SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: saypha® ChIQ™

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: P250021

Date of FDA Notice of Approval: 6/12/2026

II. INDICATIONS FOR USE

saypha® ChIQ™ is indicated for use in cheek augmentation and restoring midface volume deficits in patients over the age of 21. The device is indicated to be administered by subcutaneous and/or supraperiosteal injection.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the saypha® ChIQ™ labeling.

V. DEVICE DESCRIPTION

saypha® ChIQ™ is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, and homogeneous gel used as soft tissue filler. It consists of hyaluronic acid (HA), produced by *Streptococcus* species of bacteria, which is cross-linked with BDDE (1,4-butanediol diglycidyl ether). It is formulated to a concentration of 23 mg/mL in a phosphate buffered saline at physiological pH and contains 3 mg/mL lidocaine hydrochloride to reduce pain and discomfort upon injection. The gel is supplied in a prefilled glass syringe, and the contents of the syringe are steam sterilized.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for cheek augmentation and correction of midface volume deficits including other hyaluronic acid dermal filler products, autologous fat injection or transposition, surgery, and acellular dermal graft treatment. 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® ChIQ™ received the CE Mark in March 2016 for creating volume in order to correct wrinkles, folds, and moderate to severe nasolabial folds. Currently, saypha® ChIQ™ 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® ChIQ™ 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.

Common treatment responses which can occur with the use of saypha® ChIQ™ include tenderness, swelling, firmness (induration), lumps/bumps (mass), bruising, pain, redness, discoloration, and itching.

In addition to the common treatment responses noted above, the following adverse events reported in the pivotal clinical study include headache, palpatory finding abnormal, injection site pain, injection site bruising, injection site swelling, injection site mass and mastication disorder, jaw disorder, nodule and skin laxity.

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 viscoelastic dermal filler implants and are considered as potential risks for this device: abscess, angioedema, bacterial infection, device dislocation, dizziness, fever, fibrosis, granuloma, hematoma, hemorrhage/bleeding, herpes simplex reactivation, hypersensitivity/allergic reaction, hypoesthesia, itching sensation, malaise, medical device site induration, nausea, necrosis, numbness, obstruction/occlusion, paresthesia, peeling, phlebitis, physical asymmetry, presyncope, rash, scleroderma, sebaceous hyperplasia, skin burning sensation, skin disorders, skin inflammation/irritation, syncope/fainting, tactile disorder.

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

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

Table 1. Summary of Key Bench Testing on saypha® ChIQ™

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

Test	Purpose	Results
Content Sodium Hyaluronate	Ensures content sodium hyaluronate meets specification	Passed
Residual Crosslinker	Ensures residual crosslinker meets specification	Passed
Endotoxin	Ensures endotoxin meets specification	Passed
Sterility	Ensures sterility meets specification	Passed
Content Lidocaine	Ensures content lidocaine meets specification	Passed
Purity Lidocaine	Ensures purity lidocaine meets specification	Passed

B. Biocompatibility Testing

A biological evaluation was performed on saypha® ChIQ™ 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® ChIQ™ 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 saypha® ChIQ™ is biocompatible.

Table 2. Summary of Biocompatibility Testing on saypha® ChIQ™

Test	Method	ISO Standard	Results
Chemical Characterization and Toxicological Risk Assessment	HS GC-MS GC-MS, HPLC-MS, ICP-MS	ISO 10993-18 ISO 10993-17	Passed
Cytotoxicity	Agarose overlay, XTT 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	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

Test	Method	ISO Standard	Results
Pyrogenicity	Rabbit pyrogen study	USP <151>	Non pyrogenic
Genotoxicity	Bacterial reverse mutation, chromosomal aberration, micronucleus	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® ChIQ™ are minimal and in the same range of acceptable cancer risks as other previously approved dermal filler products.

C. Additional Studies

Filled syringes were sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle was validated according to ISO 17665-1 sterilization standard. The validated sterilization cycle provided 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.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of saypha® ChIQ™ for midface augmentation in order to correct volume deficit in the US under IDE G210347. Data from this clinical study were the basis for the PMA approval decision.

A summary of the clinical study is presented below.

A. Study Design

Patients were treated between September 16, 2022 and June 17, 2024. The database for this PMA reflected data collected through February 11, 2025 and included 483 patients. There were 16 investigational sites.

The study was a randomized, subject- and evaluator-blinded, controlled, non-inferiority multicenter, parallel group comparison study to evaluate effectiveness and safety of saypha® ChIQ™ for midface augmentation in order to correct volume deficit.

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

The primary endpoint was non-inferiority in the effectiveness of saypha® ChIQ™ for midface augmentation to correct moderate to severe volume deficit versus Control, based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase and compared to baseline assessments.

Secondary objectives were to assess the effectiveness of saypha® ChIQ™ versus Control for correction of moderate to severe midface volume deficit, based on the blinded evaluator's live assessment (except Week 24 after last injection of initial treatment phase for responder rate), and on the independent blinded photographic reviewers assessment (initial treatment phase only). Further secondary objectives were to assess the mean change in midface volume deficit as measured by volumetric change measurement by using 3D digital photographic images (initial treatment phase only), and to assess the effect of midface treatment with saypha® ChIQ™ on the nasolabial folds (NLFs) based on the blinded evaluator´s live assessment.

Other secondary objectives included the evaluation of global aesthetic improvement based on subject's assessments (initial treatment phase only) and based on the blinded evaluator's assessments (initial treatment

phase only), the subject's satisfaction with outcome and appearance appraisal, and the subject's pain assessment and injection volume.

Eligible subjects were randomized in a 2:1 ratio (test device:comparator device) to receive bilateral midface augmentation treatment with either saypha® ChIQ™ or Control. The dosage (volume) of filler administered depended on the severity of the midface volume deficit to be corrected and was decided in each case by the treating investigator, but the maximum volume (left and right side of the midface together) was not allowed to exceed 10 mL in total per treatment phase (initial and repeat-treatment, respectively, including touch-up treatments) or 20 mL per 60 kg (130 lbs) body mass per year. The treating investigator administered the treatment unblinded. Subjects were blinded to the treatments they received until finalization of Visit 9 (SV1). The blinded evaluator at the site performing live assessments of treatment effectiveness during the initial treatment phase, as well as the central independent blinded photographic reviewers were blinded to the treatment administered.

Clinical data sources included investigator assessments (Midface Volume Deficit Severity Scale (MVDSS), Nasolabial Folds Severity Rating Scale (NLF-SRS) and modified Global Aesthetic Improvement Scale (GAIS)) central independent blinded photographic reviewer assessments (MVDSS), subject-reported outcome measures (FACE-Q™ questionnaires and modified GAIS), volumetric change measurements based on standardized 3D photography, subject diaries, clinical examinations, and adverse event reporting.

The primary effectiveness endpoint was analyzed in both the Per-Protocol Set (PPS) and Full Analysis Set (FAS). A hierarchical testing procedure was applied, with initial testing performed in the PPS and subsequent testing in the FAS. Non-inferiority was considered demonstrated only if results were consistent across both analysis populations. Safety analyses were performed using the Safety Analysis Set (SAF).

1. Clinical Inclusion and Exclusion Criteria

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

- Male or female subjects aged 22 – 75 years (inclusive) of age at Screening
- Subjects with bilateral, approximately symmetric moderate to severe midface volume deficit (severity scores of 2 or 3 on the 5-point MVDSS), as assessed by the blinded evaluator at the site
- Females of childbearing potential must have a negative urine pregnancy test and must agree to use an effective method of birth control throughout the entire study
- Male subjects with female partners of child-bearing potential must agree to use contraception throughout the entire study (surgical sterilization or a physical barrier such as a condom)
- Healthy skin in the midface 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 entire investigation, including botulinum toxin injection (except glabella or forehead botulinum toxin treatment)
- Subjects who understand the purpose and conduct of the study and having given written informed consent and are willing and able to attend the study visits as judged by the investigator

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

- Females, who are pregnant and/or, lactating or planning to become pregnant during the clinical investigation
- History of severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies
- History of hypersensitivity to hyaluronic acid preparations, lidocaine or any amide-based anesthetic
- Tendency to keloid formation and/or hypertrophic scars and/ or have pigment disorders
- Known human immune deficiency virus-positive individuals
- Presence of infectious, inflammatory or proliferative cancerous or pre-cancerous lesions in the treatment area

- Re-current (three times a year over the last year) herpes simplex in the treatment area
- History or presence of any autoimmune or connective tissue disease, or current treatment with immuno-modulating therapy
- Uncontrolled (or unstable) diabetes mellitus or systemic diseases as per investigator discretion
- Previous facial plastic surgery, tissue augmentation with silicone, fat or another non-absorbable substance (permanent fillers) and semi-permanent / long-lasting fillers (e.g., *poly*-L-*lactic* acid (PLLA), Polymethylmethacrylate (PMMA) filler) in the area of device application and during the entire investigation
- Implantation of dermal fillers in the treatment area within the preceding 24 months prior to Visit 1 (Screening) and during the entire investigation
- Subject has received any of the following aesthetic treatments in the midface area: e.g., laser therapy, absorbable and non-absorbable sutures (threads), dermabrasion, mesotherapy, micro-needling and/or botulinum toxin (including treatment of crow´s feet in the outer eye region) within the last 12 months prior to Visit 1, chemical peeling within the last three months prior to Visit 1 or is planning to undergo such procedures during entire investigation
- Facial lipolysis, including submental fat treatments, within the previous 12 months prior to Visit 1 (Screening) and during the entire investigation
- Bariatric surgery within 12 months prior to Visit 1 (Screening) and during the entire investigation
- History of bleeding disorder and/or use of anticoagulant, antiplatelet, thrombolytic medication, anti-inflammatory drugs (oral/injectable corticosteroids or non-steroidal anti-inflammatory drugs, e.g., Motrin® or Advil®) or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., St. John's Wort, high doses of vitamin E supplements) from ten days pre- to seven days post injection (baseline treatment and touch-up treatment)
- Planned dental/oral surgery or modification (bridge-work, implants) within four weeks prior to each injection and to a minimum of four weeks post injection (baseline treatment and touch-up treatment)
- Beard longer than three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator
- Subjects who have one of the following assessments during the visual examinations at Visit 2 (Baseline): Snellen visual acuity test worse than 20/40 (with corrective eyewear, if applicable), abnormal confrontational visual field test, or abnormal ocular motility test.
- Subjects with active COVID-19 infection and subjects with symptoms consistent with COVID-19 infection including any other respiratory symptoms/illnesses within the past 14 days unless tested negative prior to Visit 1 (Screening)
- Any medical condition prohibiting the inclusion in the study according to the judgment of the treating investigator
- Previous enrollment in this clinical investigation
- Current participation in another clinical trial, or treatment with any investigational drug/medical device within 30 days prior to Visit 1 (Screening) or within five half-lives of an investigational drug, whichever is longer and during the entire investigation
- Midface volume deficit due to a congenital defect, trauma, or abnormalities in facial adipose tissue distribution such as those associated with HIV related lipodystrophy
- Subjects who experienced weight loss for a minimum of 10% over the last 12 months (e.g., post bariatric patients), or subjects who have the intention to change eating habits that result in a weight gain or loss >10% during the entire investigation
- Any individual whose willingness to volunteer in this clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate (e.g., persons with a legal

custodian appointed due to mental disability, prisoners, soldiers and other members of the armed forces, civil servants)

- Close affiliation with the investigator (e.g., a close relative, financially dependent on the study site) or subject who is an employee of the Sponsor's company or group companies of the Sponsor.

2. Follow-up Schedule

All patients were scheduled to return for follow up examinations at 4, 8, 16, 24, 36 and 48 weeks after last treatment.

Subjects who were eligible and willing could receive optional repeat-treatment (with saypha® ChIQ™ only) 48 to 60 weeks after initial treatment (or touch-up treatment). If necessary, an optional touch-up treatment was performed 2 weeks after the repeat-treatment. Follow-up visits were performed at Weeks 4, 12 and 24 after last treatment of the repeat-treatment phase. In case of touch-up treatment during initial and repeat-treatment phase, an additional safety follow-up visit 2 weeks after touch-up injections occurred. Subjects who did not qualify for any retreatment had their end of study visit at Week 48 (Visit 9).

Clinical photography was taken at Screening, and at the follow-up visits for 4, 8, 16, 24, 36, and 48 weeks.

At the end of each treatment session, subjects received a web-based electronic diary to record the injection site reactions (ISRs) and AEs (including those that were potentially associated with unintended intravascular injection) that occurred during the first 4 weeks (28 days) after each treatment (i.e., 4 weeks after baseline and repeat-treatment, respectively, and 6 weeks in case of touch-up treatment).

Preoperatively, pretreatment procedures and evaluations included: Informed Consent, medical/aesthetic procedure history, demographics, Fitzpatrick Skin Type, body weight, visual examinations, urine pregnancy test, MVDSS – blinded evaluator at site, MVDSS – central blinded photographic reviewer, NLF-SRS –blinded evaluator at site, Volumetric Change Measurements, Assessment of eligibility, randomization, clinical photography, FACE-Q™ "Satisfaction with Cheeks" – subject, ", and prior concomitant treatments.

Postoperatively, the objective parameters measured during the study included body weight, visual examinations, neurological examination, urine pregnancy test, prior concomitant treatments, MVDSS – blinded evaluator at site, MVDSS – central blinded photographic reviewer, NLF-SRS –blinded evaluator at site, Volumetric Change Measurements, Assessment of eligibility, clinical photography, Assessment of eligibility, Modified GAIS – blinded evaluator at site, Modified GAIS – subject, FACE-Q™ "Satisfaction with Outcome" – subject, FACE-Q™ "Satisfaction with Cheeks" – subject, Evaluation of pain – subject (Numeric Pain Rating Scale (NPRS). Adverse events and complications were recorded at all visits.

The key timepoints are shown below in Tables 3, 4 and 5.

Table 3. *Schedule of procedures and assessments for the initial treatment phase (Visit 1-to Visit 9 (SV1) (all subjects)*

			Follow-up for initial treatment (baseline and touch-up treatment) (initial treatment phase)									
Visit	**Visit 1 Screening [0]**	**Visit 2 Baseline [0]**	**Visit 2a Phone contact**	**Visit 3 TUP1**	**Visit 3a Phone contact [13]**	**Visit 3b Safety Follow-up[13]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9 (SV1)[21, 24]**
Day / week	Day-14 to Day 0	Day 0	24 – 48 hours after Day 0	2 weeks after BL injection	24 – 48 hours after Visit 3	2 weeks after TUP1 injection	4 weeks after last injection [22]	8 weeks after last injection [22]	16 weeks after last injection [22]	24 weeks after last injection [22]	36 weeks after last injection [22]	48 weeks after last injection[22]
Visit window			± 4 hours	± 3 days	±4 hours	±3 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days
Procedure												
Informed consent	X*											
Medical History [10]	X	X*										
Aesthetic History	X	X*										
Prior and concomitant treatments [1]	X	X*	X	X	X	X	X	X	X	X	X	X
Demographics [2]	X*											
Fitzpatrick skin type	X*											
Body weight	X*						X	X	X	X	X	X
Urine pregnancy test [3]	X	X*		X*		X	X	X	X	X	X	X
Visual examinations [11]		X[11]		X [11]		X	X	X	X	X	X	X
Neurological examinations [17]		X		X		X	X	X	X	X	X	X
Clinical photography	X*[25]						X	X	X	X	X	X
MVDSS – blinded evaluator at site	X*[4]			X*			X	X	X	X	X	X[4]
MVDSS – central blinded photographic reviewer [5]	X						X	X	X	X	X	X

			Follow-up for initial treatment (baseline and touch-up treatment) (initial treatment phase)									
Visit	**Visit 1 Screening [0]**	**Visit 2 Baseline [0]**	**Visit 2a Phone contact**	**Visit 3 TUP1**	**Visit 3a Phone contact [13]**	**Visit 3b Safety Follow-up[13]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9 (SV1)[21, 24]**
Day / week	Day-14 to Day 0	Day 0	24 – 48 hours after Day 0	2 weeks after BL injection	24 – 48 hours after Visit 3	2 weeks after TUP1 injection	4 weeks after last injection [22]	8 weeks after last injection [22]	16 weeks after last injection [22]	24 weeks after last injection [22]	36 weeks after last injection [22]	48 weeks after last injection[22]
Visit window			± 4 hours	± 3 days	±4 hours	±3 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days
Procedure												
NLF-SRS – blinded evaluator at site [18]	X*			X*			X	X	X	X	X	X
Volumetric Change Measurements [12]	X						X	X	X	X	X	X
Assessment of eligibility	X	X*		X*[13]								X[15]
Randomization		X*										
Treatment		X		X [16]								
Modified GAIS [6] – blinded evaluator at site							X	X	X	X	X	X
Modified GAIS [6] – subject							X	X	X	X	X	X
FACE-Q™ "Satisfaction with Outcome" – subject [7]							X	X	X	X	X	X
FACE-Q™ "Satisfaction with Cheeks" – subject [8]		X*					X	X	X	X	X	X
Evaluation of pain – subject (NPRS) [9]		X		X[13]								
Injection volume [23]		X		X[13]								

			Follow-up for initial treatment (baseline and touch-up treatment) (initial treatment phase)									
Visit	**Visit 1 Screening [0]**	**Visit 2 Baseline [0]**	**Visit 2a Phone contact**	**Visit 3 TUP1**	**Visit 3a Phone contact [13]**	**Visit 3b Safety Follow-up[13]**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9 (SV1)[21, 24]**
Day / week	Day-14 to Day 0	Day 0	24 – 48 hours after Day 0	2 weeks after BL injection	24 – 48 hours after Visit 3	2 weeks after TUP1 injection	4 weeks after last injection [22]	8 weeks after last injection [22]	16 weeks after last injection [22]	24 weeks after last injection [22]	36 weeks after last injection [22]	48 weeks after last injection[22]
Visit window			± 4 hours	± 3 days	±4 hours	±3 days	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days
Procedure												
Initiate / Explain subject diary [19]		X		X[13]								
Review subject diary [20]				X		X	X					
Adverse events [14]	X	X	X	X	X	X	X	X	X	X	X	X
Device deficiencies		X		X[13]								

*	Prior to injection (i.e., either at baseline or touch-up treatment (TUP1))
0	Screening and Baseline visits may be performed as **one visit**
1	Includes information on prior treatments, defined as all medications and non-drug therapies taken/received within the previous ten days prior to Screening up to end of study
2	Includes date of birth, sex, race and ethnicity
3	In women of childbearing potential only, including those who are postmenopausal for less than 12 months
4	Evaluation and grading of midface volume deficit by the **blinded evaluator at the site** (live assessment) using the 5-point MVDSS. The score does not have to be the same on both sides but must be 2 or 3.
5	Evaluation and grading of midface volume deficit severity by the **central independent blinded photographic reviewer** using the 5-point MVDSS and based on photographs
6	Evaluation of global aesthetic improvement using the modified GAIS against subject's photographs obtained at the Visit 1
7	Subject satisfaction will be determined using the FACE-Q™ questionnaire "Satisfaction with Outcome"
8	Evaluation of subject appearance appraisal using the FACE-Q™ questionnaire "Satisfaction with Cheeks"
9	NPRS starting immediately and every 15 min after last injection for 60 min post-treatment. Separate pain assessments will be performed for the right and left midface area treated.
10	Relevant medical history includes prior and ongoing concomitant diseases and possibly recurring conditions
11	Visual exams (including Snellen visual acuity, confrontational visual fields and ocular motility). The subject should wear the same corrective eyewear (i.e., glasses/contact lenses) at each assessment, if appropriate. **At treatment visits:** Examination will be performed **both before and 30 min after the injection**. For subjects **not** receiving TUP, exams will only be performed **once**.
12	Volumetric change measurement on photographs will be done centrally by the photography provider once the photography images are received at the photography provider after all subjects have finalized Visit 9 (SV1). The left and right midface will be evaluated separately.
13	Concerning only subjects who receive touch-up treatment
14	All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection or other events indicating an embolic event.

15	Repeat-treatment is optional and possible for all subjects who fulfill the eligibility criteria, irrespective of the treatment (either test device or comparator device) they received in the initial treatment (baseline plus touch-up). The subject does NOT have to return to his/her baseline severity to be permitted to receive a repeat-treatment, but the present condition of midface volume deficit has to meet the initial inclusion level of severity scores of 2 or 3 on the 5-point MVDSS. The score does not have to be the same on both sides but must be 2 or 3. In case the subject is eligible in MVDSS score at Visit 9 (SV1), a full eligibility assessment for repeat-treatment will be performed.
16	Touch-up treatment for optimal correction if deemed necessary in the discretion of **treating investigator**
17	A basic neurological examination (F.A.S.T) will be performed for all subjects who show signs of ophthalmic complications due to filler injection in visual exams
18	Evaluation and grading of nasolabial folds severity by the **blinded evaluator at the site** (live assessment) using the 5-point NLF-SRS
19	Explain diary use incl. documentation of injection site reactions / symptoms of interest to the subject.
20	Review subject diary regarding injection site reactions / symptoms of interest; confirm review. **Note:** Subjects will record injection site reactions, and symptoms of interest (i.e., changes in vision or symptoms of stroke) over the first four weeks (28 days) after each treatment (i.e., 4 weeks after baseline treatment, and 6 weeks in case of touch-up treatment).
21	In case of Early Termination attempts should be made to perform the assessments described for Visit 9 (SV1).
22	Last injection always either refers to initial treatment (BL) or touch-up treatment (TUP1)
23	Injection volume will be documented by site of the midface (left/right) and for each of the 3 anatomical areas of midface treatment (anteromedial cheek, submalar, and zygomaticomalar)
24	Visit 9 (SV1) will be the end of study visit, in case an inclusion criterion is not met / an exclusion criterion is met for optional repeat-treatment and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment.
25	In addition to clinical photography (3D photos), another baseline photo (2D) should be taken on-site at Visit 1.
Abbreviations: MVDSS: Midface Volume Deficit Severity Scale; NLF-SRS: Nasolabial Folds Severity Rating Scale; GAIS: Global Aesthetic Improvement Scale; NPRS: Numerical Pain Rating Scale; SV: Screening Visit; TUP1: Touch-up treatment after baseline treatment	

Table 4*. Schedule of procedures and assessments for screening phase for repeat-treatment (Visit SV2 to SV4)*

	Screening phase for repeat-treatment		
Visit	**Visit SV2** [3] (optional)*	**Visit SV3** [3] (optional)*	**Visit SV4** [3] (optional)*
Day / week	4 weeks after Visit 9 (SV1)	8 weeks after Visit 9 (SV1)	12 weeks after Visit 9 (SV1)
Visit window	±7 days	±7 days	±7 days
MVDSS [1]– blinded evaluator at site [2]	X	X	X
Concomitant treatments [4]	X	X	X
Adverse events [5]	X	X	X

*	Visits SV2 to SV4 are optional. As soon as the subject is eligible in MVDSS score, a full eligibility assessment for optional repeat-treatment will be done and Visit RT1 will be performed.
1	Subjects do not have to return to their baseline severity of midface volume deficit to be eligible and receive a repeat-treatment, but the present condition of midface volume deficit has to meet the initial inclusion level of severity scores of 2 or 3 on the 5-point MVDSS. The score does not have to be the same on both sides but must be 2 or 3.
2	Midface volume deficit severity is determined by the blinded evaluator. **Note:** The **blinded evaluator at the site** is *not* blinded for treatment allocation during the repeat-treatment phase. However, he/she will be still blinded for the treatment a subject received during the initial treatment phase
3	Visit SV4 will be the end of study visit for subjects who do *not* qualify for repeat-treatment. In case an inclusion criterion is not met / an exclusion criterion is met during the screening phase for repeat-treatment and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment, SV 2 or SV 3 will be the end of study visit for the respective subject.
4	All medications taken and non-pharmacological procedures applied by a subject during the course of a clinical study.
5	All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection or other events indicating an embolic event.
Abbreviations: MVDSS: Midface Volume Deficit Severity Scale; SV: Screening Visit; RT: Repeat Treatment	

Table 5. *Schedule of procedures and assessments for repeat-treatment phase (Visits RT1 to RT5)*

	Repeat-treatment and Follow-up for repeat-treatment (repeat-treatment phase)							
Visit	**Visit RT1 [0]**	**Visit RT1a** **Phone contact**	**Visit RT2** **TUP2**	**Visit RT2a [13]** **Phone contact**	**Visit RT2b[13]** **Safety Follow-up**	**Visit RT3**	**Visit RT4**	**Visit RT5** **(EOS)[21]**
Day / week	Up to 14 days after Screening Visit †	24 – 48 hours after RT1	2 weeks after RT1 injection	24 – 48 hours after RT2	2 weeks after TUP2 injection	4 weeks after last injection [22]	12 weeks after last injection [22]	24 weeks after last injection [22]
Visit window		± 4 hours	± 3 days	± 4 hours	±3 days	± 5 days	± 7 days	± 7 days
Procedure								
Assessment of eligibility	X*		X*[13]					
Concomitant treatments [1]	X*	X	X	X	X	X	X	X
Body weight	X*		X			X	X	X
Urine pregnancy test [2]	X*		X*		X	X	X	X
Visual examinations [8]	X		X		X	X	X	X
Neurological examinations [17]	X		X		X	X	X	X
MVDSS – blinded evaluator at site [3]	X*		X*			X	X	X
NLF-SRS – blinded evaluator at site [4]	X*		X*			X	X	X
Treatment	X		X [16]					
FACE-Q™ "Satisfaction with Outcome" – subject [6]	X*		X*			X	X	X

	Repeat-treatment and Follow-up for repeat-treatment (repeat-treatment phase)							
Visit	**Visit RT1 [0]**	**Visit RT1a**	**Visit RT2**	**Visit RT2a [13]**	**Visit RT2b[13]**	**Visit RT3**	**Visit RT4**	**Visit RT5**
		Phone contact	**TUP2**	**Phone contact**	**Safety Follow-up**			**(EOS)[21]**
Day / week	Up to 14 days after Screening Visit †	24 – 48 hours after RT1	2 weeks after RT1 injection	24 – 48 hours after RT2	2 weeks after TUP2 injection	4 weeks after last injection [22]	12 weeks after last injection [22]	24 weeks after last injection [22]
Visit window		± 4 hours	± 3 days	± 4 hours	±3 days	± 5 days	± 7 days	± 7 days
Procedure								
FACE-Q™ "Satisfaction with Cheeks" – subject [7]	X*		X*			X	X	X
Evaluation of pain – subject (NPRS) [9]	X		X[13]					
Injection volume [23]	X		X[13]					
Initiate / Explain subject diary [19]	X		X[13]					
Review subject diary [20]			X		X	X		
Adverse events [10]	X	X	X	X	X	X	X	X
Device deficiencies	X		X[13]					

*	Prior to injection (i.e., either at repeat-treatment or touch-up treatment (TUP2))
†	Visit RT1 may be performed up to 14 days after Screening Visit case the subject qualifies for repeat-treatment at one of these Visits. Screening Visit are Visit 9 (SV1) to SV4.
0	Screening Visits (i.e., Visit 9 (SV1) to SV4) and Visit RT1 may be performed as **one visit** in case the subject qualifies for repeat-treatment at one of these visits. In case of only one visit, the following assessments do not need to be done twice - Visit 9 (SV1) = RT1: * pre-treatment assessments at Visit RT1 - Visits SV2 to SV4 = RT1: MVDSS by blinded evaluator, concomitant treatments, adverse events
1	Defined as all medications and non-drug therapies taken/received within the previous ten days prior to initial Screening up to end of study
2	In women of childbearing potential only, including those who are postmenopausal for less than 12 months
3	Evaluation and grading of midface volume deficit by the **blinded evaluator at the site** (live assessment) using the 5-point MVDSS. Note: The **blinded evaluator at the site** is *not* blinded for treatment allocation during the repeat-treatment phase. However, he/she will be still blinded for the treatment a subject received during the initial treatment phase.
4	Evaluation and grading of nasolabial folds severity by the **blinded evaluator at the site** (live assessment) using the 5-point NLF-SRS.
6	Subject satisfaction will be determined using the FACE-Q™ questionnaire "Satisfaction with Outcome"
7	Evaluation of subject appearance appraisal using the FACE-Q™ questionnaire "Satisfaction with Cheeks"
8	Visual exams (including Snellen visual acuity, confrontational visual fields and ocular motility). The subject should wear the same corrective eyewear (i.e., glasses/contact lenses) at each assessment, if appropriate. **At treatment visits:** Examination will be performed **both before and 30 min after the injection**. For subjects **not** receiving TUP, exams will only be performed **once**.

9	NPRS starting immediately and every 15 min after last injection for 60 min post-treatment
10	All subjects must be asked if they are experiencing or have experienced any signs/symptoms of vision changes or stroke since the injection or other events indicating an embolic event.
13	Concerning only subjects who receive touch-up treatment.
16	Touch-up treatment for optimal correction if deemed necessary in the discretion of **treating investigator**
17	A basic neurological examination (F.A.S.T) will be performed for all subjects who show signs of ophthalmic complications due to filler injection in visual exams
19	Explain diary use incl. documentation of injection site reactions / symptoms of interest to the subject.
20	Review subject diary regarding injection site reactions / symptoms of interest; confirm review. **Note:** Subjects will record injection site reactions, and symptoms of interest (i.e., changes in vision or symptoms of stroke) over the first four weeks (28 days) after each treatment (i.e., 4 weeks after repeat-treatment, and 6 weeks in case of touch-up treatment.
21	In case of Early Termination attempts should be made to perform the assessments described for Visit RT5.
22	Last injection in repeat treatment phase always either refers to repeat-treatment (RT1) or touch-up treatment (TUP2)
23	Injection volume will be documented by site of the midface (left/right) and for each of the 3 anatomical areas of midface treatment (anteromedial cheek, submalar, and zygomaticomalar)

Abbreviations: MVDSS: Midface Volume Deficit Severity Scale; NLF-SRS: Nasolabial Folds Severity Rating Scale; GAIS: Global Aesthetic Improvement Scale, NPRS: Numerical Pain Rating Scale; SV: Screening Visit; RT: Repeat Treatment; TUP2: Touch-up treatment after repeat-treatment

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 included events reported by subjects in diaries during the 4 weeks after each treatment (i.e., 4 weeks after baseline and repeat-treatment, respectively, and 6 weeks in case of touch-up treatment).

With regards to effectiveness, the saypha® ChIQ™ was assessed for correction of midface volume deficit, evaluated live by the blinded evaluator at the site using the validated 5-point MVDSS during follow-up visits of the initial and repeat-treatment phase. MVDSS scores were ranked as follows:

0 (none/minimal):	Zygomaticomalar region, anteromedial cheek, and/or submalar region show convexity; appearance of a full round face with no volume deficit in the midface; no to minimal loss of fullness
1 (mild):	Zygomaticomalar region, anteromedial cheek, and/or submalar region are somewhat flattened; fairly full face appearance; mild loss of fullness
2 (moderate):	Zygomaticomalar region, anteromedial cheek, and/or submalar region have slightly concave shape; moderate loss of fullness in the midface area
3 (severe):	Zygomaticomalar region, anteromedial cheek, and/or submalar region are more concave; underlying bone structure may start to show; severe loss of fullness
4 (very severe):	Zygomaticomalar region and/or anteromedial cheek showing deep concavity; bone structure is prominent, sagging features and visible hollowing below malar prominence; very severe loss of fullness

A central independent blinded photographic reviewer assessed the MVDSS at the same time points of the initial treatment phase based on photographs taken during the subject´s visits. In addition, volume changes were measured using 3D photographs.

Severity of nasolabial folds (NLFs) was assessed live using the validated 5-point NLF-SRS during initial and repeat-treatment phase at each onsite visit by the blinded evaluator at the site. NLF-SRS scores were ranked as 0 (none/minimal), 1 (mild), 2 (moderate), 3 (severe), and 4 (extreme).

The global aesthetic improvement after correction of midface volume deficit was independently evaluated by the blinded evaluator at the site and the subject using the modified Global Aesthetic Improvement Scale (modified GAIS). mGAIS scores ranged from 1 (much improved), to 2 (improved), 3 (no change), 4 (worse), and 5 (much worse).

Subject satisfaction was evaluated using FACE-Q™ questionnaires on 'Satisfaction with Outcome' and 'Satisfaction with Cheeks'. 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 'Satisfaction with Cheeks' Questionnaire consisted of 5 questions with answers of 1 (very dissatisfied), 2 (somewhat dissatisfied), 3 (somewhat satisfied), or 4 (very satisfied). The raw sum scores were each converted into equivalent Rasch transformed scores which ranged from 0 (worst) to 100 (best).

Pain assessment using the 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 regards to success/failure criteria, the primary endpoint was the percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase compared to the pre-treatment score at Baseline visit. Subjects were defined as responders on the MVDSS if they had a clinically meaningful improvement (≥1 point) relative to baseline.

The hypothesis for the primary effectiveness endpoint was that saypha® ChIQ™ was non-inferior to Control, which was evaluated by means of a one-sided two-group Farrington-Manning test for the difference between proportions with the following hypotheses:

H0: pA – pB ≤ – 10%

H1: pA – pB > – 10%

At this, pA is the percent response rate for saypha® ChIQ™ based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase, while pB was the corresponding response rate for Control. Thus, a negative value of the difference meant that the response rate of saypha® ChIQ™ was lower than the response rate for Control. The non-inferiority margin was -10%.

B. Accountability of PMA Cohort

At the time of database lock, of 486 patients enrolled in the PMA study, 423 (87.0%; 423/486) patients were available for analysis at the completion of the initial treatment phase, the 48-week post-treatment visit (Visit 9), which was the final visit for the primary effectiveness evaluation.

In addition, 192 patients (39.5%; 192/486) were eligible for the repeat-treatment phase, and of these, 178 (36.6%; 178/486) patients completed the study through the Week 24 follow-up visit after repeat treatment (Visit RT5), which represented the final study visit.

A total of 486 subjects passed screening and were randomized. Of these, 324 subjects were randomized to the saypha® ChIQ™ group, and 162 subjects were randomized to the Control group. Of the 486 subjects randomized, 483 subjects were treated (322 subjects with saypha® ChIQ™ and 161 subjects with the Control).

At Week 2, 218 subjects received a touch-up treatment with saypha® ChIQ™ and 111 subjects received a touch-up treatment with Control. The median injection volume (both sides combined) of saypha® ChIQ™ required to achieve optimal correction was 4.0 mL at initial treatment and 1.0 mL at touch-up treatment.

Subjects who were eligible and willing could receive optional repeat-treatment (with saypha® ChIQ™ only) 48 to 60 weeks after initial treatment (or touch-up treatment). A total of 192 subjects (118 subjects in the saypha® ChIQ™ group and 74 subjects in the Control group) received a repeat-treatment. The repeat-treatment was performed with saypha® ChIQ™ on both patient groups and the median injection volume required to achieve optimal correction was 2.0 mL at repeat- treatment and 1.0 mL at touch-up treatment.

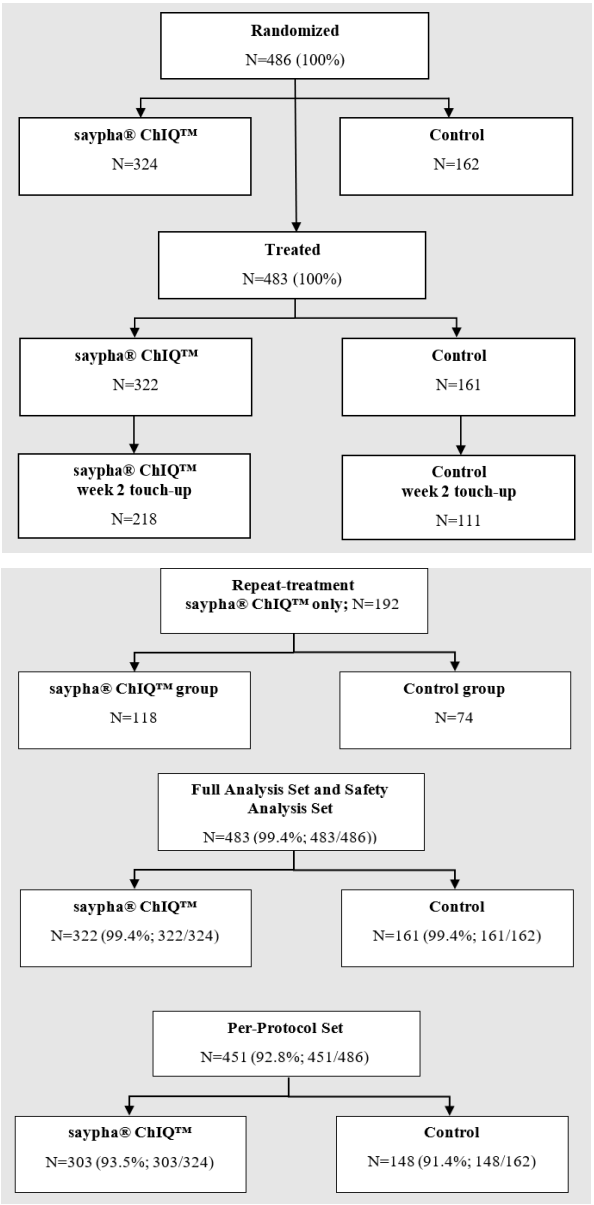
Of the 486 subjects randomized, 483 (99.4%; 483/486) subjects overall were valid for the Full Analysis Set (FAS) and for the Safety Analysis Set (SAF): 322 (99.4%; 322/324) subjects in the saypha® ChIQ™ group and 161 (99.4%; 161/162) subjects in the Control group.

A total of 451 (92.8%; 451/486) subjects overall were included in the Per-Protocol Set (PPS): 303 (93.5%; 303/324) subjects in the saypha® ChIQ™ group and 148 (91.4%; 148/162) subjects in the Control group. Overall, 35 (7.2%; 35/486) subjects were excluded from PPS. Thereof, 32 (91.4%; 32/35) subjects overall were excluded due to a major PD, and 3 (8.6%; 3/35) subjects overall were not treated.

Overall, 423 (87.0%; 423/486) subjects completed the study (or completed Visit 9). The most common reasons for discontinuation from the study were ‘withdrawal of consent’ (30 [47.6%; 30/63] subjects) and ‘lost to follow-up’ (26 [41.3%; 26/63] subjects).

A flowchart of the disposition of subjects per treatment phase is shown in Figure 1.

Figure 1. Disposition of Subjects per Treatment Phase



C. Study Population Demographics and Baseline Parameters

Subject Demographic and Baseline Characteristics for initial treatment phase are provided in Table 6. Subject Demographic Characteristics for repeat-treatment phase are summarized in Table 7. Baseline MVDSS scores were comparable between the 2 treatment groups with individual MVDSS grades of 2 (288 [59.6%; 288/483] subjects overall) and 3 (195 [40.4%; 195/483] subjects overall).

Demographics and baseline characteristics in the PPS were comparable to those in the FAS.

Table 6. Subject Demographic and Baseline Characteristics (FAS)

Characteristics	saypha® ChIQ™ (N=322)	Control (N=161)	Overall (N=483)
Age (years)			
Mean (SD)	54.6 (10.7)	56.0 (9.5)	55.1 (10.3)
Median (Q1, Q3)	55.0 (49.0, 62.0)	56.0 (50.0, 63.0)	55.0 (49.0, 62.0)
Min, Max	24, 75	30, 75	24, 75
Age Category, (%; n/N)			
22 – 45 years	17.7%; 57/322	14.3%; 23/161	16.6%; 80/483
≥46 – 65 years	65.5%; 211/322	70.2%; 113/161	67.1%; 324/483
≥66 – 75 years	16.8%; 54/322	15.5%; 25/161	16.4%; 79/483
Gender, (%; n/N)			
Male	5.9%; 19/322	4.3%; 7/161	5.4%; 26/483
Female	94.1%; 303/322	95.7%; 154/161	94.6%; 457/483
Childbearing Potential[1]	23.4%; 71/303	20.1%; 31/154	22.3%; 102/457
Not of Childbearing Potential[1]	76.6%; 232/303	79.9%; 123/154	77.7%; 355/457
Baseline Body Weight (kg)			
Mean (SD)	68.6 (13.0)	70.3 (16.1)	69.2 (14.1)
Median (Q1, Q3)	66.5 (59.0, 76.0)	68.0 (60.0, 77.0)	67.0 (59.0, 77.0)
Min, Max	44, 116	45, 150	44, 150
Race, (%; n/N)			
White	87.9%; 283/322	87.0%; 140/161	87.6%; 423/483
Asian	1.6%; 5/322	4.3%; 7/161	2.5%; 12/483
Black or African American	6.2%; 20/322	4.3%; 7/161	5.6%; 27/483
American Indian or Alaska Native	2.8%; 9/322	4.3%; 7/161	3.3%; 16/483
Native Hawaiian or Other Pacific Islander	0.6%; 2/322	0%; 0/0	0.4%; 2/483
Other, n (%)			
Afghan	0.3%; 1/322	0%; 0/0	0.2%; 1/483
Bi-racial	0.3%; 1/322	0%; 0/0	0.2%; 1/483
Black/white	0.3%; 1/322	0%; 0/0	0.2%; 1/483
Ethnicity, (%; n/N)			
Hispanic or Latino	21.1%; 68/322	17.4%; 28/161	19.9%; 96/483
Not Hispanic or Latino	78.9%; 254/322	82.6%; 133/161	80.1%; 387/483
Fitzpatrick skin type[2], (%; n/N)			
Type I	1.6%; 5/322	3.1%; 5/161	2.1%; 10/483
Type II	31.4%; 101/322	27.3%; 44/161	30.0%; 145/483
Type III	34.2%; 110/322	38.5%; 62/161	35.6%; 172/483
Type IV	23.9%; 77/322	22.4%; 36/161	23.4%; 113/483
Type V	5.3%; 17/322	5.0%; 8/161	5.2%; 25/483
Type VI	3.7%; 12/322	3.7%; 6/161	3.7%; 18/483

Characteristics	saypha® ChIQ™ (N=322)	Control (N=161)	Overall (N=483)
Fitzpatrick skin type categories, (%; n/N)			
Type I, II and III	67.1%; 216/322	68.9%; 111/161	67.7%; 327/483
Type IV, V and VI	32.9%; 106/322	31.1%; 50/161	32.3%; 156/483
Type V and VI	9.0%; 29/322	8.7%; 14/161	8.9%; 43/483
MVDSS at baseline[3], (%; n/N)			
2 (moderate)	58.7%; 189/322	61.5%; 99/161	59.6%; 288/483
3 (severe)	41.3%; 133/322	38.5%; 62/161	40.4%; 195/483

Note: N = Number of subjects in analysis population. n (%) = Number and percentage of subjects among N. SD = Standard deviation. Q1 = First quartile. Q3 = Third quartile. FAS = Full Analysis Set. MVDSS = Midface Volume Deficit Severity Scale.
[1] Percentage denominator is the number of females
[2] FST were defined as I (always burns easily, never tans), II (always burns easily, tans minimally), III (burns moderately, tans gradually (light brown)), IV (burns minimally, always tans well (moderate brown)), V (barely burns, tans very well (moderate brown)), VI (never burns, deeply pigmented).
[3] By blinded evaluator at site. Baseline was defined as the last assessment prior to initial administration of the medical devices.

Table 7. Repeat-Treatment Phase: Demographic Characteristics (mFAS)

Characteristics	saypha® ChIQ™ (N=118)	Control (N=74)	Overall (N=192)
Age (years)			
Mean (SD)	54.1 (11.5)	56.3 (9.5)	55.0 (10.8)
Median (Q1, Q3)	55.0 (48.0, 63.0)	56.5 (52.0, 63.0)	56.0 (49.0, 63.0)
Min, Max	26, 75	33, 75	26, 75
Age Category, (%; n/N)			
22 – 45 years	19.5%; 23/118	13.5%; 10/74	17.2%; 33/192
≥46 – 65 years	61.9%; 73/118	71.6%; 53/74	65.6%; 126/192
≥66 – 75 years	18.6%; 22/118	14.9%; 11/74	17.2%; 33/192
Gender, (%; n/N)			
Male	6.8%; 8/118	2.7%; 2/74	5.2%; 10/192
Female	93.2%; 110/118	97.3%; 72/74	94.8%; 182/192
Childbearing Potential[1]	26.4%; 29/110	22.2%; 16/72	24.7%; 45/182
Not of Childbearing Potential[1]	73.6%; 81/110	77.8%; 56/72	75.3%; 137/182
Baseline Body Weight (kg)			
Mean (SD)	68.5 (13.4)	70.3 (17.8)	69.2 (15.2)
Median (Q1, Q3)	66.5 (58.0, 75.0)	67.0 (59.0, 75.0)	67.0 (59.0, 75.0)
Min, Max	45, 117	45, 151	45, 151

Characteristics	saypha® ChIQ™ (N=118)	Control (N=74)	Overall (N=192)
Race, (%; n/N)			
White	87.3%; 103/118	87.8%; 65/74	87.5%; 168/192
Asian	2.5%; 3/118	8.1%; 6/74	4.7%; 9/192
Black or African American	6.8%; 8/118	4.1%; 3/74	5.7%; 11/192
American Indian or Alaska Native	1.7%; 2/118	0%; 0/0	1.0%; 2/192
Native Hawaiian or Other Pacific Islander	0.8%; 1/118	0%; 0/0	0.5%; 1/192
Other	0.8%; 1/118	0%; 0/0	0.5%; 1/192
Black/white	0.8%; 1/118	0%; 0/0	0.5%; 1/192
Ethnicity, (%; n/N)			
Hispanic or Latino	22.0%; 26/118	16.2%; 12/74	19.8%; 38/192
Not Hispanic or Latino	78.0%; 92/118	83.8%; 62/74	80.2%; 154/192
Fitzpatrick skin type[2], (%; n/N)			
Type I	2.5%; 3/118	4.1%; 3/74	3.1%; 6/192
Type II	29.7%; 35/118	21.6%; 16/74	26.6%; 51/192
Type III	30.5%; 36/118	44.6%; 33/74	35.9%; 69/192
Type IV	25.4%; 30/118	16.2%; 12/74	21.9%; 42/192
Type V	8.5%; 10/118	10.8%; 8/74	9.4%; 18/192
Type VI	3.4%; 4/118	2.7%; 2/74	3.1%; 6/192
Fitzpatrick skin type categories, (%; n/N)			
Type I, II and III	62.7%; 74/118	70.3%; 52/74	65.6%; 126/192
Type IV, V and VI	37.3%; 44/118	29.7%; 22/74	34.4%; 66/192
Type V and VI	11.9%; 14/118	13.5%; 10/74	12.5%; 24/192
MVDSS at baseline[3], (%; n/N)			
2 (moderate)	97.5%; 115/118	91.9%; 68/74	95.3%; 183/192
3 (severe)	2.5%; 3/118	8.1%; 6/74	4.7%; 9/192

Note: N = Number of subjects in analysis population. n (%) = Number and percentage of subjects among N. SD = Standard deviation. Q1 = First quartile. Q3 = Third quartile. mFAS = Modified Full Analysis Set. MVDSS = Midface Volume Deficit Severity Scale.

[1] Percentage denominator is the number of females

[2] FST were defined as I (always burns easily, never tans), II (always burns easily, tans minimally), III (burns moderately, tans gradually (light brown)), IV (burns minimally, always tans well (moderate brown)), V (barely burns, tans very well (moderate brown)), VI (never burns, deeply pigmented).

[3] By blinded evaluator at site. Baseline was defined as the last assessment prior to first repeat-treatment.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 483 patients for Treatment-Emergent Adverse Events (TEAE) after initial treatment and of 467 patients for Injection Site Reactions (ISR) after initial treatment as well as of 165 patients for ISRs after repeat-treatment recorded through patient diaries. The key safety outcomes for this study are presented below in Tables 8 to 13. Adverse effects are reported in Tables 10 to 13. The ISRs are presented below in Table 8 and Table 9. An overview of the AEs documented during the initial treatment phase is given in Table 10. The most commonly reported adverse device effects (ADEs) by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOC) are presented in Table 12.

Injection Site Reactions After Initial and Repeat-Treatments

Overall, ~30% of subjects in each treatment group reported at least one ISR after the baseline injection with less subjects affected in the saypha® ChIQ™ group ([28.5%; 89/312] subjects) compared to Control ([34.2%; 53/155] subjects).

The most common ISRs reported in both treatment groups were tenderness to touch, firmness, lumps/bumps, swelling, pain after injection, bruising, and redness (Table 8).

Subjects documenting severe ISR were comparable between treatment groups with the (4.5% (14/312) for saypha® ChIQ™ vs 5.2% (8/155) for the control.

A lower proportion of subjects (17% subjects overall) reported ISRs after repeat-treatments. Documented ISRs of severe maximum intensity also reduced to 1.8% subjects overall.

Table 8. Initial Treatment Phase: Injection Site Reactions from Diary by Maximum Intensity (SAF)

Type of ISR Intensity	Baseline Treatment[1]		Touch-up Treatment	
	saypha® ChIQ™ (N = 312) (%; n/N)	**Control (N = 155) (%; n/N)**	**saypha® ChIQ™ (N = 214) (%; n/N)**	**Control (N = 108) (%; n/N)**
At least one ISR	**28.5; 89/312**	**34.2; 53/155**	**19.6; 42/214**	**23.1; 25/108**
Mild	9.3; 29/312	14.8; 23/155	11.7; 25/214	13.0; 14/108
Moderate	14.7; 46/312	14.2; 22/155	7.0; 15/214	9.3; 10/108
Severe	4.5; 14/312	5.2; 8/155	0.9; 2/214	0.9; 1/108
Bruising	**20.2; 63/312**	**22.6; 35/155**	**11.2; 24/214**	**13.9; 15/108**
Mild	9.9; 31/312	11.6; 18/155	7.9; 17/214	10.2; 11/108
Moderate	8.3; 26/312	7.7; 12/155	3.3; 7/214	3.7; 4/108
Severe	1.9; 6/312	3.2; 5/155	0; 0/214	0; 0/108
Discoloration[2]	**9.9; 31/312**	**8.4; 13/155**	**2.8; 6/214**	**5.6; 6/108**
Mild	7.1; 22/312	6.5; 10/155	2.3; 5/214	5.6; 6/108
Moderate	2.6; 8/312	1.9; 3/155	0; 0/214	0; 0/108
Severe	0.3; 1/312	0; 0/155	0.5; 1/214	0; 0/108
Firmness	**24.7; 77/312**	**27.7; 43/155**	**17.3; 37/214**	**15.7; 17/108**
Mild	11.9; 37/312	13.5; 21/155	13.6; 29/214	10.2; 11/108
Moderate	11.5; 36/312	12.9; 20/155	3.7; 8/214	5.6; 6/108
Severe	1.3; 4/312	1.3; 2/155	0; 0/214	0; 0/108
Itching	**4.5; 14/312**	**7.1; 11/155**	**3.7; 8/214**	**1.9; 2/108**
Mild	3.2; 10/312	7.1; 11/155	2.3; 5/214	1.9; 2/108
Moderate	1.3; 4/312	0; 0/155	1.4; 3/214	0; 0/108
Severe	0; 0/312	0; 0/155	0; 0/214	0; 0/108
Lumps/Bumps	**23.7; 74/312**	**27.7; 43/155**	**15.9; 34/214**	**16.7; 18/108**
Mild	13.1; 41/312	20.0; 31/155	11.7; 25/214	14.8; 16/108
Moderate	8.7; 27/312	7.1; 11/155	3.7; 8/214	1.9; 2/108
Severe	1.9; 6/312	0.6; 1/155	0.5; 1/214	0; 0/108

Type of ISR Intensity	Baseline Treatment[1]		Touch-up Treatment	
	saypha® ChIQ™ (N = 312) (%; n/N)	Control (N = 155) (%; n/N)	saypha® ChIQ™ (N = 214) (%; n/N)	Control (N = 108) (%; n/N)
Pain after injection	**20.2; 63/312**	**26.5; 41/155**	**10.7; 23/214**	**13.0; 14/108**
Mild	12.5; 39/312	17.4; 27/155	8.9; 19/214	9.3; 10/108
Moderate	6.4; 20/312	8.4; 13/155	1.9; 4/214	3.7; 4/108
Severe	1.3; 4/312	0.6; 1/155	0; 0/214	0; 0/108
Redness	**17.9; 56/312**	**23.2; 36/155**	**7.5; 16/214**	**8.3; 9/108**
Mild	13.1; 41/312	18.7; 29/155	7.0; 15/214	6.5; 7/108
Moderate	4.2; 13/312	4.5; 7/155	0.5; 1/214	1.9; 2/108
Severe	0.6; 2/312	0; 0/155	0; 0/214	0; 0/108
Swelling	**22.8; 71/312**	**28.4; 44/155**	**15.0; 32/214**	**16.7; 18/108**
Mild	11.9; 37/312	18.1; 28/155	10.3; 22/214	12.0; 13/108
Moderate	9.0; 28/312	9.7; 15/155	4.2; 9/214	3.7; 4/108
Severe	1.9; 6/312	0.6; 1/155	0.5; 1/214	0.9; 1/108
Tenderness to touch	**24.7; 77/312**	**30.3; 47/155**	**15.0; 32/214**	**21.3; 23/108**
Mild	15.4; 48/312	16.1; 25/155	10.3; 22/214	15.7; 17/108
Moderate	8.0; 25/312	13.5; 21/155	4.2; 9/214	5.6; 6/108
Severe	1.3; 4/312	0.6; 1/155	0.5; 1/214	0; 0/108
Other[3]	**5.1; 16/312**	**8.4; 13/155**	**3.3; 7/214**	**0.9; 1/108**

Note: N = Number of subjects in analysis population with at least one entry in the diary. n (%) = Number and percentage of subjects reporting at least one injection site reaction with the specification among N. SAF = Safety Analysis Set. ISR = Injection Site Reaction.

Note: Injections site reactions were documented daily by subjects and per side of the midface treated. ISRs with the specification at either left side, right side, or both sides of the midface are displayed.

Note: Injection site reactions with intensity assessed as 'mild', 'moderate' or 'severe' were included. For computations of 'both', the maximum intensity of both sides of the midface was used.

Note: Injection site reactions with 'Other' type were excluded from the analysis.

[1] For subjects without touch-up treatment in the initial treatment phase, all diary entries were included in the analysis. For subjects who received touch-up treatment, all diary entries up to (and including) the last day before touch-up treatment were included in the analysis.

[2] Other than Redness or Bruising

[3] '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 (see Table 9). After baseline treatment with saypha® ChIQ™, firmness, lumps/bumps, tenderness to touch, swelling, pain after injection and bruising were the ISRs that lasting up to 27 days, while redness, discoloration and itching disappeared much faster. The duration of ISRs after touch-up treatment by category was comparable to the duration of ISRs after baseline treatment.

A lower proportion of subjects (17% subjects overall) reported ISRs after repeat-treatment. The maximum duration for reported ISRs was similar between treatment groups and compared to initial treatment.

Table 9. Initial Treatment Phase: Duration of ISR from Diary After Baseline Treatment by Categories (SAF)

Type of ISR Duration Category	Subjects without* subsequent touch-up treatment		Subjects with** subsequent touch-up treatment		Subjects with or without*** subsequent touch-up treatment	
	saypha® ChIQ™ (N = 99) (%; n/N)	Control (N = 49) (%; n/N)	saypha® ChIQ™ (N = 213) (%; n/N)	Control (N = 106) (%; n/N)	saypha® ChIQ™ (N = 312) (%; n/N)	Control (N = 155) (%; n/N)
At least one ISR	**25.3; 25/99**	**28.6; 14/49**	**30.0; 64/213**	**36.8; 39/106**	**28.5; 89/312**	**34.2; 53/155**
1-3 days	8.1; 8/99	12.2; 6/49	12.2; 26/213	17.0; 18/106	10.9; 34/312	15.5; 24/155
4-7 days	3.0; 3/99	2.0; 1/49	6.1; 13/213	5.7; 6/106	5.1; 16/312	4.5; 7/155
8-14 days	5.1; 5/99	6.1; 3/49	10.3; 22/213	14.2; 15/106	8.7; 27/312	11.6; 18/155
15-28 days	9.1; 9/99	8.2; 4/49	1.4; 3/213	0; 0/106	3.8; 12/312	2.6; 4/155
Bruising	**22.2; 22/99**	**18.4; 9/49**	**19.2; 41/213**	**24.5; 26/106**	**20.2; 63/312**	**22.6; 35/155**
1-3 days	9.1; 9/99	12.2; 6/49	7.5; 16/213	11.3; 12/106	8.0; 25/312	11.6; 18/155
4-7 days	5.1; 5/99	0; 0/49	4.7; 10/213	4.7; 5/106	4.8; 15/312	3.2; 5/155
8-14 days	4.0; 4/99	0; 0/49	6.6; 14/213	8.5; 9/106	5.8; 18/312	5.8; 9/155
15-28 days	4.0; 4/99	6.1; 3/49	0.5; 1/213	0; 0/106	1.6; 5/312	1.9; 3/155
Discoloration[1]	**11.1; 11/99**	**8.2; 4/49**	**9.4; 20/213**	**8.5; 9/106**	**9.9; 31/312**	**8.4; 13/155**
1-3 days	8.1; 8/99	2.0; 1/49	6.6; 14/213	5.7; 6/106	7.1; 22/312	4.5; 7/155
4-7 days	1.0; 1/99	2.0; 1/49	1.4; 3/213	1.9; 2/106	1.3; 4/312	1.9; 3/155
8-14 days	1.0; 1/99	4.1; 2/49	1.4; 3/213	0.9; 1/106	1.3; 4/312	1.9; 3/155
15-28 days	1.0; 1/99	0; 0/49	0; 0/213	0; 0/106	0.3; 1/312	0; 0/155
Firmness	**20.2; 20/99**	**20.4; 10/49**	**26.8; 57/213**	**31.1; 33/106**	**24.7; 77/312**	**27.7; 43/155**
1-3 days	9.1; 9/99	8.2; 4/49	13.6; 29/213	17.9; 19/106	12.2; 38/312	14.8; 23/155
4-7 days	0; 0/99	4.1; 2/49	5.2; 11/213	5.7; 6/106	3.5; 11/312	5.2; 8/155
8-14 days	3.0; 3/99	4.1; 2/49	6.6; 14/213	7.5; 8/106	5.4; 17/312	6.5; 10/155
15-28 days	8.1; 8/99	4.1; 2/49	1.4; 3/213	0; 0/106	3.5; 11/312	1.3; 2/155

Type of ISR Duration Category	Subjects without* subsequent touch-up treatment		Subjects with** subsequent touch-up treatment		Subjects with or without*** subsequent touch-up treatment	
	saypha® ChIQ™ (N = 99) (%; n/N)	Control (N = 49) (%; n/N)	saypha® ChIQ™ (N = 213) (%; n/N)	Control (N = 106) (%; n/N)	saypha® ChIQ™ (N = 312) (%; n/N)	Control (N = 155) (%; n/N)
Itching	**4.0; 4/99**	**8.2; 4/49**	**4.7; 10/213**	**6.6, 7/106**	**4.5; 14/312**	**7.1; 11/155**
1-3 days	2.0; 2/99	8.2; 4/49	3.3; 7/213	6.6; 7/106	2.9; 9/312	7.1; 11/155
4-7 days	0; 0/99	0; 0/49	0.9; 2/213	0; 0/106	0.6; 2/312	0; 0/155
8-14 days	1.0; 1/99	0; 0/49	0.5; 1/213	0; 0/106	0.6; 2/312	0; 0/155
15-28 days	1.0; 1/99	0; 0/49	0; 0/213	0; 0/106	0.3; 1/312	0; 0/155
Lumps/Bumps	**21.2; 21/99**	**22.4; 11/49**	**24.9; 53/213**	**30.2; 32/106**	**23.7; 74/312**	**27.7; 43/155**
1-3 days	8.1; 8/99	10.2; 5/49	13.1; 28/213	20.8; 22/106	11.5; 36/312	17.4; 27/155
4-7 days	3.0; 3/99	2.0; 1/49	4.7; 10/213	1.9; 2/106	4.2; 13/312	1.9; 3/155
8-14 days	4.0; 4/99	2.0, 1/49	5.6; 12/213	7.5; 8/106	5.1; 16/312	5.8; 9/155
15-28 days	6.1; 6/99	8.2; 4/49	1.4; 3/213	0; 0/106	2.9; 9/312	2.6; 4/155
Pain after injection	**20.2; 20/99**	**24.5; 12/49**	**20.2; 43/213**	**27.4; 29/106**	**20.2; 63/312**	**26.5; 41/155**
1-3 days	11.1; 11/99	16.3; 8/49	13.1; 28/213	17.0; 18/106	12.5; 39/312	16.8; 26/155
4-7 days	4.0; 4/99	6.1; 3/49	3.3; 7/213	7.5; 8/106	3.5; 11/312	7.1; 11/155
8-14 days	1.0; 1/99	0; 0/49	3.3; 7/213	2.8; 3/106	2.6; 8/312	1.9; 3/155
15-28 days	4.0; 4/99	2.0; 1/49	0.5; 1/213	0; 0/106	1.6; 5/312	0.6; 1/155
Redness	**15.2; 15/99**	**16.3; 8/49**	**19.2; 41/213**	**26.4; 28/106**	**17.9; 56/312**	**23.2; 36/155**
1-3 days	10.1; 10/99	12.2; 6/49	15.0; 32/213	18.9; 20/106	13.5; 42/312	16.8; 26/155
4-7 days	2.0; 2/99	2.0; 1/49	2.8; 6/213	4.7; 5/106	2.6; 8/312	3.9; 6/155
8-14 days	1.0; 1/99	0; 0/49	1.4; 3/213	2.8; 3/106	1.3; 4/312	1.9; 3/155
15-28 days	2.0; 2/99	2.0; 1/49	0; 0/213	0; 0/106	0.6; 2/312	0.6; 1/155

Type of ISR Duration Category	Subjects without* subsequent touch-up treatment		Subjects with** subsequent touch-up treatment		Subjects with or without*** subsequent touch-up treatment	
	saypha® ChIQ™ (N = 99) (%; n/N)	Control (N = 49) (%; n/N)	saypha® ChIQ™ (N = 213) (%; n/N)	Control (N = 106) (%; n/N)	saypha® ChIQ™ (N = 312) (%; n/N)	Control (N = 155) (%; n/N)
Swelling	**20.2; 20/99**	**24.5; 12/49**	**23.9; 51/213**	**30.2; 32/106**	**22.8; 71/312**	**28.4; 44/155**
1-3 days	11.1; 11/99	18.4; 9/49	13.6; 29/213	18.9; 20/106	12.8; 40/312	18.7; 29/155
4-7 days	3.0; 3/99	4.1; 2/49	7.0; 15/213	8.5; 9/106	5.8; 18/312	7.1; 11/155
8-14 days	1.0; 1/99	0; 0/49	2.8; 6/213	2.8; 3/106	2.2; 7/312	1.9; 3/155
15-28 days	5.1; 5/99	2.0; 1/49	0.5; 1/213	0; 0/106	1.9; 6/312	0.6; 1/155
Tenderness to touch	**22.2; 22/99**	**24.5; 12/49**	**25.8; 55/213**	**33.0; 35/106**	**24.7; 77/312**	**30.3; 47/155**
1-3 days	9.1, 9/99	10.2; 5/49	10.3; 22/213	16.0; 17/106	9.9; 31/312	14.2; 22/155
4-7 days	5.1; 5/99	4.1; 2/49	6.6; 14/213	6.6; 7/106	6.1; 19/312	5.8; 9/155
8-14 days	2.0; 2/99	2.0; 1/49	8.0; 17/213	10.4; 11/106	6.1; 19/312	7.7; 12/155
15-28 days	6.1; 6/99	8.2; 4/49	0.9; 2/213	0; 0/106	2.6; 8/312	2.6; 4/155

Note: N = Number of subjects in analysis population with at least one entry in the diary. n (%) = Number and percentage of subjects reporting at least one Injection Site Reaction with the specification among N. SAF = Safety Analysis Set. ISR = Injection Site Reaction.

Note: Injection site reactions were documented daily by subjects and per side of the midface treated.

Note: The duration in time [days] was computed as: Last stop date – First start date +1. This definition comprised both sides of the midface.

Note: Injection site reactions with 'Other' type were excluded from the analysis.

[1] Other than Redness or Bruising

* For subjects without touch-up treatment in the initial treatment phase, all diary entries were included in the analysis (maximum documentation after baseline treatment: 28 days)

** For subjects who received touch-up treatment (14±3 days) after baseline treatment, all diary entries up to (and including) the last day before touch-up treatment were included in the analysis.

*** For subjects without touch-up treatment in the initial treatment phase, all diary entries were included in the analysis. For subjects who received touch-up treatment, all diary entries up to (and including) the last day before touch-up treatment were included in the analysis.

Treatment-Emergent Adverse Events After Initial and Repeat-Treatments

Adverse events documented during the initial treatment phase are summarized in Table 10. The most commonly reported adverse device effects (ADEs) by MedDRA SOC are presented in Table 12.

142 AEs in 15.7% (76/483) subjects were considered by the investigator to have a relationship to the medical device itself and/or the procedure and were categorized as ADE. A higher proportion of subjects in the Control group (17.4%; 28/161 subjects) was affected by an ADE compared to the saypha® ChIQ™ group (14.9%; 48/322 subjects).

Overall, 1 subject (saypha® ChIQ™ group) terminated the investigation prematurely due to a TEAE. One other subject (saypha® ChIQ™ group) experienced a TEAE, which led to discontinuation of the injection (i.e., the subject was discontinued from further treatment with the medical device).

In total, 2 adverse events of special interest (AESIs) were reported in 2 subjects. One (cerebrovascular accident of unknown mechanism) was assessed as not related to medical device nor to procedure approximately 6 months after baseline treatment. One (external vascular occlusion on left side of face) was assessed as possibly related to medical device and procedure with onset on study day 5 after baseline treatment.

In total, 6 serious adverse events (SAEs) were reported in 1.2% (6/483) subjects. One SAE ('vascular skin disorder'; saypha® ChIQ™ group) was assessed by the investigator as possibly related to medical device and procedure.

Six AEs due to persisting injection-site reactions (pISR; i.e., ISR lasting more than 28 days) were reported in 2 subjects (0.4%) during initial treatment and in 1 subject (0.8%) during repeat treatment. All events were mild, non-serious, classified within the SOC General disorders and administration-site conditions, and resolved without sequelae.

Table 10. Initial Treatment Phase: Overview of Adverse Events (SAF)

Subjects with Occurrence of	**saypha® ChIQ™ (N=322) (%; n/N) [AE]**	**Control (N=161) (%; n/N) [AE]**	**Overall (N=483) (%; n/N) [AE]**
Adverse Events (AEs)	**(39.4; 127/322) [300]**	**(36.6; 59/161) [162]**	**(38.5; 186/483) [462]**
Treatment Emergent[1] AEs (TEAEs)	**(39.1; 126/322) [299]**	**(36.6; 59/161) [161]**	**(38.3; 185/483) [460]**
TEAEs of Special Interest (AESIs)	(0.6; 2/322) [2]	(0; 0/161) [0]	(0.4; 2/483) [2]
Dermatological TEAEs	(12.7; 41/322) [75]	(13.7; 22/161) [34]	(13.0; 63/483) [109]
TEAEs leading to withdrawal from investigation	(0.3; 1/322) [1]	(0; 0/161) [0]	(0.2; 1/483) [1]
TEAEs leading to discontinuation of injection	(0.3; 1/322) [1]	(0; 0/161) [0]	(0.2; 1/483) [1]
Adverse device effects[2] (ADEs)	**(14.9; 48/322) [94]**	**(17.4; 28/161) [48]**	**(15.7; 76/483) [142]**
ADEs related to device	(9.0; 29/322) [65]	(12.4; 20/161) [35]	(10.1; 49/483) [100]
ADEs related to procedure	(14.0; 45/322) [83]	(17.4; 28/161) [46]	(15.1; 73/483) [129]
Serious AEs (SAEs)	**(1.2; 4/322) [4]**	**(1.2; 2/161) [2]**	**(1.2; 6/483) [6]**
Serious ADEs[2] (SADEs)	**(0.3; 1/322) [1]**	**(0; 0/161) [0]**	**(0.2; 1/483) [1]**
SADEs related to device	(0.3; 1/322) [1]	(0; 0/161) [0]	(0.2; 1/483) [1]
SADEs related to procedure	(0.3; 1/322) [1]	(0; 0/161) [0]	(0.2; 1/483) [1]
AEs due to a Persisting Injection Site Reaction (pISRs)	**(0.3; 1/322) [5]**	**(0.6; 1/161) [1]**	**(0.4; 2/483) [6]**

Note: N = Number of subjects in analysis population. n (%) = Number and percentage of subjects reporting at least 1 AE with the specification among N. [AE] = Number of individual AEs which occurred among the n subjects. SAF = Safety Analysis Set.

[1] TEAE = AE with a start date on or after the first use of medical device or pre-existing AEs which worsened in intensity.

[2] All AEs assessed with 'possible', 'probable' or 'causal' relationship were classified as 'related' (i.e., as adverse device effect [ADE]).

An overview of all AEs reported during the repeat-treatment phase is given in Table 11 for subjects in the mSAF (N=192) separated by treatment group and overall.

In total, 16 AEs in 3.6% (7/192) subjects overall were considered by the investigator to have a relationship to the medical device itself and/or the procedure and were categorized as ADE with 5.4% (4/74) subjects affected by an ADE in the Control group compared to 2.5% (3/118) subjects in the saypha® ChIQ™ group.

Overall, 1 subject (saypha® ChIQ™ group) terminated the investigation prematurely due to a TEAE during the repeat-treatment phase. One other subject (saypha® ChIQ™ group) experienced a TEAE, which led to discontinuation of the injection, i.e., the subject was discontinued from further treatment with the medical device.

In total, 2 serious adverse events (SAEs) were reported in 1.7% (2/118) subjects of the saypha® ChIQ™ group during the repeat-treatment phase. Both events were reported as non-related to medical device and procedure.

Seven AEs due to persisting ISRs (pISRs) were documented in 0.8% (1/118) subjects of the saypha® ChIQ™ group.

Table 11. Repeat-Treatment Phase: Overview of Adverse Events (mSAF)

Subjects with Occurrence of	**saypha® ChIQ™ (N=118) (%; n/N) [AE]**	**saypha® ChIQ™ (initial treatment with Control) (N=74) (%; n/N) [AE]**	**Overall (N=192) (%; n/N) [AE]**
Adverse Events (AEs)	**(15.3; 18/118) [51]**	**(27.0; 20/74) [39]**	**(19.8; 38/192) [90]**
Treatment Emergent[1] AEs (TEAEs)	**(15.3; 18/118) [51]**	**(27.0; 20/74) [39]**	**(19.8; 38/192) [90]**
TEAEs of Special Interest (AESIs)	(0; 0/118) [0]	(0; 0/74) [0]	(0; 0/192) [0]
Dermatological TEAEs	(4.2; 5/118) [13]	(12.2; 9/74) [15]	(7.3; 14/192) [28]
TEAEs leading to withdrawal from investigation	(0.8; 1/118) [1]	(0; 0/74) [0]	(0.5; 1/192) [1]
TEAEs leading to discontinuation of injection	(0.8; 1/118) [1]	(0; 0/74) [0]	(0.5; 1/192) [1]
Adverse device effects[2] (ADEs)	**(2.5; 3/118) [11]**	**(5.4; 4/74) [5]**	**(3.6; 7/192) [16]**
ADEs related to device	(1.7; 2/118) [10]	(5.4; 4/74) [5]	(3.1; 6/192) [15]
ADEs related to procedure	(2.5; 3/118) [5]	(5.4; 4/74) [5]	(3.6; 7/192) [10]
Serious AEs (SAEs)	**(1.7; 2/118) [2]**	**(0; 0/74) [0]**	**(1.0; 2/192) [2]**
Serious ADEs[2] (SADEs)	**(0; 0/118) [0]**	**(0; 0/74) [0]**	**0 (0; 0/192) [0]**
SADEs related to device	(0; 0/118) [0]	(0; 0/74) [0]	0 (0; 0/912) [0]
SADEs related to procedure	(0; 0/118) [0]	(0; 0/74) [0]	0 (0 0/192) [0]
AEs due to a Persisting Injection Site Reaction (pISRs)	**(0.8; 1/118) [7]**	**(0; 0/74) [0]**	**(0.5; 1/192) [7]**

Note: N = Number of subjects in analysis population. n (%) = Number and percentage of subjects reporting at least 1 AE with the specification among N. [AE] = Number of individual AEs which occurred among the n subjects. mSAF = Modified Safety Analysis Set.

[1] TEAE = AE with a start date on or after the first use of medical device or pre-existing AEs which worsened in intensity.

[2] All AEs assessed with 'possible', 'probable' or 'causal' relationship were classified as 'related' (i.e., as adverse device effect [ADE]).

The most frequently affected SOC for procedure-related ADEs during initial treatment phase was nervous system disorders: 7.5% (36/483) of overall subjects experienced 48 ADEs within this SOC with equal proportion of subjects affected in each treatment group (7.5% subjects, each). Most common PT within this SOC was headache with 43 ADEs in 6.6% (32/483) subjects overall.

AEs reported during the initial treatment phase in single subjects only were:

- saypha® ChIQ™ – difficulty speaking, injection site coldness, muscle spasm, oral pain, paranasal sinus discomfort, pruritus, skin burning sensation and toothache
- Control – eye swelling, joint stiffness, muscle twitching, pain in jaw, presyncope, sensory disturbance, temperature intolerance

Table 12. Initial Treatment Phase: Adverse Device Effects by MedDRA SOC and PT >1 Subject Overall (SAF)

MedDRA[1] SOC/PT[2]	saypha® ChIQ™ (N=322) (%; n/N) [AE]	Control (N=161) (%; n/N) [AE]	Overall (N=483) (%; n/N) [AE]
At least one ADE[3]	**(14.9; 48/322) [94]**	**(17.4; 28/161) [48]**	**(15.7; 76/483) [142]**
General disorders and administration site conditions	**(5.0; 16/322) [31]**	**(5.6; 9/161) [13]**	**(5.2; 25/483) [44]**
Injection site bruising	(1.9; 6/322) [6]	(3.1; 5/161) [6]	(2.3; 11/483) [12]
Injection site pain	(2.5; 8/322) [10]	(0.6; 1/161) [1]	(1.9; 9/483) [11]
Injection site mass	(1.2; 4/322) [5]	(1.9; 3/161) [4]	(1.4; 7/483) [9]
Injection site swelling	(1.6; 5/322) [7]	(0; 0/161) [0]	(1.0; 5/483) [7]
Nodule	(0.3; 1/322) [1]	(0.6; 1/161) [1]	(0.4; 2/483) [2]
Investigations	**(3.1; 10/322) [11]**	**(5.6; 9/161) [10]**	**(3.9; 19/483) [21]**
Palpatory finding abnormal	(3.1; 10/322) [11]	(5.6; 9/161) [10]	(3.9; 19/483) [21]
Musculoskeletal and connective tissue disorders	**(1.9; 6/322) [10]**	**(3.7; 6/161) [8]**	**(2.5; 12/483) [18]**
Mastication disorder	(1.2; 4/322) [5]	(2.5; 4/161) [4]	(1.7; 8/483) [9]
Jaw disorder	(0.6; 2/322) [4]	(0.6; 1/161) [1]	(0.6; 3/483) [5]
Nervous system disorders	**(7.5; 24/322) [34]**	**(7.5; 12/161) [14]**	**(7.5; 36/483) [48]**
Headache	(7.5; 24/322) [34]	(5.0; 8/161) [9]	(6.6; 32/483) [43]
Dizziness	(0; 0/322) [0]	(1.9; 3/161) [3]	(0.6; 3/483) [3]
Skin and subcutaneous tissue disorders	**(1.2; 4/322) [5]**	**(1.2; 2/161) [2]**	**(1.2; 6/483) [7]**
Skin laxity	(0.3; 1/322) [1]	(1.2; 2/161) [2]	(0.6; 3/483) [3]

Note: N = Number of subjects in analysis population. n (%) = Number and percentage of subjects reporting at least 1 AE with the specification among N. [AE] = Number of individual AEs which occurred among the n subjects. ADE = Adverse Device Effects. SAF = Safety Analysis Set

Note: Subjects were counted only once for each PT when they had more than one ADE with the same PT. Subjects with more than one ADE within a SOC were counted for each corresponding PT within the SOC, but were counted only once for the SOC.

Note: All AEs assessed with the relationship 'possible', 'probable' or 'causal' relationship were classified as ADE.

[1] MedDRA version 27.0

[2] SOC/PT with >1 subject overall are displayed.

[3] Related to procedure and/or device

During repeat-treatment phase, the most frequently reported SOC among ADEs was general disorders and administration site conditions: 2.6% (5/192) of overall subjects experienced 12 ADEs within this SOC (saypha® ChIQ™ group: 2.5% [3/118] subjects; Control group: 2.7% [2/74] subjects).

The most reported PTs within this SOC were injection site pain (1.6% [3/192] subjects overall), and injection site mass (1.0% [2/192] subjects overall).

Nervous system disorders affected 1.0% (2/192) of overall subjects (saypha® ChIQ™: 0.8% [1/118] subjects; Control: 1.4% [1/74] subject). Only PT within this SOC was headache with 2 ADEs in 1.0% (2/192) subjects overall.

AEs reported during the repeat-treatment phase in single subjects only were: ecchymosis, injection site discomfort, Injection site erythema, Injection site induration, Injection site pruritus and palpatory finding.

Table 13. Repeat-Treatment Phase: Adverse Device Effects by MedDRA SOC and PT >1 Subject Overall (mSAF)

MedDRA[1] SOC/PT[2]	saypha® ChIQ™ (N=118) (%; n/N) [AE]	saypha® ChIQ™ (initial treatment with Control) (N=74) (%; n/N) [AE]	Overall (N=192) (%; n/N) [AE]
At least one ADE[3]	**(2.5; 3/118) [11]**	**(5.4; 4/74) [5]**	**(3.6; 7/192) [16]**
General disorders and administration site conditions	**(2.5; 3/118) [10]**	**(2.7; 2/74) [2]**	**(2.6; 5/192) [12]**
Injection site pain	(1.7; 2/118) [2]	(1.4; 1/74) [1]	(1.6; 3/192) [3]
Injection site mass	(0.8; 1/118) [1]	(1.4; 1/74) [1]	(1.0; 2/192) [2]
Nervous system disorders	**(0.8; 1/118) [1]**	**(1.4; 1/74) [1]**	**(1.0; 2/192) [2]**
Headache	(0.8; 1/118) [1]	(1.4; 1/74) [1]	(1.0; 2/192) [2]

Note: N = Number of subjects in analysis population. n (%) = Number and percentage of subjects reporting at least 1 AE with the specification among N. [AE] = Number of individual AEs which occurred among the n subjects. ADE = Adverse Device Effects. mSAF = Modified Safety Analysis Set

Note: Subjects were counted only once for each PT when they had more than one ADE with the same PT. Subjects with more than one ADE within a SOC were counted for each corresponding PT within the SOC, but were counted only once for the SOC.

Note: All AEs assessed with the relationship 'possible', 'probable' or 'causal' relationship were classified as ADE.

[1] MedDRA version 27.0

[2] SOC/PT with >1 subject overall are displayed.

[3] Related to procedure and/or device

Adverse Events of Special Interest (AESIs):

AESIs after initial/touch-up treatment affected 2 subjects and included:

- Subject experienced a 'cerebrovascular accident' (reported term: cerebrovascular accident of unknown mechanism) not related to medical device nor to procedure approximately 6 months after baseline treatment.
- Subject experienced 'vascular skin disorder' (reported term: external vascular occlusion on left side of face), which was assessed as possibly related to medical device and procedure with onset on study day 5 after baseline treatment.

No AESI was reported during the repeat-treatment phase.

Serious AEs During Initial/Touch-up Treatment:

Serious AEs after initial/touch-up treatment affected 6 subjects (saypha® ChIQ™: 4 events in 1.2% [4/322] subjects; Control: 2 events in 1.2% [2/161] subjects) and included:

- Subject experienced a fentanyl overdose with fatal outcome approximately 6 months after last treatment (saypha® ChIQ™). The AE was assessed as serious due to the fatal outcome (death), was severe in intensity and not related to the medical device or procedure.
- Subject was hospitalized due to 'mental disorder' (reported term: mental disorder). The AE started approximately 1 month after touch-up treatment (saypha® ChIQ™) and resolved after 50 days. The event was assessed as serious due to in-subject or prolonged hospitalization and severe in intensity and was not related to the medical device or procedure.
- Subject was hospitalized due to a 'cerebrovascular accident' (reported term: cerebrovascular accident of unknown mechanism) approximately 6 months after last treatment (saypha® ChIQ™). The event was assessed severe in intensity and not related to the medical device or procedure. Since subject refused to return to clinic and withdrew her consent upon requesting hospital records release signature the outcome of this SAE is unknown.

- Subject experienced a 'vascular skin disorder' (reported term: external vascular occlusion on left side of face) with onset on study day 5 after baseline treatment (saypha® ChIQ™). The event was categorized as SAE (SAE-criterion: Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function) with moderate intensity. The relationship was classified as possibly related to medical device and procedure. The outcome of the event was considered resolved after a duration of 10 days. The local treatment included dermal filler dissolution as well as antibiotic and wound healing ointments. Systemic corticosteroids, blood circulation stimulants and antibiotics completed the treatment. The subject remained in the study but was discontinued from further treatment, i.e., from touch-up treatment.
- SAEs in Control group: SAEs were reported for 2 subjects of the Control group. Both events, 'humerus fracture' and 'ectopic pregnancy', were assessed as not related to the medical device or procedure.

SAEs During Repeat Treatment:

During the repeat-treatment phase with saypha® ChIQ™, 2 SAEs were reported in 2 subjects:

- Subject was hospitalized due to 'meningioma' (reported term: Meningioma, transitional and microcystic subtype). The AE started 77 days after repeat-treatment and was considered resolved after 10 days with no action taken with the investigational device. The event was assessed as serious as it met the seriousness criterion of in-subject or prolonged hospitalization. It was severe in intensity and not related to the study device or procedure. The subject discontinued the clinical investigation due to SAE.
- Subject was hospitalized due to 'breast cancer' (reported term: breast cancer bilateral). The AE started 86 days after repeat-treatment and was considered resolved after 57 days with no action taken with the investigational device. The event was assessed as serious as it met the seriousness criterion of in-subject or prolonged hospitalization. It was moderate in intensity and not related to the study device or study intervention.

Pain at Injection:

Subject perception of pain was assessed after initial treatment with saypha® ChIQ™ and with Control using the 11-point, semi-quantitative NPRS from 0 (no pain) to 10 (worst imaginable pain).

In the FAS, after baseline treatment, subject perception of pain was similar between left and right sides of the midface and between the two treatment groups at the respective timepoints: Immediately after treatment mean (SD) pain score for the left side of the midface with saypha® ChIQ™ vs Control was 2.5 (2.3) vs 2.3 (2.2) points, and 2.5 (2.2) vs 2.3 (2.3) points for the right midface. The mean pain score for the left and right side of the midface at 15, 30, 45, and 60 minutes after baseline treatment with saypha® ChIQ™ vs Control was found similar and at low levels ≤0.8 points.

After touch-up treatment, in the FAS, subject perception of pain was also similar between left and right sides of the midface and between the two treatment groups at the respective timepoints.

Likewise, subject perception of pain in the mFAS after repeat treatment was similar between left and right sides of the midface and between the two treatment groups at the respective timepoints.

Extent of Exposure:

Total volumes applied of saypha® ChIQ™ or Control by treatment visits (baseline and touch-up treatments of the initial treatment phase) are displayed in Table 14 for the FAS.

The mean [SD] total injected volume for initial treatment (baseline plus optional touch-up treatment) was higher for saypha® ChIQ™ (5.163 [2.306] mL) than for Control (4.975 [2.251] mL).

Table 14. Initial Treatment Phase: Total Volumes Injected (FAS)

Treatment Visit Statistics [mL]	saypha® ChIQ™ (N=322)	Control (N=161)
Baseline Treatment		
N	322	161
Mean (SD)	4.235 (1.992)	3.871 (1.831)
Median (Q1, Q3)	4.000 (3.000, 6.000)	4.000 (2.000, 5.600)
Min, Max	0.80, 10.00	0.96, 9.00
Touch-up Treatment		
n	218	111
Mean (SD)	1.371 (0.999)	1.601 (1.068)
Median (Q1, Q3)	1.000 (0.600, 2.000)	1.200 (0.800, 2.000)
Min, Max	0.10, 5.00	0.10, 5.00
Total Injection Volume[1]		
n	322	161
Mean (SD)	5.163 (2.306)	4.975 (2.251)
Median (Q1, Q3)	5.000 (3.500, 7.000)	4.600 (3.000, 6.400)
Min, Max	0.80, 10.00	0.96, 10.00

N = Number of subjects in analysis population. SD = Standard deviation. Q1 = First quartile. Q3 = Third quartile. Min = Minimum. Max = Maximum. FAS = Full Analysis Set.
Note: Total volumes injected (both sides of the midface combined) are displayed.
[1] Sum of volumes (mL) applied at baseline and touch-up treatments.

The mean [SD] total injected volume in repeat-treatment phase (repeat-treatment plus optional touch-up treatment) was higher in the Control group (3.215 [1.780] mL) than in the saypha® ChIQ™ group (3.091 [1.878] mL).

Table 15. Repeat-Treatment Phase: Total Volumes Injected (mFAS)

Treatment Visit Statistics [mL]	saypha® ChIQ™ (N=118)	saypha® ChIQ™ (initial treatment with Control) (N=74)
Repeat-Treatment		
N	118	74
Mean (SD)	2.476 (1.566)	2.669 (1.578)
Median (Q1, Q3)	2.000 (1.300, 3.000)	2.250 (1.350, 4.000)
Min, Max	0.60, 8.00	0.60, 7.00
Touch-up Treatment		
n	62	36
Mean (SD)	1.169 (0.931)	1.124 (0.660)
Median (Q1, Q3)	1.000 (0.600, 1.600)	1.000 (0.750, 1.350)
Min, Max	0.15, 5.00	0.20, 3.10
Total Injection Volume[1]		
n	118	74
Mean (SD)	3.091 (1.878)	3.215 (1.780)
Median (Q1, Q3)	2.750 (2.000, 3.500)	3.000 (2.000, 4.000)
Min, Max	0.60, 10.00	0.80, 9.10

N = Number of subjects in analysis population. SD = Standard deviation. Q1 = First quartile. Q3 = Third quartile. Min = Minimum. Max = Maximum. mFAS = Modified Full Analysis Set.
Note: Total volumes injected (both sides of the midface combined) are displayed.
[1] Sum of volumes (mL) applied at repeat and touch-up treatments.

2. Effectiveness Results

The analysis of effectiveness was based on the 483 evaluable patients at the 24-week time point. Key effectiveness outcomes are presented in Table 16.

The primary effectiveness endpoint was the percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase compared to the pre-treatment score at baseline visit. Subjects were defined as responders at a given visit on the MVDSS if they had ≥1 point improvement relative to baseline.

For the FAS, higher percentages of subjects were MVDSS responders [95% CI] at Week 24 after last injection of initial treatment phase in the saypha® ChIQ™ group compared to Control (87.9% vs 83.9%).

The difference in the proportions of MVDSS responders [97.5%] between the two medical devices was 4.04% ([- 2.10%; infinity], P-value <0.0001).

Table 16. Primary Analysis: Proportion of Responders in MVDSS at Week 24 After Last Injection of Initial Treatment Phase Based on the Assessment of the Blinded Evaluator at the Site (FAS)

	saypha® ChIQ™ (N=322) (%; n/N*)	**Control (N=161) (%; n/N*)**	**Difference of Proportions[1] % (97.5% CI[2])**	**P-Value[3]**
Responder	87.9; 283 / 322	83.9; 135 / 161	4.04 (-2.10, infinity)	<0.0001
Non-Responder	12.1; 39 / 322	16.1; 26 / 161		

Note: N = Number of subjects in the analysis population. N* = Number of subjects in the analysis population with available data. n (%) = Number and percentage of responding subjects among N*. MVDSS = Midface Volume Deficit Severity Scale. FAS = Full Analysis Set. CI = Confidence Interval

Note: Subjects were defined as responder at a given visit on the MVDSS if they had a ≥1 point improvement relative to baseline. Baseline was defined as the last assessment prior to initial administration of the medical devices.

Note: Subjects with missing baseline MVDSS score and / or missing MVDSS score at Week 24 after last injection of the initial treatment phase were imputed as non-responders.

[1] saypha® ChIQ™ - Control.

[2] One-sided, exact unconditional confidence interval based on the score statistic.

[3] Derived from Farrington-Manning statistic. The non-inferiority margin was set to -10%.

Secondary effectiveness endpoints evaluated the response to treatment of midface volume deficit over time, as assessed by the blinded evaluator. The percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase compared to the score at Baseline visit is presented in Table 17 for the FAS.

For the FAS, comparable proportions of subjects in each treatment group were responders in MVDSS at Week 4 (97.3% of subjects with saypha® ChIQ™ vs 96.8% of subjects with Control), at Week 8 (98.0% vs 96.7%), and Week 16 (96.9% vs 96.7%) after last treatment of the initial treatment phase. The differences in the proportions of MVDSS responders [95% CI] between the two treatment groups were only about 1% at Week 4 (0.57% [-2.57, 4.91]), Week 8 (1.29% [-1.66%, 5.63%]), and at Week 16 (0.24% [-3,04%, 4.66%]). None was statistically significant.

The proportions of responders were higher for saypha® ChIQ™ compared to Control at Week 24 (96.9% vs 89.4%) and at Week 36 (90.1% vs 79.9%) after the last treatment of the initial treatment phase. The differences of proportions of MVDSS responders [95% CI] based on the blinded evaluator live assessment were statistically significant in favor for saypha® ChIQ™ at Week 24 (7.51% [2.82%, 13.67%]), and at Week 36 (10.21% [3.22%, 18.15%]).

At Week 48 after the last treatment of the initial treatment phase the proportion of MVDSS responders was higher for saypha® ChIQ™ than for Control (72.2% vs 62.9%). The difference in proportions [95% CI] was in favor of saypha® ChIQ™ and not statistically significant (9.30% [-0.01%, 18.90%]).

During the repeat-treatment phase, for the mFAS, comparable proportions of subjects in each treatment group (saypha® ChIQ™ vs Control) were responders in MVDSS at Week 4 (90.0% vs 90.3%) and at Week 12 (89.2% vs 87.3%) after last treatment. The proportions of MVDSS responders were higher for saypha® ChIQ™ group compared to Control group at Week 24 (87.0% vs 82.9%) after last treatment.

Table 17. Initial Treatment Phase: Proportion of Responders in MVDSS by Visit Based on the Assessment of the Blinded Evaluator at the Site (FAS)

	saypha® ChIQ™ (N=322) (%; n/N*)	Control (N=161) (%; n/N*)	Difference of Proportions[1] % (95% CI[2])
4 weeks after last injection			
Responder	97.3; 291 / 299	96.8; 149 / 154	0.57 (-2.57, 4.91)
Non-Responder	2.7; 8 / 299	3.2; 5 /154	-
Missing[3]	23	7	-
8 weeks after last injection			
Responder	98.0; 294 / 300	96.7; 147 / 152	1.29 (-1.66, 5.63)
Non-Responder	2.0; 6 / 300	3.3; 5 /152	-
Missing[3]	22	9	-
16 weeks after last injection			
Responder	96.9; 286 / 295	96.7; 147 / 152	0.24 (-3.04, 4.66)
Non-Responder	3.1; 9 /295	3.3; 5 / 152	-
Missing[3]	27	9	-
24 weeks after last injection			
Responder	96.9; 283 / 292	89.4; 135 / 151	7.51 (2.82, 13.67)
Non-Responder	3.1; 9 / 292	10.6; 16 / 151	-
Missing[3]	30	10	-
36 weeks after last injection			
Responder	90.1; 254 / 282	79.9; 115 / 144	10.21 (3.22, 18.15)
Non-Responder	9.9; 28 / 282	20.1; 29 / 144	-
Missing[3]	40	17	-
48 weeks after last injection			
Responder	72.2; 203 / 281	62.9; 90 / 143	9.30 (-0.01, 18.90)
Non-Responder	27.8; 78 /281	37.1; 53 / 143	-
Missing[3]	41	18	-

Note: N= Number of subjects in the analysis population. N* = Number of subjects in the analysis population with available data. n (%) = Number and percentage of responding subjects among N. MVDSS = Midface Volume Deficit Severity Scale. FAS = Full Analysis Set. CI = Confidence Interval.

Note: Subjects are defined as responder at a given visit on the MVDSS if they are showing an ≥1 point improvement relative to baseline. Baseline is defined as the last assessment prior to initial administration of the medical devices.

[1] saypha® ChIQ™ - Control.

[2] Two-sided CI according to Miettinen-Nurminen.

[3] Missing values were not taken into account in this analysis.

Further secondary endpoints evaluated the mean change in midface volume deficit, as measured by volumetric change measurement by using 3D digital photographic images at Week 4, 8, 16, 24, 36 and 48 after last injection of initial treatment phase compared to Baseline visit.

For the FAS, the overall volume changes (right and left midface combined) indicated an increase of the midface volume at all timepoints after initial treatment for both treatment groups. Volume changes were comparable on the respective sides of the midface (right vs left) within each treatment group.

At Week 4 after last treatment of the initial treatment phase, improvement of overall midface volume [SD] was about 2 cm^3 higher for subjects in the saypha® ChIQ™ group when compared to the Control group (8.538 [4.572] cm^3 vs 6.536 [4.163] cm^3). Over time, the mean CfB (SD) in overall midface volume decreased for both treatment groups, but there was still an improvement at Week 48 with higher volume changes for saypha® ChIQ™ compared to Control at all visits. Regarding volume changes per area of interest for both treatment groups, highest volume changes were found for submalar area, followed by zygomaticomalar and anteromedial areas.

Further secondary effectiveness endpoints entailed the evaluation of the global aesthetic improvement after correction of midface volume deficit, as assessed by the blinded evaluator at the site using the modified Global Aesthetic Improvement Scale (mGAIS). mGAIS scores ranged from 1 (much improved), to 2 (improved), 3 (no change), 4 (worse), and 5 (much worse). A summary of the proportions of mGAIS responders at Weeks 4, 8, 16, 24, 36, and 48 after last injection of the initial treatment phase based on the assessment of the blinded evaluator at the site is provided in Table 18 for the FAS.

For the FAS, comparable proportions of subjects in both treatment groups (saypha® ChIQ™ vs Control) were mGAIS responders at Week 4 (98.0% vs 97.4%), Week 8 (99.3% vs 98.0%), and Week 16 (97.6% vs 98.0%) after last injection of the initial treatment phase. At Week 24 (96.9% vs 89.4%), Week 36 (92.6% vs 87.5%), and at Week 48 (84.6% vs 73.4%) after last injection of the initial treatment phase, proportions of mGAIS responders were higher with saypha® ChIQ™ compared with Control.

The differences of proportions of mGAIS responders [95% CI] were in favor of saypha® ChIQ™ at Week 4 (0.58% [-2.23%, 4.64%]), Week 8 (1.31% [-0.78%, 5.03%], Week 24 (7.51% [2.82%, 13.67%]), Week 36 (5.05% [-0.70%, 11.98%]), and Week 48 (11.22% [3.16%, 19.93%]). At Week 16 the difference of proportions of mGAIS responders [95% CI] were in favor of Control (-0.41 % [-3.23%, 3.45%]). Only at Week 24 and Week 48 the difference of proportions of mGAIS responders between the two medical devices was statistically significant at level 5%.

Mean subject satisfaction scores for the aesthetic outcome ('Satisfaction with Outcome') were also generally comparable for both treatments as was the subjects' appearance appraisal 'Satisfaction with Cheeks'.

Table 18. Initial Treatment Phase: Proportion of Responders in Modified GAIS by Visit Based on Assessment by Blinded Evaluator at the Site (FAS)

Visit	saypha® ChIQ™ (N=322) (%; n/N*)	Control (N=161) (%; n/N*)	Difference of Proportions[1] % (95% CI[2])
4 weeks after last injection			
Responder	98.0; 292 / 298	97.4; 150 / 154	0.58 (-2.23, 4.64)
Non-Responder	2.0; 6 / 298	2.6; 4 /154	-
Missing[3]	24	7	-
8 weeks after last injection			
Responder	99.3; 298 / 300	98.0; 149 / 152	1.31 (-0.78, 5.03)
Non-Responder	0.7; 2 / 300	2.0; 3 / 152	-
Missing[3]	22	9	-
16 weeks after last injection			
Responder	97.6; 287 / 294	98.0; 149 / 152	-0.41 (-3.23, 3.45)
Non-Responder	2.4; 7 / 294	2.0; 3 / 152	-
Missing[3]	28	9	-
24 weeks after last injection			
Responder	96.9; 283 / 292	89.4; 135 / 151	7.51 (2.82, 13.67)
Non-Responder	3.1; 9 / 292	10.6; 16 / 151	-
Missing[3]	30	10	-
36 weeks after last injection			
Responder	92.6; 261 / 282	87.5; 126 / 144	5.05 (-0.70, 11.98)
Non-Responder	7.4; 21 / 282	12.5; 18 / 144	-
Missing[3]	40	17	-

Visit	saypha® ChIQ™ (N=322) (%; n/N*)	Control (N=161) (%; n/N*)	Difference of Proportions[1] % (95% CI[2])
48 weeks after last injection			
Responder	84.6; 237 / 280	73.4; 105 / 143	11.22 (3.16, 19.93)
Non-Responder	15.4; 43 /280	26.6; 38 / 143	-
Missing[3]	42	18	-

Note: N= Number of subjects in the analysis population. N* = Number of subjects in the analysis population with available data. n (%) = Number and percentage of subjects among N*. GAIS = Global Aesthetic Improvement Scale. FAS = Full Analysis Set. CI = Confidence Interval.

Note: Subjects were defined as responders at a given visit on the modified GAIS if they were rated as 'Much improved' or 'Improved'.

[1] saypha® ChIQ™ - Control.

[2] Two-sided CI according to Miettinen-Nurminen.

[3] Missing values were not imputed and were not taken into account in this analysis.

Upon the treatment for the augmentation of midface region, indirect effects on adjacent anatomical areas including the nasolabial folds (NLFs) were observed. These secondary observations included both improvement and worsening of the NLF depth (severity) in some subjects.

Approximately half of subjects in the US clinical study with moderate to severe baseline NLF severity experienced improvement following midface treatment, while others showed no change and a small number experienced worsening. The proportion of subjects demonstrating improvement remained generally stable over time.

No injections were administered to the nasolabial folds during the study. The device is intended for the treatment of the midface region and is not intended for the treatment of nasolabial folds.

3. Subgroup Analyses

The following subgroups were evaluated for potential association with safety and effectiveness outcomes: Injection equipment, gender, Fitzpatrick skin type, race and ethnicity, age, baseline MVDSSS value, study site, injection volume (sum of baseline and touch-up treatments; categorized as follows: Group 1: ≤3 mL; Group 2: >3 mL and <7 mL; Group 3: ≥7 mL), combined race and ethnicity (white & Hispanic or Latino vs. white & not Hispanic or Latino).

Overall, the clinical investigation was not powered for subgroup analysis of the primary endpoint, and confidence levels were not adjusted for multiplicity.

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

The following results have been observed in the analysis of subgroups for saypha® ChIQ™ (analyses done in FAS):

- Injection Volume: Difference in treatment effects [two-sided 95% CI] between the two treatment groups was significant in favor of subgroup '≥7mL injection volume' compared to reference group '>3 mL and <7 mL'.
- 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 MVDSS score, and Injection Technique (needle vs. cannula).
- The model did not converge for subgroups 'Race' and 'Ethnicity'
- An exploratory analysis, difference in proportions of responders in MVDSS at Week 24 after last injection of initial treatment phase based on the assessment of the blinded evaluator at the site was analyzed for the same subgroups. However, the clinical investigation was not powered for subgroup analysis of the primary endpoint, and confidence levels were not adjusted for multiplicity. The non-inferiority margin of 10% was exceeded by the lower limit of the one-sided 97.5% CI for some of the subgroups.

- For the FAS, non-inferiority margin of -10% was exceeded by the lower limit of the one-sided 97.5% CI for these subgroups: Injection Equipment: 'Needle' and 'cannula'; Gender: 'Female'; 'FST II', 'FST III', and 'FST IV'; Race, Ethnicity and Race and Ethnicity Combined: 'White', 'Not hispanic or latino', 'White/not hispanic or latino'; Age Group: '46 to 65 years', and '66 to 75 years'; MVDSS at Baseline: 'Moderate' MVDSS, and 'severe' MVDSS; Injection Volume: '≤3mL', and '≥7mL'; Site: Site 113, Site 116.
- For the PPS, in general, analysis confirmed the results obtained for the FAS.

In addition to the overall analysis based on the SAF, the occurrence of AEs reported during the initial treatment phase was analyzed separated by several subgroups with results as follows:

- Injection equipment: the subgroup treated by means of cannula reported a higher amount of TEAEs in general compared to the subgroup treated with needle ((51 [47.2%] vs 75 [35.0%] subjects). Both subgroups were similarly affected by ADEs
- Fitzpatrick Skin Type (FST): the subgroups 'FST IV', 'FST V' and 'FST VI' all reported a lower number of TEAEs in general compared to the subgroups 'FST I', 'FST II' and 'FST III' (difference in proportion of subjects affected >10%). However, subgroups were similarly affected by ADEs
- Age Groups: no remarkable difference between age subgroups in proportion of subjects affected by ADEs was noticed
- Race and Ethnicity combined: the subgroup of 'white/not Hispanic or Latino' subjects reported a higher number of TEAEs compared to the subgroup of 'white/Hispanic or Latino' subjects (99 [44.2%] vs 17 [28.8%] subjects), with a difference in proportion of subjects affected >10% between 'white/not Hispanic or Latino' vs 'white/Hispanic or Latino'. However, both subgroups were similarly affected by ADEs

The occurrence of ISRs was analyzed separately by several subgroups:

- Injection Equipment: severe ISRs after baseline treatment affected more subjects treated with needle (needle: 13 [6.3%] subjects; cannula: 1 [1.0%] subject). No general remarkable difference between treatment with needle and cannula was found
- Age Groups: subjects aged between 66 and 75 years documented more often any ISR than younger subjects (20 [40.8%] for 66-75 years vs 16 [29.1%] for 22-45 years and 25 [25.5%] for 45-65 years old subjects)
- Race and Ethnicity Combined: the subgroup of white/not Hispanic or Latino subjects had a higher proportion of subjects with ISRs compared to the subgroup of white/Hispanic or Latino subgroup. (difference 'white/not Hispanic or Latino' (70 [32.3%]) vs 'white/Hispanic or Latino' (8 [14.3%]) was ~18%). This observation applied to all types of ISR with differences in proportions of at least 10% in favor of subgroup 'white/not Hispanic or Latino'

4. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 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 clinical study included 47 Investigators (16 Principal Investigators, 31 Evaluating 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.

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

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

advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was the percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase compared to the pre-treatment score at baseline visit. Subjects were defined as responders at a given visit on the MVDSS if they had ≥1 point improvement relative to baseline.

For the FAS, higher percentages of subjects were MVDSS responders [95% CI] at Week 24 after last injection of initial treatment phase in the saypha® ChIQ™ group compared to Control (87.9% vs 83.9%). The difference in the proportions of MVDSS responders [97.5%] between the two medical devices was 4.04% ([- 2.10%; infinity], P-value <0.0001).

The results of the primary analysis of the primary endpoint also displayed saypha® ChIQ™ compared to Control for the PPS. The one-sided 97.5% CI not only was entirely above the non-inferiority margin of -10% but also above zero.

Effectiveness results were further supported by the results of the secondary effectiveness endpoints for the initial and repeat-treatment phase.

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® ChIQ™ was generally safe and well tolerated both during initial treatment- and repeat treatment-phase, and no clinically relevant differences were seen in the safety profile of saypha® ChIQ™ compared to Control.

Initial Treatment Phase:

In total, 462 AEs were documented during the initial treatment phase and 460 of the AEs were classified as TEAE. 38.3% (185/483) subjects of the overall SAF experienced at least one TEAE. At least one TEAE was documented for 39.1% (126/322) subjects of the saypha® ChIQ™ group and 36.6% (59/161) subjects of the Control group.

142 AEs in 15.7% (76/483) subjects were considered by the investigator to have a relationship to the medical device itself and/or the procedure and were categorized as ADE with higher proportion of subjects affected by an ADE in the Control group (17.4% [28/161/] subjects) compared to the saypha® ChIQ™ group (14.9% [48/322] subjects).

Overall, 1 subject (saypha® ChIQ™ group) terminated the investigation prematurely due to a TEAE. One other subject (saypha® ChIQ™ group) experienced a TEAE, which led to discontinuation of the injection, i.e., subject was discontinued from further treatment with the medical device.

In total, 2 adverse events of special interest (AESIs) were reported in 2 subjects. One (cerebrovascular accident of unknown mechanism) was assessed as not related to medical device nor to procedure approximately 6 months after baseline treatment. One (external vascular occlusion on left side of face) was assessed as possibly related to medical device and procedure with onset on study day 5 after baseline treatment.

In total 6 serious adverse events (SAEs) were reported in 1.2% (6/483) subjects. One SAE (‘vascular skin disorder’; saypha® ChIQ™ group) was assessed by the investigator as possibly related to medical device and procedure.

Overall, about 30% of subjects in each treatment group reported at least one ISR after the baseline injection with a lower percentage of subjects affected in the saypha® ChIQ™ group (28.5% [89/312] subjects) compared to Control (34.2% [53/155] subjects). The reported ISRs were similar between the treatment groups. The majority of ISRs were mild or moderate in intensity (75%; 65/89 ISR experienced after initial injection).

Repeat-Treatment Phase:

In total, 90 AEs were documented during the repeat-treatment phase and all of these were classified as TEAEs: 19.8% (38/192) subjects of the overall mSAF experienced at least one TEAE. The proportion of subjects with at least one TEAE was higher in the Control group (27.0% [20/74] subjects) compared to the saypha® ChIQ™ group (15.3% [18/118] subjects).

In total, 16 AEs in 3.6% (7/192) subjects overall were considered by the investigator to have a relationship to the medical device itself and/or the procedure and were categorized as ADE with 5.4% (4/74) subjects affected by an ADE in the Control group compared to 2.5% (3/118) subjects in the saypha® ChIQ™ group.

Overall, 1 subject (saypha® ChIQ™ group) terminated the investigation prematurely due to a TEAE during the repeat-treatment phase. One other subject (saypha® ChIQ™ group) experienced a TEAE, which led to discontinuation of the injection, i.e., subject was discontinued from further treatment with the medical device.

During repeat-treatment phase, in total 2 SAEs were reported in 1.7% (2/118) subjects. Both events were reported as non-related to medical device and procedure.

Compared to the initial treatment phase, a lower proportion of subjects (17% subjects overall) reported ISRs after repeat-treatments. The maximum duration for reported ISRs was similar.

C. Benefit-Risk Conclusions

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

The primary effectiveness endpoint was the percentage of responders on the 5-point MVDSS, based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase compared to the pre-treatment score at baseline visit. For the FAS, higher percentages of subjects were MVDSS responders [95% CI] at Week 24 after last injection of initial treatment phase in the saypha® ChIQ™ group compared to Control (87.9% vs 83.9%). Overall, saypha® ChIQ™ was shown to be non-inferior to Control.

The results of the primary effectiveness endpoint were supported by the results of the secondary effectiveness endpoints:

For the FAS, the differences of proportions of mGAIS responders based on the assessment of the blinded evaluator at the site were in favor of saypha® ChIQ™ at Week 4, Week 8, Week 24, Week 36, and Week 48. At Week 16 the difference of proportions of mGAIS responders [95% CI] was in favor of Control. At Week 24 and Week 48 the difference of proportions of mGAIS responders between the two medical devices was statistically significant at level 5%. For the PPS the difference in proportions of mGAIS responders based on the assessment of the blinded evaluator at the site indicated a statistically significant difference also at Week 36 after last injection of the initial treatment phase in favor of saypha® ChIQ™ (6.57% [0.60%, 13.82%]).

Mean subject satisfaction scores for the aesthetic outcome ('Satisfaction with Outcome') were also generally comparable for both treatments as was the subjects' appearance appraisal 'Satisfaction with Cheeks'.

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 safety assessment was conducted in this study providing a safety dataset as further evidence of a positive benefit/risk assessment of treatment with saypha® ChIQ™.

Less than a third of all subjects (28.5%, 89/312 after initial treatment) experienced an injection site reaction, which included firmness and tenderness to touch (24.7%, 117/312 each), lumps/bumps (23.7%, 74/312), swelling (22.8%, 71/312), bruising and pain after injection (20.2%, 63/312 each), redness (17.9%, 56/312), discoloration (9.9%, 31/312) and itching (4.5%, 14/312). The vast majority of ISRs were mild or moderate in intensity. 5.2% of ISRs were considered severe.

The most commonly reported TEAEs related to the study device or procedure were headache (7.5%, 24/322), palpatory finding abnormal (3.1%, 10/322), injection site pain (2.5%, 8/322), injection site bruising (1.9%, 6/322), injection site swelling (1.6%, 5/322), injection site mass and mastication disorder (1.2%, 4/322 each), jaw disorder (0.6%, 2/322), nodule and skin laxity (0.3%, 1/322 each),

Treatment with saypha® ChIQ™ 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® ChIQ™ 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® ChIQ™ 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 MVDSS score, and Injection Technique.

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

Patient Perspective

Patient perspectives considered during the review included:

- Modified Global aesthetic improvement as assessed by the subject. mGAIS response rate based on the subject self-assessments was 87.3% (255/292) at Week 24 after initial treatment.
- Impact and effectiveness of study treatment from the subjects' perspective as assessed by the validated FACE-Q patient-reported outcome measurement. Subject satisfaction was high with a mean score of 68.2 at Week 24 after initial treatment.
- The mean pain scores based on subject perception of pain were generally low and did not exceed 2.5 immediately after treatment and 0.7 15 minutes thereafter on the 11-point pain scale at any timepoint. The mean pain scores based on subject perception of pain and assessed after initial treatment with saypha® ChIQ™ and Control were comparable in both treatment groups.

Treatment with saypha® ChIQ™ was generally safe and well tolerated both during initial treatment- and repeat treatment-phase, and no clinically relevant differences were seen in the safety profile of saypha® ChIQ™ compared to Control.

In conclusion, given the available information above, the data support that for cheek augmentation and correction of midface volume deficit 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. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIII. CDRH DECISION

CDRH issued an approval order on June 12, 2026. The final conditions of approval cited in the approval order are described below.

1. PAS/FST is a prospective, multicenter, U.S., open-label, single-arm post-approval safety study in subjects with Fitzpatrick Skin Types V and VI treated with saypha® ChlQ™ for moderate to severe midface volume deficit to further characterize the safety profile in this subpopulation.

Study purpose: To further characterize the safety profile of saypha® ChlQ™ in subjects with Fitzpatrick Skin Types V and VI treated for moderate to severe midface volume deficit.

Study design (specify control, randomization, etc.): Single arm, no comparator

Total number of subjects: Up to 50 screened; 45 treated subjects to be included in the Safety Analysis Set (SAF)

Length of follow-up and frequency of assessments: Approximately 28 weeks per subject (up to 2-week screening period+ baseline treatment+ optional touch-up at Week 2 + 24-week follow-up). Total expected study duration is approximately 12 months, including an approximately 6-month recruitment period. Subjects will be followed for 24 weeks after the last injection (Visit 8, Week 24 = End of Study Visit). Subjects will attend in-clinic visit at Visit 3b (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 16) and Visit 7 (Week 24), all times calculated as of after last injection. Safety will be assessed throughout the investigation. Patient diaries

will be used to capture injection site reactions and symptoms of interest (including vision changes) after treatment. Protocol-defined visual examinations will be performed at each visit to assess ocular safety. Visual examinations will be performed by trained site personnel according to standardized study procedures. Standardized photography will be obtained at baseline, treatment and follow-up visits. Interim safety data (number of subjects enrolled, sites enrolled, summary of AEs/AESls) will be submitted to FDA as part of the 6-month PAS Progress Reports.

Primary Safety Endpoint: Incidence, severity, seriousness, relatedness, and outcome of treatment-emergent device- and/or procedure-related adverse events through Week 24

Secondary Safety Endpoint: Injection site reactions as recorded in the subject diaries during the first 4 weeks (28 days) after each treatment (i.e., either 4 weeks after baseline or 6 weeks in case of touch-up treatment). Injection site reactions will be assessed overall and for each side of the midface (i.e., left and right side separately). Subject evaluation of pain after each treatment on an 11-point NPRS (O = no pain; 10 = worst pain imaginable).

High-level description of the data analysis plan for the primary endpoints:

Analysis Population: The Safety Analysis Set (SAF) is defined as all subjects who received at least one treatment with saypha® ChlQ™. The Full Analysis Set (FAS) similarly includes all subjects who received at least one treatment with saypha® ChlQ™.

Descriptive Methods: For categorical parameters, counts and percentages will be presented. For continuous parameters, descriptive statistics will include n, mean, standard deviation, median, and range. Two-sided 95% confidence intervals will be calculated for key incidence rates. Injection site reactions, patient diary findings, visual assessment findings, and predefined events of special interest will be summarized descriptively. No general imputation methods will be applied; methods will be described for each variable separately in the Statistical Analysis Plan (SAP).

Reference to protocol: Study outline received May 26, 2026 - VOLIDO-PAS

Plan for interim data release: Interim safety data (number of subjects enrolled, sites enrolled, summary of AEs/AESls) will be submitted to FDA as part of the 6-month PAS Progress Reports.

2. PAS/Scale Validation is described below:

Study purpose/objectives: The objective of this study is to determine the inter-rater and intra-rater reliability of the Croma Midface Volume Deficit Severity Scale when utilized in live subject ratings and to confirm that a 1-point difference on the scale is clinically relevant across all FST.

Study design: This is a single-center, non-interventional study designed to provide supplemental data to pool with the original validation data of the Croma MVDSS.

Total number of subjects: Live validation: Approximately 50 subjects; target S FST I, 13 FST V, 15 FST VI. Clinical Relevance (CR): 30 image pairs will be selected; target 10 0-point difference, 10 1-point difference, 5 2-point difference, 3 3-point difference, and 2 4-point difference; target 5 FST I, 15 FST V, 10 FST VI.

Length of follow-up and frequency of assessments: The Live Validation will consist of two (2) Rounds, two (2) weeks apart.

Live Validation (LV)

Intra-rater: Overall Cicchetti-Allison and Fleiss Cohen weighted kappa coefficients of the three (3) Live Validation (LV) Raters based on MVDSS scores assigned by LV raters during LV Rounds 1 and 2. Data will be presented independently from this study and if appropriate pooled across the original and supplemental studies.

Cicchetti-Allison weighted kappa is provided as a supportive sensitivity analysis to demonstrate the robustness of the reliability conclusions across alternative weighting approaches.

Inter-rater: Median pairwise Cicchetti-Allison and Fliess Cohen weighted kappa coefficients for each pairwise combination of the three (3) LV Raters based on MVDSS scores assigned by LV Raters during LV Round 1. Data will be presented independently from this study and if appropriate pooled across the original and supplemental studies.

Cicchetti-Allison weighted kappa is provided as a supportive sensitivity analysis to demonstrate the robustness of the reliability conclusions across alternative weighting approaches.

Clinical Relevance (CR)

Difference (and corresponding 95% Cl) in estimated marginal means of MVDSS scores assigned by CR Reviewers, for image pairs with 0-point True Grade difference versus pairs with 1-point True Grade difference, modeling rater and image pair as random effects.

High-level description of the data analysis plan for the primary endpoints:

A statistical approach to test poolability will be conducted for both studies prior to pooling data.

The Live Validation will consist of two (2) Rounds, two (2) weeks apart. Each rater will assign a score for MVD severity of zero (O) to four (4) based on the photonumeric scale. For analysis, the primary endpoint will be analyzed on the pooled data. Additionally, a sensitivity subgroup analysis will be conducted to assess the consistency of model performance between the original live validation and the supplementary validation.

Clinical Relevance consisted of two rounds: a comparative assessment where clinicians rated image pairs as clinically different or not and a static Image review where reviewers graded each image independently using the Croma MVDSS. This exercise was designed to show that a 1-point difference on the scales represents a clinically meaningful difference. The exercise will be carried out on a new set of thirty {30) image pairs

Reference to protocol:

Study outline received May 26, 2026 - Re: CROMA Midface Volume Deficit Severity Scale - Supplementary Study Protocol Synopsis

Plan for interim data release: 6-month PAS progress reports

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.