164)	16.5% (27/164)	12.8% (21/164)	22.6% (37/164)	61.8% (34/55)	20.0% (11/55)	18.2% (10/55)	1.8% (1/55)	21.8% (12/55)
Firmness / Hardness	65.2% (107/164)	9.8% (16/164)	11.6% (19/164)	14.6% (24/164)	29.3% (48/164)	60.0% (33/55)	18.2% (10/55)	7.3% (4/55)	7.3% (4/55)	27.3% (15/55)
Discoloration	28.7% (47/164)	11.0% (18/164)	9.1% (15/164)	3.0% (5/164)	5.5% (9/164)	18.2% (10/55)	5.5% (3/55)	5.5% (3/55)	0.0% (0/55)	7.3% (4/55)
Burning / Stinging	23.8% (39/164)	15.2.% (25/164)	3.0% (5/164)	1.8% (3/164)	3.7% (6/164)	27.3% (15/55)	18.2% (10/55)	1.8% (1/55)	0.0% (0/55)	7.3% (4/55)
Itching	14.0% (23/164)	7.9% (13/164)	1.8% (3/164)	1.2% (2/164)	3.0% (5/164)	20.0% (11/55)	5.5% (3/55)	3.6% (2/55)	0.0% (0/55)	10.9% (6/55)
Lower Lip										
Swelling	77.4% (127/164)	10.4% (17/164)	26.2% (43/164)	17.1% (28/164)	23.8% (39/164)	76.4% (42/55)	20.0% (11/55)	16.4% (9/55)	3.6% (2/55)	36.4% (20/55)
Lumps / Bumps	70.1% (115/164)	11.6% (19/164)	5.5% (9/164)	5.5% (9/164)	47.6% (78/164)	58.2% (32/55)	12.7% (7/55)	5.5% (3/55)	1.8% (1/55)	38.2% (21/55)
Bruising	67.7% (111/164)	10.4% (17/164)	25.0% (41/164)	16.5% (27/164)	15.9% (26/164)	56.4% (31/55)	9.1% (5/55)	18.2% (10/55)	3.6% (2/55)	25.5% (14/55)
Pain / Tenderness	65.9% (108/164)	18.9% (31/164)	14.6% (24/164)	16.5% (27/164)	15.9% (26/164)	61.8% (34/55)	12.7% (7/55)	12.7% (7/55)	9.1% (5/55)	27.3% (15/55)
Firmness / Hardness	65.2% (107/164)	16.5% (27/164)	9.8% (16/164)	15.2% (25/164)	23.8% (39/164)	58.2% (32/55)	18.2% (10/55)	5.5% (3/55)	5.5% (3/55)	29.1% (16/55)
Soreness	61.6% (101/164)	16.5% (27/164)	14.6% (24/164)	17.1% (28/164)	13.4% (22/164)	63.6% (35/55)	12.7% (7/55)	16.4% (9/55)	9.1% (5/55)	25.5% (14/55)
Redness	59.1% (97/164)	23.8% (39/164)	13.4% (22/164)	12.2% (20/164)	9.8% (16/164)	54.5% (30/55)	16.4% (9/55)	18.2% (10/55)	1.8% (1/55)	18.2% (10/55)
Discoloration	29.9% (49/164)	15.9% (26/164)	6.1% (10/164)	4.9% (8/164)	3.0% (5/164)	20.0% (11/55)	7.3% (4/55)	5.5% (3/55)	0.0% (0/55)	7.3% (4/55)
Burning / Stinging	22.0% (36/164)	14.0% (23/164)	3.7% (6/164)	1.8% (3/164)	2.4% (4/164)	34.5% (19/55)	21.8% (12/55)	7.3% (4/55)	0.0% (0/55)	5.5% (3/55)
Itching	12.8% (21/164)	7.9% (13/164)	1.2% (2/164)	0.6% (1/164)	3.0% (5/164)	21.8% (12/55)	10.9% (6/55)	1.8% (1/55)	0.0% (0/55)	9.1% (5/55)

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

Table 9: Common Treatment Site Responses by Maximum Duration After Applicable Touch-Up Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 117 / M = 117)					Comparator (N = 41 / M = 41)				
	Total % (n/M)	1-3 Days % (n/M)	4-7 Days % (n/M)	8-14 Days % (n/M)	15-28 Days % (n/M)	Total % (n/M)	1-3 Days % (n/M)	4-7 Days % (n/M)	8-14 Days % (n/M)	15-28 Days % (n/M)
Overall	82.9% (97/117)	0.0% (0/117)	1.7% (2/117)	3.4% (4/117)	77.8% (91/117)	78.5% (32/41)	0.0% (0/41)	2.4% (1/41)	0.0% (0/41)	75.6% (31/41)
Upper Lip										
Bruising	82.9% (97/117)	14.5% (17/117)	16.2% (19/117)	11.1% (13/117)	15.4% (18/117)	46.3% (19/41)	7.3% (3/41)	7.3% (3/41)	7.3% (3/41)	24.4% (10/41)
Swelling	71.8% (84/117)	17.1% (20/117)	21.4% (25/117)	8.5% (10/117)	24.8% (29/117)	75.6% (31/41)	12.2% (5/41)	19.5% (8/41)	7.3% (3/41)	36.6% (15/41)
Lumps / Bumps	57.3% (67/117)	10.3% (12/117)	6.0% (7/117)	4.3% (5117)	36.8% (43/117)	58.5% (24/41)	17.1% (7/41)	7.3% (3/41)	2.4% (1/41)	31.7% (13/41)
Pain / Tenderness	57.3% (67/117)	17.9% (21/117)	10.3% (12/117)	8.5% (10/117)	20.5% (24/117)	73.2% (30/41)	31.7% (13/41)	7.3% (3/41)	12.2% (5/41)	22.0% (9/41)
Firmness / Hardness	54.7% (64/117)	12.0% (14/117)	11.1% (13/117)	6.0% (7/117)	25.6% (30/117)	68.3% (28/41)	22.2% (9/41)	4.9% (2/41)	4.9% (2/41)	36.6% (15/41)
Soreness	53.0% (62/117)	16.2% (19/117)	6.8% (8/117)	6.8% (8/117)	23.1% (27/117)	70.7% (29/41)	34.1% (14/41)	7.3% (3/41)	4.9% (2/41)	24.4% (10/41)
Redness	43.6% (51/117)	19.7% (23/117)	8.5% (10/117)	6.0% (7/117)	9.4% (11/117)	58.5% (24/41)	31.7% (13/41)	4.9% (2/41)	2.4% (1/41)	19.5% (8/41)
Discoloration	17.9% (21/117)	9.4% (11/117)	2.6% (3/117)	1.7% (2/117)	4.3% (5/117)	17.1% (7/41)	4.9% (2/41)	2.4% (1/41)	0.0% (0/41)	9.8% (4/41)
Burning / Stinging	16.2% (19/117)	8.5% (10/117)	0.9% (1/117)	2.6% (3/117)	4.3% (5/117)	31.7% (13/41)	24.4% (10/41)	2.4% (1/41)	0.0% (0/41)	4.9% (2/41)
Itching	7.7% (9/117)	3.4% (4/117)	0.9% (1/117)	0.9% (1/117)	2.6% (3/117)	12.2% (5/41)	4.9% (2/41)	2.4% (1/41)	0.0% (0/41)	4.9% (2/41)
Lower Lip										
Swelling	60.7% (71/117)	12.8% (15/117)	15.4% (18/117)	14.5% (17/117)	17.9% (21/117)	75.6% (31/41)	9.8% (4/41)	24.4% (10/41)	4.9% (2/41)	36.6% (15/41)
Firmness / Hardness	49.6% (58/117)	7.7% (9/117)	6.8% (9/117)	6.0% (7/117)	28.2% (33/117)	65.9% (27/41)	17.1% (7/41)	4.9% (2/41)	2.4% (1/41)	41.5% (17/41)
Lumps / Bumps	47.9% (56/117)	6.0% (7/117)	4.3% (5/117)	6.0% (7/117)	31.6% (37/117)	48.8% (20/41)	2.4% (1/41)	7.3% (3/41)	0.0% (0/41)	39.0% (16/41)
Pain / Tenderness	47.9% (56/117)	16.2% (19/117)	12.0% (14/117)	4.3% (5/117)	15.4% (18/117)	73.2% (30/41)	26.8% (11/41)	9.8% (4/41)	9.8% (4/41)	26.8% (11/41)
Bruising	47.0% (55/117)	12.8% (15/117)	8.5% (10/117)	11.1% (13/117)	14.5% (17/117)	53.7% (22/41)	14.6% (6/41)	9.8% (4/41)	4.9% (2/41)	24.4% (10/41)
Soreness	46.2% (5/117)	17.9% (21/117)	6.8% (8/117)	7.7% (9/117)	13.7% (16/117)	65.9% (27/41)	22.0% (9/41)	17.1% (7/41)	2.4% (1/41)	24.4% (10/41)
Redness	39.3% (46/117)	13.7% (16/117)	8.5% (10/117)	4.3% (5/117)	12.8% (15/117)	53.7% (22/41)	29.3% (12/41)	7.3% (3/41)	0.0% (0/41)	17.1% (7/41)
Discoloration	14.5% (17/117)	7.7% (9/117)	2.6% (3/117)	1.7% (2/117)	2.6% (3/117)	17.1% (7/41)	4.9% (2/41)	4.9% (2/41)	0.0% (0/41)	7.3% (3/41)
Burning / Stinging	14.5% (17/117)	8.5% (10/117)	1.7% (2/117)	0.9% (1/117)	3.4% (4/117)	26.8% (11/41)	22.0% (9/41)	2.4% (1/41)	0.0% (0/41)	2.4% (1/41)
Itching	4.3% (5/117)	1.7% (2/117)	0.9% (1/117)	0.0% (0/117)	1.7% (2/117)	9.8% (4/41)	4.9% (2/41)	2.4% (1/41)	0.0% (0/41)	2.4% (1/41)

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

Table 10: Common Treatment Site Responses by Maximum Duration After Optional Retreatment Occurring in > 5% of Participants Treated for Lip Augmentation

Common Treatment Response	Belotero® Intense (+) Lidocaine (N = 116 / M = 114)				
	Total % (n/M)	1-3 Days % (n/M)	4-7 Days % (n/M)	8-14 Days % (n/M)	15-28 Days % (n/M)
Overall	71.9% (82/114)	0.0% (0/114)	0.0% (0/114)	0.0% (0/114)	71.9% (82/114)
Upper Lip					
Swelling	67.5% (77/114)	10.5% (12/114)	20.2% (23/114)	12.3% (14/114)	24.6% (28/114)
Lumps / Bumps	54.4% (62/114)	7.9% (9/114)	6.1% (7/114)	4.4% (5/114)	36.0% (41/114)
Bruising	54.4% (62/114)	7.0% (8/114)	14.0% (16/114)	13.2% (15/114)	20.2% (23/114)
Soreness	55.3% (63/114)	13.2% (15/114)	13.2% (15/114)	11.4% (13/114)	17.5% (20/114)
Redness	52.6% (60/114)	22.8% (26/114)	11.4% (13/114)	7.0% (8/114)	11.4% (13/114)
Pain / Tenderness	56.1% (64/114)	14.9% (17/114)	13.2% (15/114)	11.4% (13/114)	16.7% (19/114)
Firmness / Hardness	60.5% (69/114)	10.5% (12/114)	7.0% (8/114)	12.3% (14/114)	30.7% (35/114)
Discoloration	15.8% (18/114)	8.8% (10/114)	0.9% (1/114)	2.6% (3/114)	3.5% (4/114)
Burning / Stinging	17.5% (20/114)	9.6% (11/114)	2.6% (3/114)	2.6% (3/114)	2.6% (3/114)
Itching	10.5% (12/114)	5.3% (6/114)	2.6% (3/114)	0.9% (1/114)	1.8% (2/114)
Lower Lip					
Swelling	60.5% (69/114)	12.3% (14/114)	18.4% (21/114)	12.3% (14/114)	17.5% (20/114)
Lumps / Bumps	49.1% (56/114)	12.3% (14/114)	4.4% (5/114)	7.0% (8/114)	25.4% (29/114)
Bruising	50.0% (57/114)	8.8% (10/114)	20.2% (23/114)	7.9% (9/114)	13.2% (15/114)
Pain / Tenderness	50.9% (58/114)	17.5% (20/114)	7.9% (9/114)	10.5% (12/114)	14.9% (17/114)
Firmness / Hardness	53.5% (61/114)	9.6% (11/114)	8.8% (10/114)	9.6% (11/114)	25.4% (29/114)
Soreness	50.9% (58/114)	14.9% (17/114)	12.3% (14/114)	9.6% (11/114)	14.0% (16/114)
Redness	43.0% (49/114)	17.5% (20/114)	9.6% (11/114)	6.1% (7/114)	9.6% (11/114)
Discoloration	14.0% (16/114)	5.3% (6/114)	1.8% (2/114)	3.5% (4/114)	3.5% (4/114)
Burning / Stinging	18.4% (21/114)	10.5% (12/114)	1.8% (2/114)	2.6% (3/114)	3.5% (4/114)
Itching	6.1% (7/114)	1.8% (2/114)	2.6% (3/114)	0.0% (0/114)	1.8% (2/114)

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

- **Treatment-Related Treatment Emergent Adverse Events**

Adverse Events (AEs) were also reported by the Treating Investigators at follow up visits. A treatment-emergent AE (TEAE) was defined as an AE that initially occurred or increased in severity on or after the treatment start date for the Belotero® Intense (+) Lidocaine or comparator group. An AE was considered to be related to the device or the injection procedure (i.e., "treatment-related") if a causal relationship between the device or the injection procedure and the AE was at least reasonably possible. CTRs that lasted beyond 28 days were considered AEs.

After initial treatment (or touch-up treatment if performed), a total of 73 treatment-related TEAEs were reported in 17.0% (28/165) of participants treated with Belotero® Intense (+) Lidocaine. Thirty (30) treatment-related TEAEs were reported in 14.5% (8/55) of participants treated with the comparator product. After repeat treatment in the Belotero® Intense (+) Lidocaine group, a total of 38 treatment-related TEAEs were reported in 11.2% (13/116) of participants. Related TEAEs occurring in > 5% of treated participants in either treatment group are summarized in Table 11 . Overall, related TEAEs were typically mild in intensity and all resolved without sequelae. There were no serious treatment-related adverse events reported.

Table 11: Treatment-Related TEAE > 5% of Treated Participants for Lip Augmentation by Adverse Event Preferred Term

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

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

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

- **Safety Subgroup Analyses**

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

- **Treatment-Related Delayed-Onset TEAEs**

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

- **Other Safety Assessments**

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

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

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

2. Effectiveness Results:

The analysis of effectiveness was based on 158 evaluable participants (PPS) and 162 evaluable participants (ITT, Observed Cases) at the primary endpoint visit at Week 8. Comparator group had 52 evaluable participants (PPS and ITT Observed Cases) at the Week 8 time point. Key effectiveness outcomes are presented in Table 12 and Table 13.

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

Table 12: Co-primary: Responder Rate in MLFAS at Week 8 Post-Last Treatment as Assessed by the Blinded Evaluator

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

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

Table 13: Primary: Change from Baseline to Week 8 Post-Last Treatment in MLFAS as Assessed by the Blinded Evaluator

	PPS		ITT (Observed Cases)	
	Belotero® Intense (+) Lidocaine (N=158)	Comparator (N=52)	Belotero® Intense (+) Lidocaine (N=162)	Comparator (N=52)
Observed means	1.31	1.23	1.31	1.23
Between group difference, 95% CI*	0.1 (0.0, 0.3)		0.1 (0.0, 0.3)	

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

Throughout the follow-up period, Belotero® Intense (+) Lidocaine continued to provide a clinically significant improvement in lip fullness, with the majority of participants demonstrating improvement up to 48 weeks after treatment. The proportion MLFAS responders (≥ 1 point mean change on MLFAS as assessed by blinded evaluator) by time point is presented in Table 14. Up to Week 48 in the Belotero® Intense (+) Lidocaine group, improvements in upper and lower lip fullness were similar to the improvements observed in overall lip fullness.

Table 14: Effectiveness Results through Week 48 (PPS) By Blinded Evaluator

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

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

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

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

At Week 8, participants treated with Belotero® Intense (+) Lidocaine reported improvement in satisfaction with their lips, based on the *Satisfaction with Lips* module of the FACE Q

questionnaire. The mean score increased from 37.9 at baseline to 88.7 eight weeks post-last treatment, corroborating the GAIS findings that indicate participants were satisfied with the appearance of their lips. Similarly, participants reported being satisfied with the outcome of Belotero® Intense (+) Lidocaine treatment up to 48 weeks, based on the *Satisfaction with Outcomes* module of the FACE Q questionnaire. Participants treated with Belotero® Intense (+) Lidocaine also self-reported improvements on the FACE-Q *Psychological Function* module, with an increase of mean scores from 72.9 at baseline to 88.5 at Week 8 post-last treatment. These improvements were maintained to Week 48 post-last treatment, with participants self-reporting a mean score of 84.9. This validated quality-of-life scale asks respondents to answer 10 questions with their facial appearance in mind measuring concepts such as feeling happy, positive, confidence, self-acceptance, etc. which evaluated how confident, attractive or happy the participants felt after treatment.

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

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

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

Follow-Up After Repeat Treatment

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

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

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes:

The study was not specifically powered for sex, age, race or ethnicity. No clinically significant tolerability concerns were observed when stratifying related TEAEs by sex, age group, FST categories, race, or ethnicity.

Safety Analysis:

FST: Overall rates for related TEAEs were higher among participants with FST I to III (21.0% participants) compared to IV to VI (13.2% participants). This effect was observed in both treatment groups: Belotero® Intense (+) Lidocaine (FST I to III: 21.9%; FST IV to VI 16.2%) and comparator (FST I to III: 17.9%; FST IV to VI: 6.3%) but was more pronounced in the comparator group. Only 16 participants with FST IV to VI were treated with comparator. Due to the low sample size in this subgroup, the results of the comparator subgroup with FST IV to VI should be interpreted with caution. The most frequently reported related TEAEs were injection-site mass (I to III: 27/167 participants, 16.2%; IV to VI: 6/53 participants, 11.3%) followed by injection-site induration (I to III: 14/167 participants, 8.4%; IV to VI: 2/53 participants, 3.8%).

Race: In terms of race, participants were analyzed separately as White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and more than one race. Overall, the proportion of participants with at least one treatment-related TEAE was 20.2% in participants with White race and 50.0% in participants with Asian race. There were no treatment-related TEAEs in participants with Black or African American race, American Indian or Alaska Native race, Native Hawaiian or Other Pacific Islander race or more than one race. A similar pattern was observed in the Belotero® Intense (+) Lidocaine group, with treatment-related TEAEs reported in 21.6% of White participants and in the single Asian participant enrolled (100.0%).

Age: In terms of age, safety data were grouped into participants of 21-30 years, 31-40 years, 41-50 years and 51-65 years. Treatment-related TEAE rates were generally similar among participants aged 21–30 years (17.2%), 41–50 years (18.3%), and 51–65 years (15.8%) but were higher in participants aged 31–40 years (30.6%). A similar pattern was observed in the Belotero® Intense (+) Lidocaine group, where treatment-related TEAEs occurred in 16.0%, 17.1%, and 16.4% of participants aged 21–30, 41–50, and 51–65 years, respectively, compared with 42.3% of participants aged 31–40 years.

Sex: In terms of sex, treatment-related TEAEs were analyzed in female and male participants separately. Overall, female participants experienced at least one treatment-related TEAE (19.8%), and there was no treatment-related TEAEs for male participants.

Ethnicity: In terms of ethnicity, treatment-related TEAEs were analyzed for Hispanic or Latino vs. Not Hispanic or Latino. Overall, treatment-related TEAEs were less frequent in Hispanic or Latino participants (14.9%) than in Not Hispanic or Latino participants (20.2%). A similar trend was observed in the Belotero® Intense (+) Lidocaine group, with treatment-related TEAEs reported in

15.2% of Hispanic or Latino participants compared with 22.0% of Not Hispanic or Latino participants.

Effectiveness Analysis:

All subgroup analysis are based on the MLFAS assessments by the blinded evaluators at Week 8 post last treatment. Responders were categorized as participants with ≥ 1-point MLFAS improvement compared to baseline on treated lip(s). If both lips were treated, the participant was categorized as a responder only if MLFAS improvement was attained on both lips.

FST: FST effectiveness data were stratified by FST I-III (lower FST) and IV-VI (higher FST). 91.1% (112/123) of Belotero® Intense (+) Lidocaine treated participants with FST I-III were assessed as responders at Week 8 post last treatment. Results for FST I-III participants randomized to the comparator device showed comparable results of 89.2% (33/37).

Responder rates were slightly higher for participants with FST IV-VI independently if treated with Belotero® Intense (+) Lidocaine (91.4%; 32/35) or the comparator (93.3%, 14/15).

Race: 91.1% (133/146) of White participants treated with Belotero® Intense (+) Lidocaine were assessed as responders at Week 8 post last treatment, similarly 89.4% (42/47) participants treated with the comparator were assessed as responders.

Black or African American participants treated with Belotero® Intense (+) Lidocaine showed responder rates of 83.3% (5/6) vs. all comparator treated participants (100%; 2/2) were assessed as responders. Due to the small comparator subgroup (n=2), the result is not representative. Similar limitations apply to Asian or More than One Race categories.

Age: For age effectiveness data were stratified by four age groups of participants of 21-30 years, 31-40 years, 41-50 years, and 51-65 years, respectively. For Belotero® Intense (+) Lidocaine treated participants the responder rates in the two younger age groups was minimally higher compared to the two older age groups: 21-30 years = 95.7% (22/23), 31-40 years = 96.0% (24/25), 41-50 years = 89.5% (34/38) and 51-65 years = 88.9% (64/72).

Participants treated with the comparator device showed similar results for the higher age groups 41-50 years = 94.1% (16/17) and 51-65 years = 90.9% (20/22). Results in the younger age groups 21-30 years = 100% (4/4), 31-40 years = 77.8% (7/9) should be interpreted cautiously due to the small sample size.

Sex: Responder rates at Week 8 post last treatment showed 100% for male participants treated with Belotero® Intense (+) Lidocaine (4/4) and with the comparator (3/3). For female participants the responder rate at Week 8 was 90.9% (140/154) for those treated with Belotero® Intense (+) and 89.8% (44/49) for those treated with the comparator. Given the small sample size of the male cohort, the results should be interpreted cautiously and should not be overinterpreted.

Ethnicity: Effectiveness data assessed at Week 8 post last treatment between Hispanic or Latino and Not Hispanic or Latino participants did not show clinically relevant differences between both groups

as well as the treatment groups. Belotero® Intense (+) Lidocaine treated participants with Hispanic or Latino ethnicity showed a responder rate of 90.3% (28/31) while participants with Non-Hispanic or Latino ethnicity reported 91.3% (116/127). Data for the comparator device are comparable with 92.3% (12/13) for participants with Hispanic or Latino ethnicity and 89.7% (35/39) for participants with Non-Hispanic or Latino ethnic background.

Overall, the subgroup effectiveness analyses did not reveal any population in which Belotero® Intense (+) Lidocaine appeared to perform less effectively than expected. Treatment effects were generally consistent across demographic and baseline characteristic subgroups, with responder rates remaining high and comparable to those observed in the overall study population. The results support the consistency and robustness of the effectiveness findings across the evaluated subgroups, while recognizing the limitations associated with small sample sizes in certain categories.

The results of these subgroup analyses were consistent with the co-primary and the primary effectiveness endpoint analyses in the overall population.

4. Pediatric Extrapolation:

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

XI. 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 fourteen investigators. Thirteen of the fourteen investigators have, by way of a signed financial disclosure/certification form, verified that they had no applicable financial arrangements with Merz North America Inc. as defined in 21 CFR Part 54.

One of the fourteen investigators had financial arrangements with the sponsor to be disclosed under 21 CFR 54.2 (b), not affecting the outcome of the pivotal clinical study. The nature of these disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) is described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: one
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XII. 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Belotero Intense® (+) Lidocaine met the pre-specified primary endpoint, and the secondary endpoints to support product effectiveness.

The responder rate of Belotero® Intense (+) Lidocaine, demonstrated a statistically significant treatment effect as the lower limit of the 95% CI exceeded the 50% margin (95% CI: [85.6, 95.1]) in PPS. Results of supportive analysis in the Intent-to-Treat Set based on worst-case imputation were consistent with primary analysis.

Non-inferiority of Belotero® Intense (+) Lidocaine compared with an approved HA dermal filler was demonstrated. In the PPS, the lower bound of the ANCOVA-based 95% confidence interval for the difference in least squares (LS) mean change from baseline to Week 8 (post-treatment or touch-up) (Belotero® Intense (+) Lidocaine minus comparator) was 0.0, exceeding the non-inferiority margin of −0.5 (95% CI: [0.0, 0.3]). This finding was consistent with the supportive analysis in the Intent-to-Treat Set based on observed cases.

The data confirms that Belotero Intense® (+) Lidocaine is effective for submucosal and/or subcutaneous implantation for lip augmentation in adults over the age of 21. See data above.

Subgroup analyses were performed on gender, Fitzpatrick Skin Type, age, etc. Treatment group participants showed consistent responder rates across the different subgroups.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above.

No device-related serious adverse events were reported. Overall, a total of 141 related non-serious adverse events were reported in 42/220 (19.1%) participants – 34/165 (20.6%) in Belotero® Intense (+) Lidocaine participants and 8/55 (14.5%) in comparator participants, with

111 and 30 related AEs, respectively. Overall, related AEs were typically mild (39/220 participants, 17.7%) and all events resolved without sequelae (42/220 participants, 19.1%). Three Belotero® Intense (+) Lidocaine (1.8%) participants experienced a related AE of moderate intensity (i.e., injection-site mass in two participants and oral herpes in one participant) that resolved by end of study. Related AEs with duration > 28 days ranged from 29 to 119 days for Belotero® Intense (+) Lidocaine and 49 to 129 days for the comparator. None of these events were delayed onset events.

Overall, no clinically significant tolerability concerns were observed when stratifying related AEs by sex, age group, FST categories, race, or ethnicity.

The data submitted provides a reasonable assurance that the device is safe for submucosal and/or subcutaneous implantation for lip augmentation in adults over the age of 21.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. This pivotal study was a prospective, multicenter, randomized, comparator-controlled, evaluator-blinded, pivotal clinical study (M930041001) by demonstrating noninferiority to a comparator, an FDA-approved hyaluronic-acid dermal filler.

Belotero Intense® (+) Lidocaine injected into lips proved noninferior to the approved dermal filler. When assessed by blinded evaluators using the MLFAS, participants treated with Belotero Intense® (+) Lidocaine showed clinically relevant, sustained post-treatment improvement (up to 60 weeks). This objective measure was further supported by additional effectiveness endpoints, including GAIS, reported by investigators and participants, and validated FACE-Q modules, which consistently indicated overall lip satisfaction following Belotero Intense® (+) Lidocaine treatment.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

Given that most related AEs were mild and non-serious in nature, and all resolved without sequelae, it can be concluded that treatment with Belotero® Intense (+) Lidocaine for aesthetic improvement of lip volume is a safe and well-tolerated procedure. The safety of Belotero Intense® (+) Lidocaine treatment in the lips was evaluated by secondary safety endpoints (i.e., incidence of related serious or delayed-onset AEs following the first treatment including touchup until Week 48) as well as other safety endpoints (e.g., treatment-related TEAEs and TEAEs). This pivotal study demonstrated an acceptable safety profile, with no treatment-related SAEs, no severe treatment-related AEs, no AEs leading to discontinuation, and no unexpected or atypical events associated with Belotero Intense® (+) Lidocaine injection. The majority of related AEs were mild, and all resolved by EOS. Additionally, CTRs were assessed using a participant eDiary. Overall, these safety findings suggest that investigator-reported AEs and participant-reported CTRs are consistent with treatment-related events typically reported following Belotero Intense® (+) Lidocaine and other dermal HA fillers. None of the treatment-related AEs or CTRs were considered to be unexpected or atypical for Belotero Intense® (+) Lidocaine treatment.

The safety of Belotero Intense® (+) Lidocaine for single and repeat use in lip augmentation was demonstrated, thereby achieving the study's secondary objective. Overall, the current findings establish that Belotero Intense® (+) Lidocaine was well tolerated and safe in its intended-use population; safety results from the current study are consistent with the known Belotero Intense® (+) Lidocaine safety profile and further substantiate its positive benefit-risk profile for lip augmentation.

Additional factors to be considered in determining probable risks and benefits for the Belotero Intense® (+) Lidocaine device included:

- No meaningful outcome differences regarding safety and effectiveness were found in the subgroup analyses for Fitzpatrick Skin Type, Race, Age, Sex and Ethnicity.

    1) Participant Perspective

    Participant perspectives considered during the review included:

    - Subject GAIS assessments: compared to baseline photographs, all (100.0%) Belotero Intense® (+) Lidocaine treated participants reported some level of improvement, according to the sGAIS, at Week 8 post-last treatment

    - Time Course of FACE-Q Satisfaction with Lips: participants maintained high improvement in their reported satisfaction with lips throughout the study. Belotero Intense® (+) Lidocaine treated participants resulted in an average improvement of Rasch-transformed scores by 47.1 points at Visit V8 (12 weeks after retreatment or 60 weeks post-last treatment [i.e., without retreatment])

    - Time Course of FACE-Q Satisfaction with Outcome: Belotero Intense® (+) Lidocaine treated participants maintained high Rasch-transformed scores with a mean of 78.2 at Visit V8 (12 weeks after retreatment or 60 weeks post last treatment [i.e., without retreatment])

    - Time Course of FACE-Q Psychological Function: Rasch-transformed Psychological Function scores for Belotero Intense® (+) Lidocaine treated participants increased from 72.9 at baseline reaching the highest mean Rasch-transformed score of 89.4 at Visit V8 (12 weeks after retreatment or 60 weeks post last treatment [i.e., without retreatment])

    - Likelihood of Retreatment: The majority of Belotero Intense® (+) Lidocaine participants were satisfied with treatment, and most reported being extremely likely (66.7%) to receive future BIL treatment.

    2) Robustness of Study Analysis: Several sensitivity analyses of primary and co-primary effectiveness endpoint confirmed the robustness of the results.

In conclusion, given the available information above, the data support that for lip augmentation in adults over the age of 21, 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.

XIV. CDRH DECISION

CDRH issued an approval order on July 9, 2026. The final clinical conditions of approval cited in the approval order are described below.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below.

1. The PAS is a prospective, post-market, open-label, multicenter, single arm study investigating the safety and effectiveness of Belotero® Intense (+) Lidocaine for lip augmentation in participants with Fitzpatrick Skin Types V or VI to further characterize the safety and effectiveness profile in this subpopulation.

   - **Study purpose/objectives:** This post-approval study is intended to expand the clinical evidence base in this underrepresented population and further characterize treatment-related safety.
   - **Study design (specify control, randomization, etc.):** Prospective, Post-market, Open-label, Multicenter, Single arm Study
   - **Total number of subjects:** Approximately 20 participants will be screened to achieve approximately 16 participants assigned to Belotero® Intense (+) Lidocaine treatment.
   - **Length of follow-up and frequency of assessments:** The expected study duration per participant excluding visit window is up to 30 weeks (up to 10 days screening period + baseline treatment + optional touch-up at Week 4 + 24-week follow-up). After the screening period participants will be followed for 24 weeks post last treatment (initial or touch-up treatment). Participants who do not receive a touch-up treatment will have seven on-site visits (including the screening visit), and participants who receive a touch-up treatment will have nine on-site visits (including the screening visit). After the baseline visit, follow-up visits will occur at Weeks 2, 4, 8, 16, and 24 for participants without touch-up treatment and Weeks 2, 4, 6, 8, 16, 20, and 28 for participants with touch-up treatment.
   - **Endpoints:**

     Primary Safety Endpoint

     Occurrence of related TEAEs, as documented by the investigator throughout the study (i.e. device and/or procedure-related)

     Additional Safety Variables

     - Occurrence of TEAEs
     - Occurrence of serious TEAEs
     - Occurrence of TEAEs leading to discontinuation from the study
     - Occurrence of device deficiencies
     - Occurrence of prespecified CTRs as documented by the participant for 28 day

Effectiveness Endpoint

- Responder rate at Visit V3, according to the MLFAS, as assessed live by the treating investigator, where response is defined as ≥ 1-point improvement on participant's treated lips compared to baseline

Exploratory Effectiveness Endpoints

- Global Aesthetic Improvement Scale (GAIS) scores for treated participants at all post-baseline visits, as completed by the treating investigator (iGAIS).
- GAIS scores for treated participants post-baseline visit, as completed by the participant (pGAIS).

- **High-level description of the data analysis plan for the primary endpoints:** Adverse events (AEs) will be coded to a Preferred Term (PT) and a System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time of database lock. A treatment-emergent event (TEAE) is defined as an event that emerges during treatment having been absent from pre-treatment or worsens relative to the pre-treatment state.
  The number and percentage of participants experiencing at least one event, as well as the total number of events, will be summarized by SOC and PT for the following events: TEAEs, related TEAEs, and serious TEAEs. Listings will be provided for all AEs, related TEAEs, serious TEAEs, serious TEAEs with fatal outcome, and TEAEs leading to study discontinuation.
  Incidences of common treatment responses (CTRs) will be summarized by worst severity and maximum duration.
  Effectiveness endpoints will be analysis descriptively in an explorative manner without any confirmatory statistical hypothesis testing.
  In general, qualitative variables will be summarized using frequency tables including the number of values analyzed, absolute frequencies and percentages. Descriptive statistics for metric variables will include the number of values analyzed, mean, standard deviation, median, quartiles, minimum and maximum.
- **Reference to protocol:** Study outline received July 7, 2026 (version 0.3)
- **Plan for interim data release:** Interim safety data will be submitted to FDA as part of the 6-month PAS progress reports.

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

XV. 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.