SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: saypha® MagIQ™

Device Procode: LMH (Implant, Dermal, For Aesthetic Use)

Applicant's Name and Address: CROMA-PHARMA GmbH
Industriezeile 6
2100 Leobendorf
Austria

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P240008

Date of FDA Notice of Approval: September 8, 2025

II. INDICATIONS FOR USE

saypha MagIQ is indicated for injection into the mid and deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) in adults over the age of 21.

III. CONTRAINDICATIONS

- saypha MagIQ is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- saypha MagIQ contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- saypha MagIQ contains lidocaine and is contraindicated for patients with a history of allergies to such material.
- saypha MagIQ is contraindicated for patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the saypha MagIQ labeling.

V. DEVICE DESCRIPTION

saypha MagIQ is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. The gel consists of hyaluronic acid (HA) produced by Streptococcus species of bacteria, which is crosslinked with 1,4-butanediol diglycidyl ether (BDDE). It is formulated to a concentration of 23 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of moderate to severe wrinkles and folds, such as nasolabial folds. Alternatives in the treatment of wrinkles, depressed lesions, and scars include invasive surgery (face-lift, rhytidectomy, etc.).

Less invasive alternatives include injection of other dermal fillers (collagen, calcium hydroxylapatite, microparticles of poly-L-lactic acid or other hyaluronic acid gels) or autologous fat transfer.

Treatment of very superficial and fine wrinkles and superficial texture of photo-damaged skin may also be accomplished using other technologies such as laser resurfacing, chemical peeling procedures or use of topical creams containing active ingredients such as retinoids or glycolic acid.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

saypha MagIQ received the CE Mark in May 2016 for creating volume in order to correct wrinkles, folds, and moderate to severe nasolabial folds, as well as for lips augmentation.

Currently, saypha MagIQ is marketed under different trade names in more than 70 countries. In addition to being marketed throughout the European Union, it is available in the following regions: North America, Latin America, South America, Eastern Europe, Middle-East, Africa, Asia-Pacific and Australia/New Zealand.

saypha MagIQ has not been withdrawn from marketing in any country for reasons related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Potential adverse effects (e.g., complications) associated with the use of the device, as well as for other devices in the same category, as reported in the clinical study, include tenderness, swelling, firmness (induration), lumps/bumps (mass), bruising, pain, redness, discoloration, and itching.

The following reported adverse events were received from post-market surveillance of the use of saypha MagIQ for treatment of nasolabial folds outside the United States and were not observed in the clinical study. These adverse events are listed in order of prevalence: device dislocation, skin inflammation/irritation, hematoma, obstruction/occlusion, herpes simplex reactivation, hypersensitivity/allergic reaction, itching sensation, hemorrhage/bleeding, bruise/contusion, phlebitis, granuloma and necrosis.

Additionally, the following rare but serious adverse events that are associated with intravascular injection of other soft tissue 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 viscoelastic implants and are considered as potential risks for this device: abscess, angioedema, bacterial infection, capsular contracture, dizziness, fever, fibrosis, hypoesthesia, malaise, medical device site induration, nausea, numbness, paresthesia, peeling, physical asymmetry, presyncope, rash, scleroderma, sebaceous hyperplasia, skin burning sensation, skin disorders, syncope/fainting, tactile disorder.

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

saypha MagIQ has been extensively tested and characterized through physical and chemical analyses (**Table 1**). Degradation assays were also performed to ensure that saypha MagIQ naturally degrades in the body during its clinical lifespan.

Table 1: Summary of Key Bench Testing on saypha MagIQ

Test	Purpose	Results
pH	Ensures pH meets specification	Passed
Osmolality	Ensures osmolality meets specification	Passed
Rheology	Ensures rheology meets specification	Passed
Extractable Volume	Ensures extractable volume meets specification	Passed
Injection Force	Ensures injection force meets specification	Passed
Sodium Hyaluronate Content	Ensures content sodium hyaluronate content meets specification	Passed
Residual Crosslinker	Ensures residual crosslinker meets specification	Passed
Endotoxin	Ensures endotoxin meets specification	Passed
Sterility	Ensures sterility meets specification	Passed

Test	Purpose	Results
Lidocaine Content	Ensures content lidocaine content meets specification	Passed
Lidocaine Purity	Ensures purity lidocaine purity meets specification	Passed

B. Biocompatibility Studies

A biological evaluation was performed on saypha MagIQ according to ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process (**Table 2**). According to ISO 10993-1, saypha MagIQ is categorized as implant device in contact with tissue where the contact duration is more than 30 days. All tests were performed according to Good Laboratory Practices (GLP), which are consistent with the requirements of the Federal Good Laboratory Practices Regulation (21 CFR § 58). The requirements of all tests were met demonstrating that the saypha MagIQ is biocompatible.

Table 2: Summary of Biocompatibility Testing on saypha MagIQ

Test	Method	ISO Standard	Results
Chemical Characterization and Toxicological Risk Assessment	GC-MS, HS GC-MS, UHPLC-MS, ICP-MS	ISO 10993-18 ISO 10993-17	Passed
Cytotoxicity	Agarose overlay, XTT staining, MTS staining	ISO 10993-5	Non cytotoxic
Irritation	Intracutaneous reactivity in rabbits	ISO 10993-10	Non irritant
Skin sensitization	Maximization test in guinea pigs	ISO 10993-10	Non sensitizer
Implantation	Intradermal implantation in rabbits (i.d.)	ISO 10993-6	Locally safe
Acute systemic toxicity	Intraperitoneal injection in mice	ISO 10993-11	Not systemically toxic
Subacute systemic toxicity (4-week)	Subcutaneous implantation in rats	ISO 10993-11	Not systemically toxic
Subchronic systemic toxicity (13-week)	Subcutaneous implantation in rats	ISO 10993-11	Not systemically toxic
Chronic systemic toxicity (26-week)	Subcutaneous implantation in rats	ISO 10993-11	Not systemically toxic
Pyrogenicity	Rabbit pyrogen study	USO <151>	Non pyrogenic
Genotoxicity	Bacterial reverse mutation, chromosomal aberration	ISO 10993-3	Non genotoxic, non clastogenic

Carcinogenicity risks: the biological evaluation concluded that the cancer risks from lifetime exposure to residual BDDE (limited to 2 ppm) in saypha MagIQ are minimal and in the same range of acceptable cancer risks as other previously approved dermal filler products.

C. Additional Studies

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 minimum Sterility Assurance Level (SAL) of 10^{-6}.

Stability data have been collected through 36 months at 25°C / 60% relative humidity, at 30°C / 65% relative humidity, at 2-8°C / 60% relative humidity, and through 13 months at 40°C / 20% relative humidity. Conformance with all specifications was confirmed to support a shelf life of 36 months at storage conditions of 5°C to 25°C (41-77°F).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of injection into the mid to deep dermis with saypha MagIQ for the correction of moderate to severe wrinkles and folds, such as nasolabial folds in the US under IDE # G160257. Data from this clinical study were the basis for the PMA approval decision. A supportive study (CPH-401-201324) for saypha MagIQ was conducted in Austria.

A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between 18-Jun-2019 and 23-Nov-2021. The database for this PMA reflected data collected through 15-Feb-2022 and included 270 subjects. There were 10 investigational sites.

The study was a randomized, subject- and evaluating investigator-blinded, controlled, multicenter, split-face, comparison clinical study. The study had one primary effectiveness endpoint and two key secondary effectiveness endpoints. The full analysis set (FAS) and the per protocol set (PPS) were the primary effectiveness analysis population. A hierarchical testing procedure was applied for primary and key secondary endpoints analyses to control multiplicity.

The primary effectiveness endpoint was defined as the response to treatment (i.e., a responder analysis) at week 24 based on the independent blinded evaluating investigator. The two key secondary effectiveness endpoints were responder analysis at week 24 based on the independent blinded photographic reviewers and the treating investigator live assessment, respectively.

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

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal study was limited to patients who met the following inclusion criteria:

- Male or female subjects, 22 years of age or older, at the Screening visit
- Subjects with 2 fully visible, approximately symmetrical moderate to severe NLFs (same severity) with severity scores of 2 or 3 on the 5-point NLF-SRS for both NLFs, as judged by the treating investigator in conjunction with the independent blinded evaluating investigator
- Females of childbearing potential had to have a negative urine pregnancy test at injection visits and had to agree to use an adequate method of contraception for the duration of the clinical investigation
- Healthy skin in the nasolabial area and free of diseases that could interfere in cutaneous aging evaluation
- Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation, including botulinum toxin injections (except glabellar or forehead botulinum toxin treatment)
- Understanding of the purpose and conduct of the clinical investigation and written informed consent provided.

Patients were not permitted to enroll in the pivotal study if they met any of the following exclusion criteria:

- For females: pregnant and/or lactating or planning to become pregnant during the clinical investigation
- History of allergies or hypersensitivity to HA preparations, lidocaine, or anesthetics of any amide-based anesthetic
- Since Control contains trace amounts of Gram-positive bacterial proteins: history of allergies to such material
- Tendency to keloid formation, hypertrophic scars, and/or pigmentation disorders
- Known to be human immune deficiency virus-positive
- Presence of infectious, inflammatory, or proliferative cancerous or pre-cancerous lesions in the area to be treated
- Recurrent herpes simplex in the treatment area
- History or presence of any autoimmune or connective tissue disease, or current treatment with immunomodulating therapy
- Uncontrolled (or unstable) diabetes mellitus or systemic diseases
- Facial plastic surgery or tissue augmentation with silicone, fat, or another non-absorbable substance (permanent fillers) in the area of device application
- Implantation of facial dermal fillers in the treatment area in the preceding 12 months
- Skin of the nasolabial region affected by aesthetic treatments (e.g., laser therapy, absorbable and non-absorbable sutures (threads), microneedling, and/or botulinum toxin within the last 12 months; dermabrasion and

mesotherapy within the last 6 months; chemical peeling within the last 3 months) or planning to undergo such procedures during the clinical investigation
- Facial lipolysis, including submental fat treatments, within last month prior to enrollment and during the clinical investigation
- Bariatric surgery within 12 months prior to enrollment and during the clinical investigation
- History of bleeding disorders and/or use of anticoagulant, antiplatelet, or thrombolytic medication from 10 days prior to injection to 3 days postinjection
- Planned dental/oral surgery or modification (bridge work, implants) within 2 weeks prior to injection and to a minimum of 4 weeks postinjection
- Any medical condition prohibiting inclusion in the clinical investigation according to the judgment of the treating investigator
- Previous enrollment in this clinical investigation
- Current participation in another clinical investigation, or treatment with any investigational drug/medical device within 30 days prior to clinical investigation enrollment
- Any dependency of the subject to the treating investigator, the independent blinded evaluating investigator, or clinical investigation site (e.g., employees of the Sponsor), or subjects who are employees or relatives of the treating investigator and/or the independent blinded evaluating investigator
- Having 1 of the following results during the visual examinations at Baseline:
    - Snellen visual acuity test worse than 20/40 (with corrective eyewear, if applicable)
    - Abnormal confrontational visual field test
    - Abnormal ocular motility test

2. Follow-up Schedule

All subjects were randomized in one of the treatment groups and given an initial treatment (Group A, saypha MagIQ in the left NLF and Control in the right NLF; Group B, saypha MagIQ in the right NLF and Control in the left NLF). An optional touch-up treatment was offered 2 weeks after initial treatment (Week 2; Visit 3a) to achieve optimal correction. All subjects were scheduled to return for follow-up examinations at 2, 12, 24, and 36 and/or 48 weeks after treatment for effectiveness and safety evaluation, as well as at Weeks 4, 6, 40, and/or 52, and/or 60 after treatment. All subjects were also scheduled a safety follow up remote visit within 3 days after Touch-up treatment visit and Repeat treatment visit. Subjects were followed for up to 48 weeks after initial treatment, with an optional repeat treatment offered at 36 or 48 weeks (Visits 6 and 7, respectively) using only saypha MagIQ for both NLFs. After any repeat treatment, subjects were followed an additional 12 weeks for safety assessments. Subjects who did not qualify for any retreatment had their end of study visit at Week 48 (Visit 7).

At the end of each treatment session, subjects received a diary to record the injection site reactions (ISRs) and AEs (including those that were potentially associated with unintended intravascular injection) that occurred within 4 weeks after initial, touch-up, and repeat treatments.

Pretreatment procedures and evaluations included: Informed Consent, medical/aesthetic procedure history, demographics, Fitzpatrick Skin Type, body weight, visual examinations, urine pregnancy test, Investigator baseline assessment of severity rating of nasolabial folds on the NLF-SRS, clinical photography, patient self-assessment questionnaire: FACE-Q subject appearance "Appraisal of NLFs", and concomitant medication.

Posttreatment the objective parameters measured during the study included body weight, visual examinations, urine pregnancy test, Investigator assessment: nasolabial fold severity on the NLF-SRS, GAIS; and patient self-assessment questionnaire: FACE-Q subject appearance "Appraisal of NLFs" and FACE-Q "Satisfaction with outcome", GAIS, subject diary, and pain assessment (NPRS). Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the **Table 3**.

Table 3: Schedule of Clinical Investigation Procedures and Assessments

		Initial /touch-up Tretament			**Follow-up for initial -/touch-up treatment**			**Evaluation for repeat-treatment/repeat-treatment[4]**		**Follow-up for repeat-treatment[5]**	
	Screening[1]	**Baseline[1]**	**Day 3**	**Touch-up**	**Day 3 aftertouch-uptreatment**	**4 and 6Week Follow-up**	**12 and 24 Weeks Follow-up**	**36/48 Weeks Follow-up**	**Day 3 after Repeat treatment**	**4 Weeks Follow up after Repeat treatment**	**12 Weeks Follow up after Repeat treatment**
	Visit 1	**Visit 2**	**Phone[11].**	**Visit 3a[2]**	**Phone.[3, 11]**	**Visit 3b, 3c**	**Visit 4, 5**	**Visit 6, 7[13]**	**Phone[11]**	**Visit 8**	**Visit 9**
	Day-14 to Day 0	**Day 0**	**Day 3 (±1 day)**	**Week 2 (± 3 days)**	**Day 3 after Visit 3a (± 1 day)**	**Week 6 (± 5 days)**	**Week 12/ 24 (±5 days)**	**Week 36/ 48 (±5 days)**	**Day 3 after Visit 6 / 7 (± 1 day)**	**Week 40 OR Week 52 (±5 days)**	**Week 48 (±5 days) OR Week 60 (±5 days)**
Procedure											
Informed consent	X										
Medical /aesthetic procedures history[a]	X										
Demographics[b]	X										
Fitzpatrick skin type	X										
Body weight		X		X		X	X	X		X	X
Visual examinations[c]		X		X[2]		X[8]	X	X[10]		X[10]	X[10]
Eligibility assessment	X	X[12]						X[5, 6]			
Randomization		X[6]									
Treatment		X		X[7]				X[9]			
Urine pregnancy test[d]	X	X[6]		X[6,8]				X[6,10]			
NLF-SRS[e]	X						X	X[6]			
Clinical photography[f]	X	X[6]					X	X[6]			
FACE-Q subject "Satisfaction with Outcome"[g]							X	X[6]			
FACE-Q subject appearance "Appraisal of NLFs"[h]		X[6]					X	X[6]			
GAIS[i] independent blinded evaluating investigator							X	X[6]			
GAIS[i] subject							X	X[6]			
Subject diary[j]		X		X		X[8]		X[10]		X[10]	

		Initial /touch-up Tretament			Follow-up for initial -/touch-up treatment			Evaluation for repeat-treatment/repeat-treatment[4]		Follow-up for repeat-treatment[5]	
	Screening[1]	Baseline[1]	Day 3	Touch-up	Day 3 aftertouch-uptreatment	4 and 6Week Follow-up	12 and 24 Weeks Follow-up	36/48 Weeks Follow-up	Day 3 after Repeat treatment	4 Weeks Follow up after Repeat treatment	12 Weeks Follow up after Repeat treatment
	Visit 1	Visit 2	Phone[11].	Visit 3a[2]	Phone.[3, 11]	Visit 3b, 3c	Visit 4, 5	Visit 6, 7[13]	Phone[11]	Visit 8	Visit 9
	Day-14 to Day 0	Day 0	Day 3 (±1 day)	Week 2 (± 3 days)	Day 3 after Visit 3a (± 1 day)	Week 6 (± 5 days)	Week 12/ 24 (±5 days)	Week 36/ 48 (±5 days)	Day 3 after Visit 6 / 7 (± 1 day)	Week 40 OR Week 52 (±5 days)	Week 48 (±5 days) OR Week 60 (±5 days)
Evaluation of pain[k]		X						X[10]			
Injection volume		X		X[7]				X[9]			
Concomitant medications/procedures		X[6]	X	X[6]	X	X	X	X[6]	X	X	X[10]
Adverse events		X[6]	X	X[6]	X	X	X	X[6]	X	X	X[10]

Abbreviations: C. = call; FACE-Q = Patient-reported outcome questionnaires measuring experience and outcomes of aesthetic facial procedures ; GAIS = Global Aesthetic Improvement Scale; NLF(s) = nasolabial folds; NLF-SRS = Nasolabial Folds-Severity Rating Scale; NPRS = Numeric Pain Rating Scale.

1 Screening and Baseline visits may be performed as one visit

2 Evaluation at Week 2 if a touch-up treatment is needed for optimal correction

3 Concerning only subjects who received a touch-up treatment. Subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection.

4 Evaluation if a repeat-treatment is needed will be performed at Week 36 (Visit 6) AND/OR at Week 48 (Visit 7)

5 The first Follow-up visit for repeat-treatment will take place 4 weeks (± 5 days) after repeat-treatment. The second Follow-up visit for repeat-treatment will take place 12 weeks (± 5 days) after repeat-treatment.

6 Prior to the treatment or any procedure, as applicable

7 Touch-up treatment if appropriate for optimal correction

8 At week 6 only if touch-up treatment occurred at Week 2

9 Repeat-treatment at Week 36 (Visit 6) OR Week 48 (Visit 7)

10 Only if repeat-treatment occurred at Week 36 (Visit 6) OR Week 48 (Visit 7)

11 All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection

12 Exclusion criterion based on visual examinations at Baseline

13 Visit 7 (re-treatment) could be performed at a later time point, as permitted by the protocol. In such cases, the schedule of assessments remained the same: re-treatment visit, follow-up phone call at Day 3, and on-site follow-up visits at Weeks 4 and 12 post-treatment.

a Includes information on prior medication, defined as all medication taken/received within the previous ten days

b Includes date of birth, sex, race and ethnicity

c Visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) to be performed at Baseline and at Week 4; in case of touch-up treatment, to be done as well at Week 2 and at Week 6; in case of repeat-treatment, to be performed at 4 and 12 weeks after repeat-treatment visit. To be performed prior to- and 30 min after any treatment after all other assessments. The subject should wear the same corrective eyewear (i.e. glasses/contact lenses) at each assessment, if appropriate. The definition of clinically significant changes and action to be taken is presented in Section 10.8.4 of the protocol.

d In women of childbearing potential only, including those who are postmenopausal for less than twelve months

e Evaluation and grading of nasolabial folds (NLFs) severity by the treating investigator and by the independent blinded evaluating investigator (separate assessments) will be done using the 5-point NLF-SRS. The Baseline severity is the severity grade assigned at Screening as determined by the treating investigator in conjunction with the independent blinded evaluator. The left and right cheek will be separately evaluated.

f Clinical photography will be performed; the evaluation and grading of nasolabial folds severity by the independent blinded photographic reviewers using the 5-point NLF-SRS and based on photographs will take place at the end of the clinical investigation. The left and right cheek will be separately evaluated

g Evaluation of subject satisfaction using the FACE-Q questionnaire “Satisfaction with Outcome”

h Evaluation of subject appearance appraisal using the FACE-Q questionnaire on ”Appraisal of Nasolabial Folds”

i Evaluation of aesthetic improvement using the GAIS

j Subject diary to be collected and reviewed two and four weeks after initial-/touch-up treatment, and four weeks after repeat-treatment

k Starting 15 min after last injection and at 15 min-intervals for 60 min post-treatment using the adapted NPRS.

3. Clinical Endpoints

With regards to safety, applied measures included the frequency, severity, seriousness, and causal relationship of adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs), and serious adverse device effects (SADEs) during the clinical study. This also included events reported by subjects in diaries during the 4 weeks after each treatment (initial, touch-up, and repeat).

With regards to effectiveness, the investigational device was assessed according to changes in NLF severity compared to Baseline using the validated 5-point NLF-SRS. NLF-SRS scores were ranked as 0 (none/minimal), 1 (mild), 2 (moderate), 3 (severe), and 4 (extreme). The assessment was performed by the independent blinded evaluating investigator, the treating investigator, and 3 independent blinded photographic reviewers.

The aesthetic improvement was assessed by the subject and by the independent blinded evaluating investigator (separate assessments) using the 5-point GAIS. GAIS scores ranged from 1 (very much improved), to 2 (much improved), 3 (improved), 4 (no change), and 5 (worse).

Subject satisfaction was evaluated using FACE-Q questionnaires on "Satisfaction with Outcome" and "Appraisal of Nasolabial Folds". The FACE-Q Subject Satisfaction with Outcome Questionnaire consisted of 6 questions with answers of 1 (definitely disagree), 2 (somewhat disagree), 3 (somewhat agree), or 4 (definitely agree). The FACE-Q Subject Appearance Appraisal of Nasolabial Folds Questionnaire consists of 5 questions with answers of 1 (not at all), 2 (a little), 3 (moderately), or 4 (extremely). The raw sum scores were each converted into equivalent Rasch transformed scores which ranged from 0 (worst) to 100 (best).

Pain assessment using the Numeric Pain Rating Scale (NPRS) ranging from 0 (no pain) to 10 (the worst pain imaginable) was done after initial and repeat treatment in 15-minute increments, starting 15 minutes after the last injection until 60 minutes post-treatment.

With regard to success/failure criteria, the primary endpoint was the percentage of NLF responders based on the independent blinded evaluating investigator live assessment at Week 24 after initial treatment and compared to Control. A responder was defined as a subject showing ≥1 grade improvement from Baseline in NLF severity as measured by NLF-SRS.

The primary effectiveness outcome measure was evaluated by the 1-sided 95% confidence interval (CI) of the difference between paired proportions pA-pB. In this, pA was the response rate for saypha MagIQ and pB was the response rate for Control. Thus, a negative value of the difference meant that the response rate of saypha MagIQ was lower than the response rate for Control. saypha MagIQ was considered non-inferior to Control if the 95% lower confidence limit did not exceed the non-inferiority margin of -10%.

B. Accountability of PMA Cohort

At the time of database lock, data from all 295 enrolled subjects were available for analysis (**Table 4**). Of the 295 subjects, 25 were screen failures primarily due to ineligibility, and 270 were randomized per protocol. Of these, 136 subjects were randomized to Group A and 134 subjects were randomized to Group B. All randomized subjects were treated. At Week 2, 147 subjects received a touch-up treatment with saypha MagIQ and 152 subjects received a touch-up treatment with Control. A total of 48 subjects (27 subjects in Group A and 21 subjects in Group B)

received a repeat treatment (i.e., saypha MagIQ on both NLFs). Mean (SD) injected volumes used for the initial and touch-up injections were 1.219 (0.5006) mL and 0.429 (0.2260) mL in the saypha MagIQ group and 1.028 (0.4382) mL and 0.384 (0.1945) mL in the Control group. A total of 48 subjects (27 subjects in Group A and 21 subjects in Group B) received a repeat treatment (i.e., saypha MagIQ on both NLFs).

All 270 randomized subjects were included in the Full Analysis Set (FAS) and Safety Analysis Set (SAS). A total of 224 (83.0%) subjects were included in the Per-Protocol Set (PPS). Overall, 222 (82.2%) subjects completed the study. The most common reasons for discontinuation from the study were other (22 [8.1%] subjects) and lost to follow-up (18 [6.7%] subjects).

Table 4: Participation Disposition

Subject Disposition	Group A	Group B	Overall
Signed informed consent	-	-	295
Number of subjects screened	-	-	295
Screen passed	-	-	270
Screen failure	-	-	25
Inclusion/Exclusion criteria	-	-	15
Withdraw consent	-	-	3
Other	-	-	7
Randomized	136	134	270
Treated	136	134	270
Repeat treatment	27	21	48
Who completed the study, n (%)	113 (83.1)	109 (81.3)	222 (82.2)
Who discontinued early, n (%)	23 (16.9)	25 (18.7)	48 (17.8)
Lost to follow-up	8 (5.9)	10 (7.5)	18 (6.7)
Withdrawal of consent	2 (1.5)	6 (4.5)	8 (3.0)
Other[1]	14 (10.3)	8 (6.0)	22 (8.1)

Abbreviations: Group A, saypha MagIQ in the left NLF and Control in the right NLF; Group B, saypha MagIQ in the right NLF and Control in the left NLF; NLF, nasolabial fold.
Note: Percentage was based on subjects in each treatment group who received treatment (full analysis set).
[1] 'Other' reasons included adverse event, noncompliance, COVID-19-related reasons, moved, changed work schedule, study hold waiting, and personal issue.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study performed in the US.

Overall, subjects had a mean (SD) age of 55.4 (9.37) years and a mean body weight of 70.92 (14.685) kg at Screening. Most subjects were female (97.8%) and White (83.7%).

The majority of subjects had Fitzpatrick skin type II (28.9%), type III (30.0%), or type IV (23.3%) at Baseline. A total of 36 (13.3%) subjects had Fitzpatrick skin type V or VI at Baseline (**Table 5**).

10% of the subjects had received a previous dermal filler injection (non-treatment-naïve).

Table 5: Subject Demographic and Baseline Characteristics (FAS)

Characteristics	**Group A (N=136)**	**Group B (N=134)**	**Overall (N=270)**	**Repeat Treatment (N=48)**
Age (years)				
n	136	134	270	48
Mean (SD)	55.8 (9.65)	55.0 (9.08)	55.4 (9.37)	57.9 (8.02)
Median	54.5	55.0	55.0	57.5
Min, Max	30, 82	33, 86	30, 86	43, 75
Sex, n (%)				
n	136	134	270	48
Male	3 (2.2)	3 (2.2)	6 (2.2)	3 (6.3)
Female	133 (97.8)	131 (97.8)	264 (97.8)	45 (93.8)
If female, is the subject of childbearing potential? n (%)				
n	133	131	264	45
Yes	38 (27.9)	43 (32.1)	81 (30.0)	10 (20.8)
No	95 (69.9)	88 (65.7)	183 (67.8)	35 (72.9)
Post-menopausal	77 (56.6)	71 (53.0)	148 (54.8)	27 (56.3)
Surgically sterile	18 (13.2)	17 (12.7)	35 (13.0)	8 (16.7)
Race, n (%)				
n	136	134	270	48
Asian	1 (0.7)	1 (0.7)	2 (0.7)	0
White	112 (82.4)	114 (85.1)	226 (83.7)	45 (93.8)
Black or African American	14 (10.3)	15 (11.2)	29 (10.7)	2 (4.2)
American Indian or Alaska Native	6 (4.4)	4 (3.0)	10 (3.7)	1 (2.1)
Native Hawaiian or Other Pacific Islander	1 (0.7)	0	1 (0.4)	0
Other	2 (1.5)	0	2 (0.7)	0

Characteristics	Group A (N=136)	Group B (N=134)	Overall (N=270)	Repeat Treatment (N=48)
Ethnicity, n (%)				
n	136	134	270	48
Hispanic or Latino	29 (21.3)	31 (23.1)	60 (22.2)	17 (35.4)
Not Hispanic or Latino	107 (78.7)	103 (76.9)	210 (77.8)	31 (64.6)
Fitzpatrick skin type, n (%)				
n	136	134	270	48
Type I	9 (6.6)	3 (2.2)	12 (4.4)	1 (2.1)
Type II	36 (26.5)	42 (31.3)	78 (28.9)	13 (27.1)
Type III	41 (30.1)	40 (29.9)	81 (30.0)	12 (25.0)
Type IV	32 (23.5)	31 (23.1)	63 (23.3)	18 (37.5)
Type V	11 (8.1)	10 (7.5)	21 (7.8)	3 (6.3)
Type VI	7 (5.1)	8 (6.0)	15 (5.6)	1 (2.1)
Body weight (kg)				
n	136	134	270	48
Mean (SD)	70.10 (14.583)	71.75 (14.795)	70.92 (14.685)	74.60 (15.917)
Median	66.30	70.65	67.90	72.80
Min, Max	44.7, 118.9	42.1, 117.9	42.1, 118.9	44.7, 118.9

Abbreviations: FAS, full analysis set; Group A, saypha MagIQ in the left NLF and Control in the right NLF; Group B, saypha MagIQ in the right NLF and Control in the left NLF; Max, maximum; Min, minimum; NLF, nasolabial fold; SD, standard deviation.
Note: Repeat treatment - Subjects who received repeat treatment from Group A or Group B at Week 36, Week 48, or Visit 7c.
Note: Percentage was based on subjects in each treatment group of the FAS.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the SAS cohort of 270 patients for Treatment-Emergent Adverse Events (TEAE) After Initial Treatment and of 255 patients for Injection Site Reactions (ISR) After Initial Treatment as well as of 35 patients for Injection Site Reactions After Repeat Treatment recorded through patient diaries, available for up to 123 weeks. The key safety outcomes for this study are presented below in **Tables 6** to **9**. Adverse effects are reported in **Tables 10** to **13**.

Adverse effects that occurred in the PMA clinical study:

Injection Site Reactions after initial and repeat treatments

Overall, 243 (95.3%) subjects reported ISRs after initial treatment with saypha MagIQ, and 238 (92.6%) subjects reported ISRs after initial treatment with Control. The reported ISRs were similar between the treatment groups. The vast majority of ISRs were mild or moderate in intensity.

The most common ISRs reported in both treatment groups were firmness, swelling, lumps/bumps, and tenderness to touch (**Table 6**). ISRs that were reported as severe by >5% of subjects after initial treatment with saypha MagIQ or Control were bruising (17 [6.7%] subjects, 15 [5.8%] subjects), lumps/bumps (13 [5.1%] subjects, 11 [4.3%] subjects), and firmness (9 [3.5%] subjects, 14 [5.4%] subjects).

Table 6: Injection Site Reactions by Maximum Severity as Recorded by Subjects in the Diary After Initial Treatment (SAS)

Injection site reaction	Maximum Severity							
	saypha MagIQ (N=255)[1] n (%)				Control (N=257)[1] n (%)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Any ISR	91 (35.7)	117 (45.9)	35 (13.7)	243 (95.3)	91 (35.4)	115 (44.7)	32 (12.5)	238 (92.6)
Redness	115 (45.1)	48 (18.8)	9 (3.5)	172 (67.5)	108 (42.0)	47 (18.3)	3 (1.2)	158 (61.5)
Pain after injection	88 (34.5)	28 (11.0)	1 (0.4)	117 (45.9)	90 (35.0)	23 (8.9)	2 (0.8)	115 (44.7)
Tenderness to touch	131 (51.4)	44 (17.3)	3 (1.2)	178 (69.8)	123 (47.9)	45 (17.5)	7 (2.7)	175 (68.1)
Firmness	100 (39.2)	96 (37.6)	9 (3.5)	205 (80.4)	103 (40.1)	82 (31.9)	14 (5.4)	199 (77.4)
Swelling	121 (47.5)	64 (25.1)	8 (3.1)	193 (75.7)	115 (44.7)	66 (25.7)	7 (2.7)	188 (73.2)
Lumps/ bumps	101 (39.6)	67 (26.3)	13 (5.1)	181 (71.0)	105 (40.9)	53 (20.6)	11 (4.3)	169 (65.8)
Bruising	101 (39.6)	53 (20.8)	17 (6.7)	171 (67.1)	80 (31.1)	58 (22.6)	15 (5.8)	153 (59.5)
Itching	60 (23.5)	7 (2.7)	6 (2.4)	73 (28.6)	56 (21.8)	3 (1.2)	4 (1.6)	63 (24.5)
Discoloration	47 (18.4)	9 (3.5)	7 (2.7)	63 (24.7)	41 (16.0)	10 (3.9)	3 (1.2)	54 (21.0)
Other[2]	35 (13.7)	8 (3.1)	6 (2.4)	49 (19.2)	24 (9.3)	14 (5.4)	2 (0.8)	40 (15.6)

Abbreviation: ISR, injection site reaction; N, number of subjects in each treatment group of the safety analysis set, who returned filled-in subject diaries after the initial treatment; SAS, safety analysis set;
Note: Treatment, saypha MagIQ or Control, was based on the ISR side of face. The percentage was based on the subjects in each treatment group who returned filled-in subject diaries. For each row category, a subject with 2 or more ISRs in that category was counted only once at the maximum level. In cases where severity was missing for an ISR, the ISR was considered to be the highest degree of severity: severe.
[1] Subject number refers to subjects who returned diaries.
[2] 'Other' was used in subject diary to describe a symptom that did not appear in the listed categories.

The maximum duration for any ISR reported was similar between treatments: 1 to 3 days for 16.1% of subjects with saypha MagIQ and 20.2% of subjects with

Control, respectively, 4 to 7 days for 20.8% and 20.6%, 8 to 14 days for 35.3% and 34.2%, and >14 days for 23.1% and 17.5%. Among the ISRs that lasted >14 days, the most common (i.e., affected >10% of subjects in either treatment group) were firmness for 15.7% of saypha MagIQ subjects and 12.8% of Control subjects, and lumps/bumps for 12.9% and 10.5%, respectively (**Table 7**).

For subjects who subsequently received touch-up treatment at Week 2, the maximum duration of ISRs reported with either treatment was generally lower than after initial treatment. For 48% of subjects who received touch-up treatment, ISRs resolved in 1 to 7 days. The only ISR that lasted >14 days for >10% of subjects in either treatment group was firmness.

Table 7: Injection Site Reactions by Maximum Duration as Recorded by Subjects in the Diary After Initial Treatment with Saypha MagIQ (SAS)

Injection site reaction	Maximum Duration							
	saypha MagIQ (N=255)[1] n (%)				Control (N=257)[1] n (%)			
	1-3 Days	4-7 Days	8-14 Days	>14 Days	1-3 Days	4-7 Days	8-14 Days	>14 Days
Any ISR	41 (16.1)	53 (20.8)	90 (35.3)	59 (23.1)	52 (20.2)	53 (20.6)	88 (34.2)	45 (17.5)
Redness	116 (45.5)	36 (14.1)	14 (5.5)	6 (2.4)	102 (39.7)	31 (12.1)	18 (7.0)	7 (2.7)
Pain after injection	86 (33.7)	17 (6.7)	13 (5.1)	1 (0.4)	84 (32.7)	17 (6.6)	11 (4.3)	3 (1.2)
Tenderness to touch	87 (34.1)	36 (14.1)	43 (16.9)	12 (4.7)	91 (35.4)	38 (14.8)	34 (13.2)	12 (4.7)
Firmness	58 (22.7)	43 (16.9)	64 (25.1)	40 (15.7)	60 (23.3)	48 (18.7)	58 (22.6)	33 (12.8)
Swelling	93 (36.5)	50 (19.6)	34 (13.3)	16 (6.3)	100 (38.9)	48 (18.7)	24 (9.3)	16 (6.2)
Lumps/ bumps	54 (21.2)	38 (14.9)	56 (22.0)	33 (12.9)	61 (23.7)	33 (12.8)	48 (18.7)	27 (10.5)
Bruising	67 (26.3)	53 (20.8)	41 (16.1)	10 (3.9)	50 (19.5)	48 (18.7)	46 (17.9)	9 (3.5)
Itching	47 (18.4)	11 (4.3)	13 (5.1)	2 (0.8)	37 (14.4)	8 (3.1)	14 (5.4)	4 (1.6)
Discoloration	43 (16.9)	10 (3.9)	8 (3.1)	2 (0.8)	34 (13.2)	8 (3.1)	7 (2.7)	5 (1.9)
Other[2]	31 (12.2)	8 (3.1)	6 (2.4)	4 (1.6)	26 (10.1)	4 (1.6)	7 (2.7)	3 (1.2)

Abbreviation: ISR, injection site reaction; N, number of subjects in each treatment group of the safety analysis set, who returned filled-in subject diaries after the initial treatment; SAS, safety analysis set;
Note: Treatment, saypha MagIQ or Control, was based on the ISR side of face. The percentage was based on the subjects in each treatment group who returned filled-in subject diaries. For each row category, a subject with 2 or more ISRs in that

category was counted only once at the maximum duration. For subjects who received a touch-up treatment only diary entries from before the touch-up treatment are used for the calculation of the duration.

[1] Subject number refers to subjects who returned diaries.

[2] 'Other' was used in subject diary to describe a symptom that did not appear in the listed categories.

Overall, 30 (85.7%) subjects reported ISRs after repeat treatment with saypha MagIQ. The most common ISRs reported after repeat treatment with saypha MagIQ were firmness (26 [74.3%] subjects), redness (21 [60.0%] subjects), and swelling (20 [57.1%] subjects). The only ISR that lasted >14 days for >10% of subjects was firmness (**Table 8**).

Table 8: Injection Site Reactions by Maximum Severity as Recorded by Subjects in the Diary After Repeat Treatment (SAS)

Injection site reaction	**Maximum Severity**							
	saypha MagIQ (N=35)[1] n (%)				**Control (initial treatment with Control) (N=35)[1] n (%)**			
	Mild	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**
Any ISR	10 (28.6)	15 (42.9)	4 (11.4)	29 (82.9)	14 (40.0)	11 (31.4)	3 (8.6)	28 (80.0)
Redness	14 (40.0)	5 (14.3)	2 (5.7)	21 (60.0)	15 (42.9)	4 (11.4)	1 (2.9)	20 (57.1)
Pain after injection	15 (42.9)	1 (2.9)	1 (2.9)	17 (48.6)	13 (37.1)	1 (2.9)	1 (2.9)	15 (42.9)
Tenderness to touch	9 (25.7)	6 (17.1)	2 (5.7)	17 (48.6)	9 (25.7)	5 (14.3)	2 (5.7)	16 (45.7)
Firmness	11 (31.4)	11 (31.4)	2 (5.7)	24 (68.6)	14 (40.0)	9 (25.7)	3 (8.6)	26 (74.3)
Swelling	14 (40.0)	4 (11.4)	1 (2.9)	19 (54.3)	13 (37.1)	4 (11.4)	1 (2.9)	18 (51.4)
Lumps/ bumps	6 (17.1)	6 (17.1)	1 (2.9)	13 (37.1)	7 (20.0)	7 (20.0)	2 (5.7)	16 (45.7)
Bruising	7 (20.0)	8 (22.9)	2 (5.7)	17 (48.6)	9 (25.7)	5 (14.3)	1 (2.9)	15 (42.9)
Itching	4 (11.4)	0	2 (5.7)	6 (17.1)	4 (11.4)	1 (2.9)	1 (2.9)	6 (17.1)
Discoloration	2 (5.7)	4 (11.4)	1 (2.9)	7 (20.0)	5 (14.3)	3 (8.6)	0	8 (22.9)
Other[2]	0	0	1 (2.9)	1 (2.9)	1 (2.9)	0	0	1 (2.9)

Abbreviation: ISR, injection site reaction; N, number of subjects in each treatment group of the safety analysis set, who returned filled-in subject diaries after the initial treatment; SAS, safety analysis set;

Note: Treatment, saypha MagIQ or Control, was based on the ISR side of face. The percentage was based on the subjects in each treatment group who returned filled-in subject diaries. For each row category, a subject with 2 or more ISRs in that category was counted only once at the maximum level. In cases where severity was missing for an ISR, the ISR was considered to be the highest degree of severity: severe.

[1] Subject number refers to subjects who returned diaries

[2] 'Other' was used in subject diary to describe a symptom that did not appear in the listed categories.

The maximum duration for any ISR reported after repeat treatment with saypha MagIQ was similar between subjects who had initial treatments of saypha MagIQ or Control: 1 to 3 days for 25.7% of subjects and 22.9% of subjects, respectively, 4 to 7 days for 11.4% and 14.3%, 8 to 14 days for 14.3% and 17.1%, and >14 days for 31.4% and 25.7%. The only ISR that lasted >14 days for >10% of subjects was firmness for 25.7% of subjects and 22.9% of subjects, respectively (**Table 9**).

Table 9: Injection Site Reactions by Maximum Duration as Recorded by Subjects in the Diary After Repeat Treatment (SAS)

Injection site reaction	**Maximum Duration**							
	saypha MagIQ (N=35)[1] n (%)				**Control (initial treatment with Control) (N=35)[1] n (%)**			
	1-3 Days	**4-7 Days**	**8-14 Days**	**>14 Days**	**1-3 Days**	**4-7 Days**	**8-14 Days**	**>14 Days**
Any ISR	9 (25.7)	4 (11.4)	5 (14.3)	11 (31.4)	8 (22.9)	5 (14.3)	6 (17.1)	9 (25.7)
Redness	12 (34.3)	4 (11.4)	2 (5.7)	3 (8.6)	14 (40.0)	3 (8.6)	2 (5.7)	1 (2.9)
Pain after injection	13 (37.1)	2 (5.7)	2 (5.7)	0	11 (31.4)	2 (5.7)	2 (5.7)	0
Tenderness to touch	6 (17.1)	3 (8.6)	5 (14.3)	3 (8.6)	6 (17.1)	4 (11.4)	3 (8.6)	3 (8.6)
Firmness	7 (20.0)	6 (17.1)	2 (5.7)	9 (25.7)	8 (22.9)	7 (20.0)	3 (8.6)	8 (22.9)
Swelling	12 (34.3)	4 (11.4)	2 (5.7)	1 (2.9)	11 (31.4)	4 (11.4)	2 (5.7)	1 (2.9)
Lumps/ bumps	5 (14.3)	2 (5.7)	3 (8.6)	3 (8.6)	6 (17.1)	4 (11.4)	3 (8.6)	3 (8.6)
Bruising	5 (14.3)	9 (25.7)	1 (2.9)	2 (5.7)	5 (14.3)	6 (17.1)	2 (5.7)	2 (5.7)
Itching	3 (8.6)	2 (5.7)	1 (2.9)	0	3 (8.6)	2 (5.7)	1 (2.9)	0
Discoloration	5 (14.3)	1 (2.9)	0	1 (2.9)	6 (17.1)	0	0	2 (5.7)
Other[2]	1 (2.9)	0	0	0	1 (2.9)	0	0	0

Abbreviation: ISR, injection site reaction; N, number of subjects in each treatment group of the safety analysis set, who returned filled-in subject diaries after the initial treatment; SAS, safety analysis set;

Note: Treatment, saypha MagIQ or Control, was based on the ISR side of face. The percentage was based on the subjects in each treatment group who returned filled-in subject diaries. For each row category, a subject with 2 or more ISRs in that category was counted only once at the maximum level. In cases where severity was missing for an ISR, the ISR was considered to be the highest degree of severity: severe.

[1] Subject number refers to subjects who returned diaries.

[2] 'Other' was used in subject diary to describe a symptom that did not appear in the listed categories.

The maximum duration reported for ISRs overall were as follows: firmness (38 days), swelling (38 days), lumps/bumps (38 days), tenderness to touch (31 days), redness (29 days), bruising (33 days), pain (18 days), itching (29 days), discoloration (30 days), other (29 days).

Treatment-Emergent Adverse Events after initial and repeat treatments

TEAEs were reported for 66 (24.4%) subjects after initial/touch-up treatment with saypha MagIQ and 63 (23.3%) subjects after initial/touch-up treatment with Control. For a total of 26 (9.6%) subjects in the saypha MagIQ and 24 (8.9%) subjects in the Control groups, the TEAEs were considered related to the intradermal filler treatment, i.e. were reported as treatment-emergent adverse device effects (TEADEs). TEAEs that were considered related to the study procedure were reported for 21 (7.8%) subjects in the saypha MagIQ group and 21 (7.8%) subjects in the Control group. TEAEs that were considered related to the study device were reported for 15 (5.6%) subjects in the saypha MagIQ and 14 (5.2%) subjects in the Control group. Most TEAEs were mild or moderate in severity.

Serious TEAEs were reported for 3 (1.1%) subjects after initial/touch-up treatment with saypha MagIQ and Control. Of these, 1 subject had a serious TEADE (vascular compression), which was also considered as an unanticipated serious TEADE. Although the event occurred on the left, Control-treated NLF, it was reported and analyzed for both treatment groups in this split-face study. No TEAE or TEADE leading to death was reported.

TEAEs of special interest were reported for 3 (1.1%) subjects after initial/touch-up treatment with saypha MagIQ and Control. A TEAE/TEADE that led to study withdrawal (vascular compression) was reported for 1 (0.4%) subject after initial/touch-up treatment with saypha MagIQ and Control. The event resolved within 28 days (**Table 10**).

TEAEs were reported for 4 (8.3%) subjects after repeat treatment with saypha MagIQ. No TEAE after repeat treatment was considered related to the study device or study procedure. One (1) subject experienced a serious TEAE after repeat treatment that was considered severe and led to study withdrawal.

Table 10: Overall Summary of Treatment-Emergent Adverse Events After Initial/Touch-up Treatment (SAS)

TEAE / TEADE	**saypha MagIQ (N=270) n (%)**	**Control (N=270) n (%)**	**Total (N=270) n (%)**
all TEAEs[1]	66 (24.4)	63 (23.3)	67 (24.8)
Study device-related	15 (5.6)	14 (5.2)	16 (5.9)
Study procedure-related	21 (7.8)	21 (7.8)	22 (8.1)
TEAEs by relationship (including study device and study procedure)			

TEAE / TEADE	saypha MagIQ (N=270) n (%)	Control (N=270) n (%)	Total (N=270) n (%)
Related	26 (9.6)	24 (8.9)	27 (10.0)
Not related	40 (14.8)	39 (14.4)	40 (14.8)
Serious TEAEs	3 (1.1)	3 (1.1)	3 (1.1)
TEAEs by maximum severity			
Severe	5 (1.9)	5 (1.9)	5 (1.9)
Moderate	18 (6.7)	17 (6.3)	18 (6.7)
Mild	43 (15.9)	41 (15.2)	44 (16.3)
TEAEs leading to study withdrawal	1 (0.4)	1 (0.4)	1 (0.4)
TEAEs leading to subject death	0	0	0
TEAEs of special interest[2]	3 (1.1)	3 (1.1)	3 (1.1)
Serious TEADEs	1 (0.4)	1 (0.4)	1 (0.4)
Unanticipated serious TEADEs[3]	1 (0.4)	1 (0.4)	1 (0.4)
Anticipated serious TEADEs	0	0	0
TEADEs maximum severity			
Severe	3 (1.1)	3 (1.1)	3 (1.1)
Moderate	3 (1.1)	2 (0.7)	3 (1.1)
Mild	20 (7.4)	19 (7.0)	21 (7.8)
TEADEs leading to study withdrawal	1 (0.4)	1 (0.4)	1 (0.4)
TEADEs leading to subject death	0	0	0

Abbreviations: ADE, adverse device effect; ASADE, anticipated serious adverse device effect; eCRF, electronic case report form; SAS, safety analysis set; TEADE, treatment-emergent adverse device effect; TEAE, treatment-emergent adverse event; USADE, unanticipated serious adverse device effect.

Note: Allocation to a particular Treatment column, saypha MagIQ or Control, was based on the AE side of face; if the AE side was not applicable, the AE was allocated to both sides of the face. For each row category, a subject with 2 or more AEs in that category was counted only once. For the maximum relationship and maximum severity categories, a subject with 2 or more AEs in that category was counted only once at the maximum level.

[1] All TEAEs including device effects.

[2] TEAEs that led to changes in vision and/or skin changing color around the eyelids or around the site of injection that were recorded as AEs of special interest in the eCRF.

[3] A USADE was defined as a serious ADE which by its nature, incidence, severity, or outcome had not been identified in the current version of the Investigator's Brochure or the Instructions for Use. An ASADE was an effect which by its nature, incidence, severity, or outcome had been identified in the risk analysis report.

The most commonly reported TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) after initial/touch-up treatment are presented in **Table 11**. The most frequent TEAEs reported in both groups were headache (12 [4.4%] subjects) and eyelid margin crusting (6 [2.2%] subjects). The only common TEAEs that occurred more frequently under saypha MagIQ compared to Control treatment were swelling (4 [1.5%] vs. 2 [0.7%] subjects) and

injection site erythema (3 [1.1%] vs. 1 [0.4%] subjects), although these differences were so small as to be considered not clinically meaningful. None of the commonly reported TEAEs were reported as severe, although events with unreported severity were assumed to be 'severe' to simulate worst-case for the AE analysis this applied to for two (2) subjects with eyelid margin crusting of unreported severity.

Table 11: Treatment-Emergent Adverse Events by Preferred Term (Reported in >2 Subjects in Total Group) After Initial/Touch-up Treatment (SAS)

Preferred Term	saypha MagIQ (N=270) n (%)	Control (N=270) n (%)	Total (N=270) n (%)
all TEAEs[1]	66 (24.4)	63 (23.3)	67 (24.8)
Headache	12 (4.4)	12 (4.4)	12 (4.4)
Eyelid margin crusting	6 (2.2)	6 (2.2)	6 (2.2)
COVID-19	5 (1.9)	5 (1.9)	5 (1.9)
Contusion	4 (1.5)	4 (1.5)	4 (1.5)
Skin discoloration	4 (1.5)	4 (1.5)	4 (1.5)
Swelling	4 (1.5)	2 (0.7)	4 (1.5)
Basal cell carcinoma	3 (1.1)	3 (1.1)	3 (1.1)
Discomfort	3 (1.1)	3 (1.1)	3 (1.1)
Dizziness	3 (1.1)	3 (1.1)	3 (1.1)
Injection site erythema	3 (1.1)	1 (0.4)	3 (1.1)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

Note: Treatment, saypha MagIQ or Control, was based on the AE side of face; if AE side was not applicable, it was considered that the AE happened to both sides of the face. For each row category, a subject with 2 or more AEs in that category was counted only once. AEs were coded using MedDRA version 25.0.

[1] All TEAEs including device effects.

The most commonly reported study device-related TEAEs were discomfort and eyelid margin crusting (3 [1.1%] subjects each), and swelling, erythema, pruritus, headache, and feeding disorder (2 [0.7%] subjects each). The most commonly reported study procedure-related TEAEs were headache (6 [2.2%] subjects), contusion (4 [1.5%] subjects), discomfort and injection site erythema (3 [1.1%] subjects each), and swelling and eyelid margin crusting (2 [0.7%] subjects each). As shown by the example of discomfort, TEAEs could be assessed as both device- and procedure-related.

The maximum duration reported for these TEAEs were as follows: headache (2 days), contusion (14 days), swelling (14 days), eyelid margin crusting (10 days), discomfort (14 days), redness (5 days), feeding disorder (6 days) and itching (38 days). One case of mild erythema was reported starting 91 days after initial treatment and was ongoing at the end of the study without intervention taken. A mild papule was reported for a single patient 44 days after initial treatment and went away on its own after 211 days.

A summary of the most frequent TEADEs is provided in **Table 12**. Overall, the most frequent TEADEs in both treatment groups were headache and contusion.

Table 12: Treatment-Emergent Adverse Device Effects by Preferred Term (Reported in >2 Subjects in Total Group) After Initial/Touch-up Treatment (SAS)

Preferred Term	saypha MagIQ (N=270) n (%)	Control (N=270) n (%)	Total (N=270) n (%)
TEADEs	26 (9.6)	24 (8.9)	27 (10.0)
Headache	6 (2.2)	6 (2.2)	6 (2.2)
Contusion	4 (1.5)	4 (1.5)	4 (1.5)
Swelling	4 (1.5)	2 (0.7)	4 (1.5)
Eyelid margin crusting	3 (1.1)	3 (1.1)	3 (1.1)
Discomfort	3 (1.1)	3 (1.1)	3 (1.1)
Injection site erythema	3 (1.1)	1 (0.4)	3 (1.1)
Feeding disorder	2 (0.7)	2 (0.7)	2 (0.7)
Pruritus	2 (0.7)	1 (0.4)	2 (0.7)
Erythema	1 (0.4)	2 (0.7)	2 (0.7)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; TEADE, treatment-emergent device effect.
Note: Treatment, saypha MagIQ or Control, was based on the AE side of face; if AE side was not applicable, it was considered that the AE happened to both sides of the face. For each row category, a subject with 2 or more AEs in that category was counted only once. AEs were coded using MedDRA version 25.0.

Serious TEAEs after initial/touch-up treatment affected 3 subjects and included:

- Subject experienced retinal detachment (verbatim term: right eye retinal detachment) approximately 4 months after initial treatment (Control on left NLF and saypha MagIQ on right NLF), which required surgical intervention to prevent permanent damage.
  The event was moderate in severity and resolved with sequelae within 14 days. The event was considered not related to the study device and study procedure.
- Subject experienced vascular compression (verbatim term: external compression on aberrant vessel in left NLF) on the day of initial treatment with study device (Control on left NLF and saypha MagIQ on right NLF). Study device was explanted due to the event to prevent permanent damage.

  The event was moderate in severity and resolved within 28 days. The subject was withdrawn from the study due to the event. The event was considered related to the study device and study procedure. The event was rated as an Unanticipated Serious TEADE.
- Subject was hospitalized due to transient ischemic attack, 137 days after touch-up treatment with Control on the left NLF. The event was severe in severity and resolved

within 1 day with treatment. The event was considered not related to the study device and study procedure.

After repeat treatment with saypha MagIQ, TEAEs were reported for 4 (8.3%) subjects: COVID-19 (2 subjects), diabetes mellitus (1 subject), and tooth infection (1 subject). None of these events were considered related to the study device or study procedure.

The TEAE diabetes mellitus was considered **serious**:

- Subject was hospitalized due to diabetes mellitus (verbatim term: diabetes complication) 80 days after repeat treatment with study device (saypha MagIQ on both NLFs). The event was severe in severity and resolved within 50 days without treatment. The subject was withdrawn from the study due to the event.

  The event was considered not related to the study device and study procedure.

Pain at injection

Mean pain scores based on subject perception of pain at 15, 30, 45, and 60 minutes after initial or repeat treatment were comparable for saypha MagIQ and Control and did not exceed 0.4 at any time point for neither the initial nor the repeat treatment.

Extent of exposure

The mean injected volume required to achieve optimal correction at initial and touch-up treatment (combined) was 1.453 mL and 1.244 mL for the subjects who received treatment with saypha MagIQ and Control, respectively. The mean injected volume required to achieve optimal correction at repeat treatment at any visit with saypha MagIQ was 0.77 mL for NLFs that were initially treated with saypha MagIQ and 0.78 mL for NLFs that were initially treated with Control (**Table 13**).

Table 13: Volume Needed for Optimal Correction in Milliliter (mL) (SAF)

Injection Volume	**saypha MagIQ (N=270)**	**Control (N=270)**
Initial Treatment		
n (missing)	270 (0)	270 (0)
Mean (SD)	1.219 (0.5006)	1.028 (0.4382)
Touch-up Treatment		
n (missing)	147 (123)	152 (118)
Mean (SD)	0.429 (0.2260)	0.384 (0.1945)
Total of Initial and Touch-up Treatment		
n (missing)	270 (0)	270 (0)
Mean (SD)	1.453 (0.5208)	1.244 (0.4607)
Repeat Treatment - Week 36		
n (missing)	13 (257)	13 (257)
Mean (SD)	0.62 (0.282)	0.58 (0.209)

Injection Volume	saypha MagIQ (N=270)	Control (N=270)
Repeat Treatment - Week 48		
n (missing)	1 (269)	1 (269)
Mean (SD)	0.70 (N/A)	0.80 (N/A)
Repeat Treatment - Visit 7c		
n (missing)	34 (236)	34 (236)
Mean (SD)	0.83 (0.391)	0.86 (0.391)
Repeat Treatment – at any Visit		
n (missing)	48 (222)	48 (222)
Mean (SD)	0.77 (0.370)	0.78 (0.367)

Abbreviations: SAF, safety analysis set; N/A, not applicable
Note: n = Number of subjects who received repeat treatment. The repeat-treatment is performed with saypha MagIQ on both nasolabial folds.
Visit 7c denotes post repeat-treatment hold follow-up visit.

2. Effectiveness Results

The analysis of effectiveness was based on the 270 evaluable patients at the 24 week time point. Key effectiveness outcomes are presented in Tables **14** to **20**.

The primary effectiveness endpoint was the proportion of NLF-SRS responders at Week 24 compared with Control based on the independent blinded evaluating investigator's live assessments. Similar proportions of NLF-SRS responders showing at least a clinically significant 1-point improvement were found in the two treatment groups of the full analysis set (FAS) (82.2% of subjects with saypha MagIQ vs 81.9% of subjects with Control). The difference in the proportions of NLF-SRS was 0.37%, with the lower boundary of the 95% CI, -2.96, being above the non-inferiority margin of -10% (p-value <0.0001) (**Table 14**). Primary effectiveness endpoint analysis for the per-protocol set (PPS) is shown in **Table 15** and is consistent with the results obtained in the FAS. Therefore, saypha MagIQ was shown to be non-inferior to Control.

In the FAS, the proportion of subjects who had a 2-point (34.1% vs 30.4%) or 3-point (8.5% vs 6.7%) improvement from Baseline on the NLF-SRS was slightly higher after initial treatment with saypha MagIQ compared to Control. In the PPS, the proportion of subjects with improvement from Baseline on the NLF-SRS was with 34.8% vs 30.8% and 10.3% vs 7.6% for 2-point and 3- point improvement, respectively, higher in the saypha MagIQ group compared to the Control group, as with the FAS.

Table 14: Primary Effectiveness Endpoint: NLF-SRS Response Rate at Week 24 - Independent Blinded Evaluating Investigator (FAS)

NLF-SRS Change From Baseline	saypha MagIQ (N=270) n (%)	Control (N=270) n (%)	Difference of Proportions (%) (95% CI)[1]	p-value[2]
Responder[3]	222 (82.2)	221 (81.9)	0.37 (-2.96, 3.70)	<0.0001
Non-Responder (incl. missing)	48 (17.8)	49 (18.1)	-	-
Missing[4]	23 (8.5)	23 (8.5)	-	-

Abbreviations: FAS, full analysis set; NLF-SRS, nasolabial folds-severity rating scale.
Note: Percentage was based on the subjects in each treatment group of the FAS.
[1] Difference in proportion of responders saypha MagIQ – Control with respective 95% CI (calculated using the empirical standard error).
[2] The p-value corresponded to the 1-sided null hypothesis of equality to 10% (non-inferiority margin) of the difference between the paired proportions (McNemar type test).
[3] Responder was defined as a subject with at least 1 grade improvement from Baseline in NLF-SRS.
[4] Missing values at Week 24 were imputed as non-responder.

Table 15: Primary Effectiveness Endpoint: NLF-SRS Response Rate at Week 24 - Independent Blinded Evaluating Investigator (PPS)

NLF-SRS Change From Baseline	saypha MagIQ (N=224) n (%)	Control (N=224) n (%)	Difference of Proportions (%) (95% CI)[1]	p-value[2]
Responder[3]	187 (83.5)	187 (83.5)	-0.00 (-3.71, 3.71)	<0.0001
Non-Responder (incl. missing)	37 (16.5)	37 (16.5)	-	-
Missing[4]	15 (6.7)	15 (6.7)	-	-

Abbreviations: PPS, per-protocol analysis set; NLF-SRS, nasolabial folds-severity rating scale.
Note: Percentage was based on the subjects in each treatment group of the PPS.
[1] Difference in proportion of responders saypha MagIQ – Control with respective 95% CI (calculated using the empirical standard error).
[2] The p-value corresponded to the 1-sided null hypothesis of equality to 10% (non-inferiority margin) of the difference between the paired proportions (McNemar type test).
[3] Responder was defined as a subject with at least 1 grade improvement from Baseline in NLF-SRS.
[4] Missing values at Week 24 were imputed as non-responder.

The proportion of NLF-SRS responders as rated by the independent blinded evaluating investigator in the FAS was slightly higher after initial treatment with saypha MagIQ compared with Control at Week 12 (93.4% vs 91.1%), Week 36 (80.6% vs 78.8%), and Week 48 (76.9% vs 70.4%) (**Table 16**). In the PPS, the proportion of NLF-SRS responders after initial treatment with saypha MagIQ compared with Control was as follows: Week 12 (93.0% vs 91.5%), Week 36 (80.4% vs 78.3%) and Week 48 (76.8 vs 70.2%) (**Table 17**), consistent with the results obtained in the FAS.

Table 16: NLF-SRS Response Rate Over Time - Blinded Evaluating Investigator (FAS)

Timepoint	NLF-SRS Change From Baseline	saypha MagIQ (N=270) n (%)	Control (N=270) n (%)	Difference of Proportions (%)[c]
week 12 (n[d] = 257)	Responder[a]	240 (93.4)	234 (91.1)	2.33
	Non-Responder	17 (6.6)	23 (8.9)	-
	Missing[b]	13	13	-
week 36 (n[d] = 170)	Responder[a]	137 (80.6)	134 (78.8)	1.76
	Non-Responder	33 (19.4)	36 (21.2)	-
	Missing[b]	100	100	-
week 48 (n[d] = 186)	Responder[a]	143 (76.9)	131 (70.4)	6.45
	Non-Responder	43 (23.1)	55 (29.6)	-
	Missing[b]	84	84	-

Abbreviations: FAS, full analysis set. NLF-SRS = Nasolabial Folds Severity Rating Scale

[a] 'Responder' is defined as a subject with at least one grade improvement from Baseline in NLF-SRS.

[b] Subjects who do not have NLF-SRS assessment at baseline and/or at respective post-baseline visit are not considered in this analysis.

[c] Difference in proportion of responders saypha MagIQ – Control.

[d] n = Number of participants with available data at the specified time point.

The percentage is based on the subjects with results available at baseline and at respective post-baseline visit in each treatment group of Full Analysis Set.

Table 17: NLF-SRS Response Rate Over Time - Blinded Evaluating Investigator (PPS)

Timepoint	NLF-SRS Change From Baseline	saypha MagIQ (N=224) n (%)	Control (N=224) n (%)	Difference of Proportions (%)[c]
week 12 (n[d] = 213)	Responder[a]	198 (93.0)	195 (91.5)	1.41
	Non-Responder	15 (7.0)	18 (8.5)	-
	Missing[b]	11	11	-
week 36 (n[d] = 143)	Responder[a]	115 (80.4)	112 (78.3)	2.10
	Non-Responder	28 (19.6)	31 (21.7)	-
	Missing[b]	81	81	-
week 48 (n[d] = 151)	Responder[a]	116 (76.8)	106 (70.2)	6.62
	Non-Responder	35 (23.2)	45 (29.8)	-
	Missing[b]	73	73	-

Abbreviations: PPS, per-protocol analysis set. NLF-SRS = Nasolabial Folds Severity Rating Scale

[a] 'Responder' is defined as a subject with at least one grade improvement from Baseline in NLF-SRS.

[b] Subjects who do not have NLF-SRS assessment at baseline and/or at respective post-baseline visit are not considered in this analysis.

[c] Difference in proportion of responders saypha MagIQ – Control.

[d] n = Number of participants with available data at the specified time point.

The percentage is based on the subjects with results available at baseline and at respective post-baseline visit in each treatment group of Per-Protocol Set.

For both saypha MagIQ and Control, results showed a progressive increase in NLF-SRS, consistent with the reduced effect of the dermal fillers over time. A summary of actual values on the NLF-SRS and changes from Baseline over time is presented as assessed by the independent blinded photographic reviewers in **Table 18**.

Table 18: Summary of NLF-SRS Actual Values and Changes from Baseline Over Time - Independent Blinded Photographic Reviewer (FAS)

NLF-SRS Change From Baseline	n	saypha MagIQ		Control	
		NFL-SRS mean	change from baseline mean	NFL-SRS mean	change from baseline mean
baseline	270	2.3	-	2.4	-
week 12	258	1.2	-1.1	1.3	-1.1
week 24	247	1.3	-1.0	1.5	-0.9
week 36	192	1.3	-1.0	1.5	-0.9
week 48	191	1.3	-1.0	1.5	-0.9

Abbreviations: FAS, full analysis set; NLF-SRS, nasolabial folds-severity rating scale.

The GAIS Response Rate at Week 24, were determined by the independent blinded evaluating investigator and separately determined by the subject.

Similar proportions of subjects in each treatment group were GAIS responders at Week 24 based on the independent blinded evaluating investigator's live assessment (93.2% of subjects with saypha MagIQ, 92.8% of subjects with Control). The difference in the proportion of GAIS responders between treatments (saypha MagIQ vs Control) was 0.40% (**Table 19**).

The GAIS response rate based on the subject self-assessments (91.6% for each treatment) was consistent with the results based on the independent blinded evaluating investigator assessment (**Table 20**).

Table 19: GAIS Response Rate at Week 24 - Blinded Evaluating Investigator (FAS)

GAIS	saypha MagIQ (N=270) n (%)	Control (N=270) n (%)	Difference of Proportions (%)[1]
Responder[2]	232 (93.2)	231 (92.8)	0.40
Non-Responder	17 (6.8)	18 (7.2)	-
Missing[3]	21	21	-

Abbreviations: FAS, full analysis set; GAIS, Global Aesthetic Improvement Scale.
Note: Percentage was based on the subjects in each treatment group of the FAS.
[1] Difference in proportion of responders saypha MagIQ – Control.

[2] 'Responder' is defined as a subject with grading of 'improved', 'much improved' or 'very much improved' on the GAIS assessment.
[3] Subjects who do not have GAIS assessment at week 24 are not considered in this analysis.

Table 20: GAIS Response Rate at Week 24 - Subject (FAS)

GAIS	saypha MagIQ (N=270) n (%)	Control (N=270) n (%)	Difference of Proportions (%)[1]
Responder[2]	229 (91.6)	228 (91.6)	0.03
Non-Responder	21 (8.4)	21 (8.4)	-
Missing[3]	20	21	-

Abbreviations: FAS, full analysis set; GAIS, Global Aesthetic Improvement Scale.
Note: Percentage was based on the subjects in each treatment group of the FAS.
[1] Difference in proportion of responders saypha MagIQ – Control.
[2] 'Responder' is defined as a subject with grading of 'improved', 'much improved' or 'very much improved' on the GAIS assessment.
[3] Subjects who do not have GAIS assessment at week 24 are not considered in this analysis

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: Fitzpatrick Skin Type, Age, Gender, Race, Clinical Sites, Volume of injection, Baseline NLF-SRS score, and Injection Technique.

The study was not specifically powered for any of the subgroups.

The saypha MagIQ responder rates based on Blinded Evaluating Investigator assessment at the primary endpoint (week 24 after initial treatment) across all subgroups were generally similar and no clinically meaningful differences were observed.

In the saypha MagIQ group the responder rate at week 24:

- was generally similar between participants with Fitzpatrick Skin Type (FST) I-III (79.5%) and FST IV-VI (86.8%).
- was generally similar between participants 18-40 years of age (73.3%), participants 41-60 years of age (82.7%) and participants >60 years of age (82.9%).
- was generally similar between male (100%) and female (81.8%) participants.
- generally similar across White participants (80.5%), Black or African American participants (93.1%), American Indian or Alaska Native participants (90.0%) and participants of other races (80.0%).
- ranged from 61.5% to 96.2% across study sites.
- was generally similar in relation to injected volume 1-2 ml (85.8%) and >2ml (83.3%), but lower with injected volume <1ml (58.8%),
- was generally similar between participants with Baseline NLF-SRS score of 2 (70.1%) and 3 (90.2%)

- was generally similar between participants who received treatment trough retrograde technique (80.0%) or fan technique (89.2%)

The incidences of related (device or procedure) adverse events were similar between the subgroups (**Table 21**).

Table 21: Incidence of Related (device or procedure) Adverse Events after Initial Treatment

Subgroup	**saypha MagIQ n/N (%)**
Fitzpatrick skin type	
I-III	22/171 (12.9)
IV-VI	4/99 (4.0)
Age	
18-40	3/15 (20.0)
41-60	14/173 (8.1)
>60	9/82 (11.0)
Gender	
male	1/6 (16.7)
female	25/264 (9.5)
Race	
White	21/226 (9.3)
Black or African American	3/29 (10.3)
American Indian or Alaska Native	1/10 (10.0)
Others	1/5 (20.0)
Site	
001	2/27 (7.4)
002	3/22 (13.6)
003	2/26 (7.7)
004	3/29 (10.3)
005	0/30 (0)
006	6/31 (19.4)
007	4/18 (22.2)
008	1/26 (3.8)
010	2/26 (7.7)
011	3/35 (8.6)
Volume	
<1ml	1/34 (2.9)
1-2ml	22/212 (10.4)
>2ml	3/24 (12.5)

Subgroup	saypha MagIQ n/N (%)
Baseline NLF-SRS score	
2	12/107 (11.2)
3	14/163 (8.6)
Injection Technique	
Retrograde	16/205 (7.8)
Fan	10/65 (15.4)

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 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 10 investigators. None of the clinical investigators had disclosable financial interests/arrangements 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.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supportive Study FINO was a prospective, open-label, multicenter study conducted in Europe. saypha MagIQ had obtained the European Conformity (CE) mark in 2016 and this clinical investigation (post-market clinical follow-up) aimed to identify possible residual risks of saypha MagIQ to confirm clinical performance and safety of the device for the correction of moderate to severe NLFs. The medical device investigated in the FINO study was the same as the one investigated in the pivotal study.

Eligible subjects had to be at least 18 years of age and had to present with two (2) fully visible, approximately symmetrical NLFs, with each of the folds scoring 2-3 according to the 5-grade NLF-SRS.

The investigation included 5 visits. Subjects received treatment with saypha MagIQ on Day 0. Follow-up visits were performed 2, 4, 24, and 36 weeks after the initial treatment. A touch-up treatment could be administered at the Week 2 visit.

Primary effectiveness endpoints were the average change versus Baseline (Day 0) in the NLF-SRS grade at Week 24 as evaluated by the investigator, and the proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus Baseline at Week 24.

Secondary effectiveness endpoints were the changes from Baseline in the NLF-SRS grade at Weeks 4 and 36, the proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus Baseline at Weeks 4 and 36, the proportion of subjects with aesthetic

improvement, as evaluated by the investigator using GAIS, the subjects' satisfaction with aesthetic outcome of the treatment, the average pain intensity during and after treatment, as evaluated by the subject using an 11-point numeric pain rating scale (NPRS), and the proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus Baseline at Week 24, as evaluated by the independent reviewer of photographs.

Analyses of the primary and secondary endpoints were performed with descriptive statistics.

Occurrence and frequency of AEs were evaluated for safety.

A total of 60 subjects were treated with saypha MagIQ and 59 subjects completed the investigation; one (1) was lost to follow-up at Week 4. The mean injected volume at Baseline was 1.48 mL for the right NLFs, and 1.54 mL for the left NLFs. At Week 2, 20 subjects received touch-up treatment using a mean injected volume of 1.06 mL for the right NLFs, and 1.02 mL for the left NLFs.

All but one (1) subject were women; all were White (Caucasian) with a median age of 55.5 years.

Safety Results:

A total of 28 subjects (46.7%) reported 38 AEs. Most reported AEs were mild (26 AEs in 20 subjects) or moderate (11 AEs in 9 subjects). One (1) subject reported one (1) severe AE (papillary thyroid gland carcinoma), which was not related to the investigational medical device or the procedure.

'General disorders and administration site disorders' were the most frequently reported AEs (in 43.3% of subjects), which were injection site hematoma (26.7% of subjects), injection site pain (20%), and injection site swelling (3.3%) (**Table 22**). The injection site related AEs were all considered as adverse device effects (ADE)s, i.e. as definitely related to the procedure. All other AEs were each reported in one (1) subject only and were not considered ADEs. None of the reported AEs were assessed as related to the investigational medical device.

Table 22: Adverse Events by Preferred Term and System Organ Class (SAS)

System Organ Class Preferred Term	**saypha MagIQ** **(N=60)** **n (%)**
Gastrointestinal disorders	**1 (1.7)**
Lip hematoma	1 (1.7)
Lip swelling	1 (1.7)
General disorders and administration site	**26 (43.3)**
Injection site hematoma	16 (26.7)
Injection site pain	12 (20.0)
Injection site swelling	2 (3.3)
Infections and infestations	**2 (3.3)**
Hematoma infection	1 (1.7)
Periodontitis	1 (1.7)

System Organ Class Preferred Term	saypha MagIQ (N=60) n (%)
Injury, poisoning and procedural	**1 (1.7)**
Face injury	1 (1.7)
Neoplasms benign, malignant and unspecified	**1 (1.7)**
Papillary thyroid cancer	1 (1.7)
Skin and subcutaneous disorders	**1 (1.7)**
Actinic keratosis	1 (1.7)
Total	**28 (46.7)**

Abbreviations: SAS, safety analysis set

Most reported AEs were mild or moderate in intensity. One (1) subject reported one (1) severe AE (papillary thyroid gland carcinoma), which was not related to the investigational medical device or the procedure. All ADEs were mild or moderate. All AEs but one (1) had resolved by Week 36. One (1) AE (periodontitis) with no relationship to the investigational medical device or the procedure was still ongoing at the end of the investigation. All ADEs had resolved within a maximum of 25 days of their onset.

No deaths occurred during the investigation.

Two (2) AEs were serious and included moderate hematoma infection and papillary thyroid cancer. Both events were assessed as unrelated to the investigational medical device or the procedure and had resolved by the end of the investigation. No serious ADEs were reported.

In the subject-assessed pain rating based on the NPRS, the mean pain score was 1.5 immediately after Baseline treatment and 2.1 immediately after touch-up treatment at Week 2. For both treatments, the mean pain score was 0.0 at 15 minutes after each treatment.

Effectiveness Results:

All results are presented for the ITT set that included a total of 60 subjects.

The average NLF severity based on the NLF-SRS had improved by a mean of 1.80 grades from Baseline to Week 24. The proportion of subjects with an improvement (reduction) of ≥1 NLF severity grade was 96.7% (**Table 23**).

For all but one (1) subject NLF severity had improved from Baseline to all post-baseline visits. Only for one (1) subject, the improvement observed at Week 4 and Week 24 was not maintained until Week 36.

Table 23: Change in NLF severity from Baseline to Week 4, 24 and 36 (ITT, modITT, PP)

Analysis set	N	Visit	Mean (SD) of change in NLF severity	Number (%)[a] of subjects with ≥1 grade reduction
ITT	59	Week 4	-1.98 (0.40)	59 (98.3)
	59	Week 24	-1.80 (0.60)	58 (96.7)
	59	Week 36	-1.67 (0.61)	58 (96.7)
PP	58	Week 4	-1.98 (0.41)	58 (100.0)
	58	Week 24	-1.79 (0.60)	57 (98.3)
	58	Week 36	-1.66 (0.61)	57 (98.3)

[a] Percentages are based on the number of subjects in the analysis set.
ITT = intent-to-treat, N = number of subjects with evaluable data, NLF = nasolabial fold, PP = per protocol, SD = standard deviation.

The aesthetic improvement assessed by the investigator using the GAIS showed aesthetic improvement (score <4) in most subjects at Week 4 (98.3%), Week 24 (98.3%), and Week 36 (96.7%). For most subjects, the improvement was rated as 'very much improved' (GAIS score = 1) at all visits (75.0% at Week 4, 80.0% at Week 24, and 65.0% at Week 3).

In line with the investigator assessment, most subjects rated their satisfaction with the treatment as 'very satisfied' at all visits (85.0% at Week 4, 78.3% at Week 24, and 81.7% at Week 36).

The proportion of subjects with an improvement of the NLF severity based on the NLF-SRS by ≥1 grade from Baseline to Week 24 was assessed by an independent reviewer of photographs as 98.3%. At Weeks 4 and 36, the respective proportions were also 98.3%.

Based on the investigator's assessment, the proportions of subjects with an improvement of ≥2 NLF severity (NLF-SRS) grades were 88.3% at Week 4, 68.3% at Week 24, and 60.0% at Week 36.

saypha MagIQ was effective in reducing NLF severity. At the primary endpoint (Week 24) assessment, 96.7% of the ITT subjects demonstrated ≥1 grade improvement in their NLF severity based on the investigator's assessment of NLF-SRS compared with the Baseline status.

saypha MagIQ was also safe and well tolerated. Reported AEs were mostly mild or moderate. The one (1) severe AE and the two (2) serious AEs were not related to the medical device or the procedures, and no deaths were reported in the investigation.

XIII. 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 Advisory, an FDA advisory committee, for review and recommendation

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

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was the proportion of NLF-SRS responders at Week 24 compared with Control based on the independent blinded evaluating investigators' live assessments. Response was defined as at least 1-point improvement on the validated 5-point NLF-SRS.

Similar proportions of subjects were NLF-SRS responders (defined by improvement in the NLF-SRS from pre-injection ≥ 1-grade) in the two treatment groups in the Full Analysis Set (FAS, 82.2% of subjects with saypha MagIQ vs 81.9% of subjects with Control). The difference in the proportions of NLF-SRS responders was 0.37%, with the lower boundary of the 95% CI, -2.96, being above the non-inferiority margin of -10% (p-value <0.0001). Therefore, saypha MagIQ was shown to be non-inferior to Control in the FAS.

These results were confirmed in the Per Protocol Set (PPS) for the primary endpoint as well as for both, FAS and PPS, for the two key secondary effectiveness endpoints (NLF-SRS response at week 24 as assessed by the Independent Blinded Photographic reviewers as well as per the treating investigator, respectively). Results were further supported by results of the other secondary effectiveness endpoints.

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.

saypha MagIQ was generally safe and well tolerated. No clinically relevant differences were seen in the safety profile of saypha MagIQ compared to Control.

Treatment emergent adverse events (TEAEs) were reported for 66 (24.4%) subjects after initial/touch-up treatment with saypha MagIQ and 63 (23.3%) subjects after initial/touch-up treatment with Control. For a total of 26 (9.6%) subjects in the saypha MagIQ and 24 (8.9%) subjects in the saypha MagIQ groups, the TEAEs were considered related to the intradermal filler treatment, i.e. were reported as treatment-emergent adverse device effects (TEADEs). TEAEs that were considered related to the study procedure were reported for 21 (7.8%) subjects in the saypha MagIQ group and 21 (7.8%) subjects in the Control group. TEAEs that were considered related to the study device were reported for 15 (5.6%) subjects in the saypha MagIQ and 14 (5.2%) subjects in the Control. Most TEAEs were mild or moderate in severity.

Serious TEAEs were reported for 3 (1.1%) subjects after initial/touch-up treatment with saypha MagIQ and saypha MagIQ. Of these, 1 subject had a serious TEADE

(vascular compression), which was also considered as an unanticipated serious TEADE. No TEAE or TEADE leading to death was reported.

TEAEs of special interest were reported for 3 (1.1%) subjects after initial/touch-up treatment with saypha MagIQ and Control. A TEAE/TEADE that led to study withdrawal was reported for 1 (0.4%) subject after initial/touch-up treatment with saypha MagIQ and Control.

Overall, 243 (95.3%) subjects reported Injection Site Reactions (ISRs) after initial treatment with saypha MagIQ, and 238 (92.6%) subjects reported ISRs after initial treatment with Control. There were only slight differences in the reporting of ISRs between the treatment groups. The vast majority of ISRs were mild or moderate in intensity.

These findings from the pivotal study conducted in the US are supported by data from the supplemental study FINO conducted previously in Europe.

Given these overall results, the Company believes that there are adequate data to support a reasonable assurance of safety and effectiveness based on an objective assessment of the effects of saypha MagIQ in the treatment of moderate to severe Nasolabial Folds

C. Benefit-Risk Determination

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

The pivotal clinical trial was a randomized, subject- and evaluating investigator-blinded, controlled, multicenter, split-face, comparison clinical investigation to evaluate effectiveness and safety of saypha MagIQ in the correction of NLFs. The study was conducted in the US and used the FDA-approved HA dermal filler (Control) as active comparator. The study included 270 subjects with moderate to severe NLFs.

The primary endpoint was the proportion of responders, defined as an improvement of ≥1 point on the validated NLF-SRS (Naso-Labial Folds Severity Rating Scale) compared to baseline, evaluated by the independent blinded investigator live assessment at Week 24. In the FAS a response rate was achieved by 82.2% (222 of 270 subjects) treated with saypha MagIQ and 81.8% (221 of 270 subjects) in the control group (p-value <0.0001). Analyses of the key secondary effectiveness endpoints confirmed the primary results. In both the assessment of independent blinded photographic reviewers, as well as the live assessment of the treating investigator, the non-inferiority criterion was fulfilled regarding the proportion of NLF-SRS responders at Week 24 (p-value = 0.025 and p-value <0.0001, respectively). These results indicate that saypha MagIQ is at least as effective as the FDA-approved Control.

The results of the primary and key secondary endpoints were supported by the results from the other secondary endpoints.

At week 12 93.4% (240 of 257) of Subjects experienced a ≥1-point improvement in the Nasolabial folds compared to 91.1% (234 of 257) of the control group. The treatment effect at Week 36 was 80.6% (137 of 170) of subjects experiencing an improvement of 1-point or greater compared to 78.8% (134 of 170) in the control group. By week 48 the responder rate of saypha MagIQ was 76.9% (143 of 186) of subjects while the control group had 70.4% (131 of 186).

The Global aesthetic improvement Response Rate as assessed by the Blinded Evaluating Investigator at Week 24 was 93.2% (232 of 270) for subjects treated with saypha MagIQ and 92.8% (231 of 270) for the control group.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. A thorough safety assessment was conducted in this study providing a robust safety dataset as further evidence of a positive benefit/risk assessment of treatment with saypha MagIQ.

Nearly all subjects (95.3%, 243/255 after initial treatment) experienced an injection site reaction, which included firmness (80.4%), swelling (75.7%), lumps/bumps (71.0%), tenderness to touch (69.8%), redness (67.5%), bruising (67.1%), pain after injection (45.9%), itching (28.6%), discoloration (24.7%) and other (19.2%). The vast majority of ISRs were mild or moderate in intensity. 13.7% of ISRs were considered severe.

The most commonly reported study device-related TEAEs were discomfort and eyelid margin crusting (1.1% each), and swelling, erythema, pruritus, headache, and feeding disorder (0.7% each). The most commonly reported study procedure-related TEAEs were headache (2.2%), contusion (1.5%), discomfort and injection site erythema (1.1% each), and swelling and eyelid margin crusting (0.7% each).

Treatment with saypha MagIQ was generally safe and well tolerated. In the pivotal study, the percentages of subjects with TEAEs as well as the types of TEAEs were comparable for the saypha MagIQ and Control treatment groups and did not occur at rates different from those expected.

Additional factors to be considered in determining probable risks and benefits for the saypha MagIQ injection included:

No meaningful outcome differences regarding safety and effectiveness were found in the subgroup analyses for Fitzpatrick Skin Type, Age, Gender, Race, Clinical Sites, Volume of injection, Baseline NLF-SRS score, and Injection Technique.

Additional factors to be considered in determining probable risks and benefits for the saypha MagIQ included:

1. Patient Perspective
   Patient perspectives considered during the review included:
   - Global aesthetic improvement as assessed by the subject. GAIS response rate based on the subject self-assessments was 91.6% at Week 24 after initial treatment.

- Impact and effectiveness of study treatment from the subjects' perspective as assessed by the nasolabial fold domain of the validated FACE-Q patient-reported outcome measurement. Subject satisfaction was high with a mean score of 70.0 at Week 24 after initial treatment.
- The mean pain scores based on subject perception of pain were generally low and did not exceed 0.4 on the 11-point pain scale at any timepoint.

Supportive Study FINO was a prospective, open-label, multicenter study conducted in Europe and aimed to identify possible residual risks of saypha MagIQ to confirm clinical performance and safety of the device for the correction of moderate to severe NLFs. The study included 60 subjects with moderate to severe NLFs.

Primary effectiveness endpoints were the average change versus baseline in the NLF-SRS grade at Week 24 as evaluated by the investigator, and the proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24. Secondary effectiveness endpoints included the proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus Baseline at Weeks 4 and 36, proportion of subjects with aesthetic improvement as evaluated by the investigator using GAIS.

At week 24 96.7 % (58 of 60) of subjects experienced a ≥1-point improvement in the NLFs

At week 12 98.3% (59 of 60) and at week 36 96.7 % (58 of 60) of subjects experienced a ≥1-point improvement in the NLFs, respectively

The aesthetic improvement assessed by the investigator using the GAIS showed aesthetic improvement in most subjects at Week 4 (98.3%), Week 24 (98.3%), and Week 36 (96.7%). For most subjects, the improvement was rated as 'very much improved' (GAIS score = 1) at all visits (75.0% at Week 4, 80.0% at Week 24, and 65.0% at Week 3).

Device or procedure related injection site reactions were reported in 43.3% (26 of 60) of subjects, which included hematoma (26.7%), pain (20.0%) and swelling (3.3%). All were mild or moderate in severity.

In conclusion, given the available information above, the data support the use of saypha MagIQ for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) 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. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XV. CDRH DECISION

CDRH issued an approval order on September 8, 2025.

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

XVI. 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.

XVII. REFERENCES