DIRECTIONS FOR USE

saypha®[®] ChIQ™

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. 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). The medical device has a sodium hyaluronate concentration of 23 mg/mL in a phosphate buffered saline at physiological pH and contains 3 mg/mL lidocaine hydrochloride.

2. INTENDED USE/INDICATIONS

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

3. 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.

4. WARNINGS

- saypha® ChIQ™ must not be injected into blood vessels. Introduction of the product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers; for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly, and apply the least amount of pressure necessary. Negative aspiration cannot be relied upon to avoid vascular complications. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face and tissue compression have been reported and include occlusion of vessels, vasospasm, and vascular compromise, resulting in ischemia, temporary or permanent visual impairment, loss of vision, ophthalmoplegia, cerebral ischemia or cerebral hemorrhage

leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of stroke, pallor, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and, possibly, evaluation by an appropriate healthcare specialist should an intravascular injection occur (see Healthcare Professional Instructions).

- Product use at specific sites in which an active inflammatory process (skin eruptions such as sores, cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, blisters, scarring, papules, and delayed onset of granulomas have been reported following the use of dermal fillers.
- Injection site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) starting early after treatment and generally resolve within 14 days. Refer to the ADVERSE EVENTS section for details.

5. PRECAUTIONS

- saypha® ChIQ™ is packaged for single use. Do not re-sterilize. Do not use if package is open or damaged.
- To minimize the risk of potential complications, this product should only be used by healthcare professionals who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the injection site.
- Healthcare professionals are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- The safety and effectiveness for the treatment of anatomic regions other than the midface have not been established in controlled clinical studies.
- As with all transcutaneous procedures, soft tissue filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- saypha® ChIQ™ should be used as supplied. Modification or use of the products outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 21 years of age has not been established.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- saypha® ChIQ™ should be used with caution in patients with a history of autoimmune or connective tissue disease and/or who are receiving immune (-modulation) or immunosuppressive therapy, or with a history of severe allergies or anaphylactic shock. Treatment decisions need to be taken on a case-to-case basis. For patients presenting with an active or evolving autoimmune disease, the treatment is not recommended.

- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants) may, as with any injection, experience increased bruising or bleeding at injection sites.
- Individual patient variability and the treatment area may affect the biodegradation kinetics of saypha® ChIQ™. Analysis of clinical data suggests that the product may remain in tissue for approximately two years following treatment.
- The syringe is made of glass, handle with care (risk of laceration when broken).
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with saypha® ChIQ™, there is a possible risk of eliciting an inflammatory reaction at the implant site. An inflammatory reaction is also possible if the product is administered before the skin has healed completely after such a procedure.
- Failure to comply with the needle attachment instructions (see section 8A) could result in needle disengagement and/or product leakage.
- saypha® ChIQ™ is a clear, transparent gel without visible particulates. If the content of a syringe shows signs of separation and/or is not clear, do not use the syringe; notify *[placeholder for contact details]*.

6. ADVERSE EVENTS (AE)

A. Clinical Evaluation of saypha® ChIQ™ in the midface region

A randomized, subject- and evaluator-blinded, active treatment controlled, parallel group, non-inferiority, multicenter clinical study was conducted to evaluate the safety and effectiveness of saypha® ChIQ™ versus another US-approved HA dermal filler plus lidocaine (Control) for midface augmentation in order to correct volume deficit. During the study, 322 subjects were treated with saypha® ChIQ™, and 161 subjects with Control. Touch-up treatment, if needed to achieve optimal correction, occurred approximately 2 weeks after the initial injection. Eligible subjects (192) received an optional repeat-treatment with saypha® ChIQ™ (regardless of the initial treatment group) 48 to 60 weeks after the initial or touch-up injection. If necessary, an optional touch-up treatment was performed 2 weeks after the repeat-treatment. At the end of each treatment session, subjects used a diary to record injection site reactions (ISRs) and AEs that occurred within 4 weeks after treatment. Subjects were instructed to rate each ISR listed in the diary as Mild, Moderate, Severe, or None.

Local ISRs after the initial treatment were recorded in 28.5% of subjects treated with saypha® ChIQ™ and 34.2% of subjects treated with Control (Table 1). The most common ISRs for both groups were tenderness to touch, firmness, lumps/bumps, swelling, pain after injection, bruising, and redness. The vast majority of ISRs were mild or moderate in intensity. ISRs after touch-up treatment were similar to those after the initial treatment, but lower in frequency.

Table 1. Injection Site Reactions After Initial Treatment by Maximum Intensity

Type of ISR Intensity	Baseline Treatment		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 [1]	**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
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[2]	**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. ISR = Injection Site Reaction.
[1] Other than Redness or Bruising
[2] 'Other' was used in subject diary to describe a symptom that did not appear in the listed categories. Symptoms synonymous with predefined ISR categories were not recorded as separate AEs; all other symptoms were further assessed by the investigator and recorded as AEs as appropriate

Table 2 shows the duration of all ISRs after initial treatment. The maximum duration for any ISR reported was similar between treatments with saypha® ChIQ™ and Control, and most ISR lasted for less than 14 days.

Table 2. Injection Site Reactions After Initial Treatment by Maximum Duration

Type of ISR Duration Category	saypha® ChIQ™ (N = 312) (%; n/N)	Control (N = 155) (%; n/N)
At least one ISR	**28.5; 89/312**	**34.2; 53/155**
1-3 days	10.9; 34/312	15.5; 24/155
4-7 days	5.1; 16/312	4.5; 7/155
8-14 days	8.7; 27/312	11.6; 18/155
15-28 days	3.8; 12/312	2.6; 4/155
Bruising	**20.2; 63/312**	**22.6; 35/155**
1-3 days	8.0; 25/312	11.6; 18/155
4-7 days	4.8; 15/312	3.2; 5/155
8-14 days	5.8; 18/312	5.8; 9/155
15-28 days	1.6; 5/312	1.9; 3/155
Discoloration [1]	**9.9; 31/312**	**8.4; 13/155**
1-3 days	7.1; 22/312	4.5; 7/155
4-7 days	1.3; 4/312	1.9; 3/155
8-14 days	1.3; 4/312	1.9; 3/155
15-28 days	0.3; 1/312	0; 0/155
Firmness	**24.7; 77/312**	**27.7; 43/155**
1-3 days	12.2; 38/312	14.8; 23/155
4-7 days	3.5; 11/312	5.2; 8/155
8-14 days	5.4; 17/312	6.5; 10/155
15-28 days	3.5; 11/312	1.3; 2/155
Itching	**4.5; 14/312**	**7.1; 11/155**
1-3 days	2.9; 9/312	7.1; 11/155
4-7 days	0.6; 2/312	0; 0/155
8-14 days	0.6; 2/312	0; 0/155
15-28 days	0.3; 1/312	0; 0/155
Lumps/Bumps	**23.7; 74/312**	**27.7; 43/155**
1-3 days	11.5; 36/312	17.4; 27/155
4-7 days	4.2; 13/312	1.9; 3/155
8-14 days	5.1; 16/312	5.8; 9/155
15-28 days	2.9; 9/312	2.6; 4/155

Type of ISR Duration Category	saypha® ChIQ™ (N = 312) (%; n/N)	Control (N = 155) (%; n/N)
Pain after injection	**20.2; 63/312**	**26.5; 41/155**
1-3 days	12.5; 39/312	16.8; 26/155
4-7 days	3.5; 11/312	7.1; 11/155
8-14 days	2.6; 8/312	1.9; 3/155
15-28 days	1.6; 5/312	0.6; 1/155
Redness	**17.9; 56/312**	**23.2; 36/155**
1-3 days	13.5; 42/312	16.8; 26/155
4-7 days	2.6; 8/312	3.9; 6/155
8-14 days	1.3; 4/312	1.9; 3/155
15-28 days	0.6; 2/312	0.6; 1/155
Swelling	**22.8; 71/312**	**28.4; 44/155**
1-3 days	12.8; 40/312	18.7; 29/155
4-7 days	5.8; 18/312	7.1; 11/155
8-14 days	2.2; 7/312	1.9; 3/155
15-28 days	1.9; 6/312	0.6; 1/155
Tenderness to touch	**24.7; 77/312**	**30.3; 47/155**
1-3 days	9.9; 31/312	14.2; 22/155
4-7 days	6.1; 19/312	5.8; 9/155
8-14 days	6.1; 19/312	7.7; 12/155
15-28 days	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. ISR = Injection Site Reaction.

[1] Other than Redness or Bruising

A lower proportion of subjects (17% subjects overall) reported ISRs after repeat-treatments. The maximum duration for reported ISRs was similar.

Persisting injection-site reactions lasting more than 28 days were reported in 0.4% (2/483) of subjects during initial treatment and in 0.8% (1/118) of subjects during repeat treatment. All events were mild, non-serious, classified within the SOC *General disorders and administration-site conditions*, and resolved without sequelae. AEs were also reported by the treating investigator at follow-up visits. Overall, 142 treatment-emergent adverse device effects (ADEs) were reported for 14.9% of subjects after initial/touch-up treatment with saypha® ChIQ™ and for 17.4% of subjects after treatment with Control. The most commonly reported ADE was headache (Table 3). The majority of ADEs were mild or moderate in severity. One (1) serious adverse event (SAE) of vascular skin disorder was classified as possibly related to medical device and procedure.

Table 3. Adverse Device Effects by Preferred Term in >1 Subject Overall During Initial Treatment Phase

MedDRA [1] 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]**
Headache	7.5; 24/322 [34]	5.0; 8/161 [9]	6.6; 32/483 [43]
Discomfort with palpation	3.1; 10/322 [11]	5.6; 9/161 [10]	3.9; 19/483 [21]
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]
Mastication disorder	1.2; 4/322 [5]	2.5; 4/161 [4]	1.7; 8/483 [9]
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]
Jaw discomfort	0.6; 2/322 [4]	0.6; 1/161 [1]	0.6; 3/483 [5]
Dizziness	0; 0/322 [0]	1.9; 3/161 [3]	0.6; 3/483 [3]
Nodule	0.3; 1/322 [1]	0.6; 1/161 [1]	0.4; 2/483 [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. ADE = Adverse Device Effects.
[1] MedDRA version 27.0
[2] PT with >1 subject overall displayed
[3] Related to procedure and/or device

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

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

AEs (number of patients) reported during the repeat-treatment phase were injection site pain (3), injections site mass (2), headache (2), ecchymosis (1), injection site discomfort (1), injection site erythema (1), injection site induration (1), injection site pruritus (1) and palpatory finding (1).

During the study, the safety profiles of saypha® ChIQ™ and Control were found to be comparable.

The following undesired side effects have been observed with similar viscoelastic implants and are considered as potential risks for this device: abscess, angioedema, bacterial infection, capsular contracture, device dislocation, fever, fibrosis, herpes simplex reactivation, hypoesthesia, malaise, nausea, nerve damage, numbness, paresthesia, peeling, phlebitis, physical asymmetry, rash, scleroderma, sebaceous hyperplasia, skin disorders, syncope/fainting, tactile disorder.

Adverse reactions should be reported to *[placeholder for contact details]*.

7. CLINICAL STUDIES

A. Pivotal Study for saypha® ChIQ™

a. Pivotal Study Design

A randomized, subject- and evaluator-blinded, active treatment controlled, parallel group, non-inferiority, multicenter clinical study was conducted to evaluate the safety and effectiveness of saypha® ChIQ™ versus the Control for midface augmentation in order to correct volume deficit. Of the 486 subjects randomized, 483 subjects were treated (322 subjects with saypha® ChIQ™ and 161 subjects with Control). An optional touch-up treatment was performed approximately 2 weeks after the initial injection to achieve optimal correction. Subjects returned for follow-up visits 4, 8, 16, 24, 36 and 48 weeks after last treatment.

A total of 192 subjects were eligible and willing to 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 repeat-treatment had their end of study visit at Week 48.

b. Study Endpoints

The primary endpoint was the percentage of responders on the validated 5-point Midface Volume Deficit Severity Scale (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 a ≥1 point improvement relative to baseline.

Secondary endpoints were the effectiveness of saypha® ChIQ™ versus the Control for correction of moderate to severe midface volume deficit based on the blinded evaluator's live assessment over time. Additional secondary effectiveness endpoints included the evaluation of global aesthetic improvement (GAIS) based on subject's assessments, as well as the subject's satisfaction with outcome and appearance appraisal, and the injection volume required to achieve optimal correction.

c. Subject Demographics

A total of 483 randomized subjects were treated. Of these, 322 subjects received treatment with saypha® ChIQ™, and 161 subjects 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. 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. Subject demographics and pre-treatment characteristics of the saypha® ChIQ™ and Control groups are presented in Table 4.

Table 4. Subject Demographics

Characteristics	Attribute	Overall (N=483) (%; n/N)
Age (years)	Median	55.0
	Range	24 - 75
Gender	Male	5.4; 26/483
	Female	94.6; 457/483
Ethnicity	White	87.6; 423/483
	Black or African American	5.6; 27/483
	American Indian or Alaska Native	3.3; 16/483
	Asian	2.5; 12/483
	Native Hawaiian or Other Pacific Islander	0.4; 2/483
	Afghan	0.2; 1/483
	Bi-racial	0.2; 1/483
	Black/white	0.2; 1/483
Fitzpatrick Skin Type	I	2.1; 10/483
	II	30.0; 145/483
	III	35.6; 172/483
	IV	23.4; 113/483
	V	5.2; 25/483
	VI	3.7; 18/483

Note: N= Number of subjects in the analysis population. n (%) = Number and percentage of subjects among N.

d. Effectiveness Results

The primary effectiveness endpoint of the study was met and non-inferiority of saypha® ChIQ™ relative to Control in terms of MVDSS responder rates was shown at 24 weeks after treatment start (Table 5). Similar proportions of MVDSS responders showing at least a clinically significant 1-point improvement were found in the two treatment groups (87.9% of subjects with saypha® ChIQ™ vs 83.9% of subjects with Control).

Table 5. Proportion of Responders in MVDSS at Week 24 - Blinded Evaluator

	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. 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%.

Analysis of secondary effectiveness endpoints revealed comparable proportions of MVDSS responders over time between the two treatment groups, as rated by the blinded evaluator (Table 6) and was confirmed in the repeat-treatment phase.

Table 6. MVDSS Response Rate Over Time – Blinded Evaluator

	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.

Aesthetic improvement based on the GAIS assessment by the subject showed comparable proportions of subjects in both treatment groups over time (Table 7).

Table 7. GAIS Response Rate - Assessment by Subject

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	94.6; 283/299	94.8; 146/154	-0.16 (-4.26, 4.98)
Non-Responder	5.4; 16/299	5.2; 8/154	-
Missing [3]	23	7	-
8 weeks after last injection			
Responder	93.0; 281/302	93.4; 142/152	-0.37 (-4.98, 5.25)
Non-Responder	7.0; 21/302	6.6; 10/152	-
Missing [3]	20	9	-
16 weeks after last injection			
Responder	91.5; 269/294	90.1; 137/152	1.37 (-4.01, 7.75)
Non-Responder	8.5; 25/294	9.9; 15/152	-
Missing [3]	28	9	-
24 weeks after last injection			
Responder	87.3; 255/292	82.8; 125/151	4.55 (-2.22, 12.18)
Non-Responder	12.7; 37/292	17.2; 26/151	-
Missing [3]	30	10	-
36 weeks after last injection			
Responder	77.7; 219/282	83.3; 120/144	-5.67 (-13.14, 2.57)
Non-Responder	22.3; 63/282	16.7; 24/144	-
Missing [3]	40	17	-
48 weeks after last injection			
Responder	76.1; 213/280	69.2; 99/143	6.84 (-1.97, 16.13)
Non-Responder	23.9; 67/280	30.8; 44/143	-
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. 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.

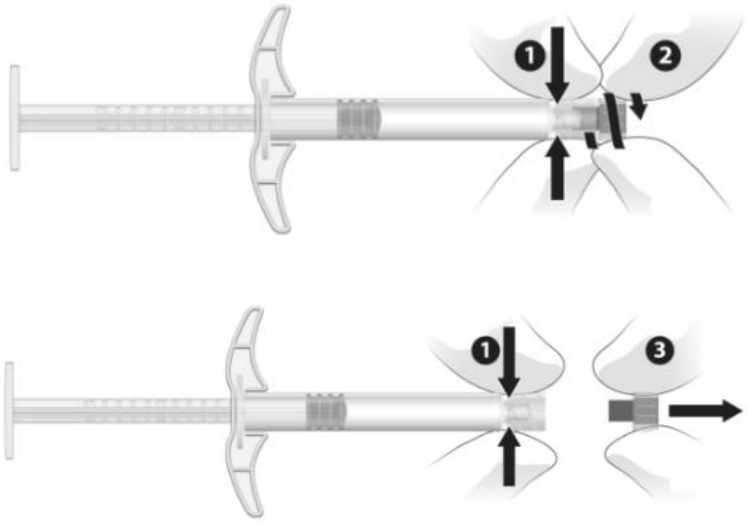
[3] Missing values were not imputed and were not taken into account in this analysis.

Mean subject satisfaction scores for the overall aesthetic treatment outcome (‘Satisfaction with Outcome’) were comparable for both treatments. Subjects’ appearance appraisal ‘Satisfaction with Cheeks’ was higher for saypha® ChIQ™ compared to Control. Treatment of the midface may result in indirect changes in the appearance of the nasolabial folds (NLFs). 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.

8. INSTRUCTIONS FOR USE

A. To Attach Needle to Syringe

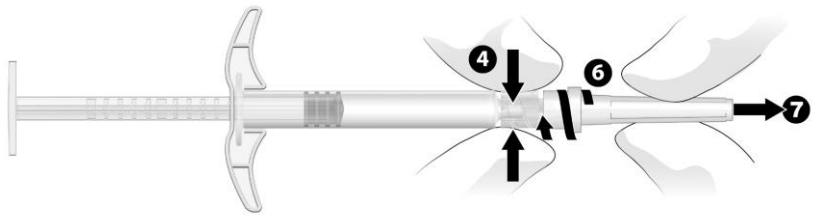
Hold the Luer-Lock adapter as shown in (1). To remove the tip cap, twist (2) and pull carefully (3).



Hold the syringe as shown in (4). Open the enclosed needle case and insert the needle firmly (5).



Holding the Luer-Lock (4), tightly secure the needle by twisting it clockwise (6) and pull off the needle cap before use (7).



Proceed in a similar fashion to affix a 25G 1½” cannula.

B. Healthcare Professional Instructions

1. saypha® ChIQ™ is a cross-linked gel formulation that can be injected using a fine gauge needle (e.g., 27G ½") or cannula (25G 1½") for correction of midface volume deficit. When using a cannula, an entry point is made in the skin, e.g. with a sharp needle of appropriate size. The use of other needles and cannulas has not been studied.
2. Before and after treatment, health care professionals are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing.
3. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:
    - Ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines [1]
    - Identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
    - Conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits
    - If a neurological complication is suspected the patient shall be sent to a local emergency room emergently.
4. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment reactions, adverse reactions, and method of administration. Patients should also be advised that supplemental touch-up treatments may be required to achieve and maintain desired correction.
5. The patient's soft tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Pre-treatment photographs are recommended.
6. Although lidocaine in saypha® ChIQ™ aids in relieving pain, supplementary anesthesia may be used for additional pain management during and after injection. As the device contains 0.3% lidocaine, additional injectable anesthetic prior to injection should be used with caution since the systemic toxic effects can be additive.
7. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic.
8. Do not attempt to bend or otherwise manipulate the needle/cannula before or during treatment.

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[1] Jones DH, Fitzgerald R, Cox SE, et al. Preventing and treating adverse events of injectable fillers: evidence-based recommendations from the American Society for Dermatologic Surgery Multidisciplinary Task Force. *Dermatol Surg*. 2021;47(2):214-226.

9. Before injection, press the plunger rod carefully until a small droplet is visible at the tip of the needle.
10. If the needle/cannula is bent or blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle/cannula.
11. After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify the needle is not intravascular. If blood is withdrawn, this could indicate intravascular placement; therefore, stop immediately, reposition the needle and repeat the retraction step again. The absence of blood does not necessarily exclude intravascular placement; therefore, it is important to inject the product slowly and apply the least amount of pressure necessary.
12. After the first small amount of material has been injected into the patient, wait a few seconds to allow the lidocaine to take effect before proceeding with the rest of the injection.
13. The injection technique, injection depth, and volume administered may vary based on the patient's treatment needs. Injecting the product too superficially or uneven may result in visible lumps and/or bluish discoloration (Tyndall effect).
14. The insertion of the needle may lead to superficial needle stick/puncture wounds.
15. Lateral movements of the needle should be avoided since these can result in a fan-like dissection of the sub-epidermal plane and vascular damage, thus increasing the risk of local undesired side effects such as hematoma, swelling, skin discoloration, pain or tenderness at the injection site.
16. Evenly inject saypha® ChIQ™ by applying slow and even pressure on the plunger rod. It is important that the injection be stopped before the needle is pulled out of the skin to prevent material from leaking out or being placed too superficially in the skin.
17. In the clinical study, the typical injection volume to achieve optimal correction of midface volume deficit for both sides of the midface combined was approximately 4.0 mL at initial treatment and 1.0 mL at touch-up treatment. This may vary depending on the goals the patient wished to achieve. Injection volumes at repeat-treatment tended to be lower, with the typical injection volume to achieve optimal correction being 2.0 mL at repeat-treatment and 1.0 mL at touch-up treatment.
18. In the clinical study, the maximum total amount of saypha® ChIQ™ injected into left and right sides combined did not exceed 10 mL per treatment phase, including any touch-up treatment. The safety of injecting volumes beyond those evaluated in the clinical study has not been established.
19. The total annual exposure should not exceed 20 mL.
20. Clinicians should determine injected volume based on patient anatomy, treatment goals, and clinical judgment while remaining within the maximum per-treatment and annual exposure limits specified above.

21. Inject low volumes in two or more sessions instead of high volumes in one session. Do not overcorrect. A new injection may be placed at a previously injected location from two weeks after the original treatment. There is no non-clinical data available regarding the safety of administering more than 4.2 mL of saypha® ChIQ™ during each treatment session.
22. If immediate blanching occurs, the injection should be stopped, and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines[2].
23. After the injections are complete, the treated site may be gently massaged so that the product contours to the surrounding tissues and is evenly distributed. If overcorrection occurs, massage the area with your fingers or against an underlying superficial bone to obtain optimal results.
24. With patients who have localized swelling, the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient back to the office for a touch-up treatment.
25. Patients may experience treatment site reactions, which typically resolve within 14 days. An ice pack may be applied using gentle pressure for a short period following treatment to minimize swelling and reduce pain.
26. The healthcare professional should instruct the patient to promptly report back any problems associated with the use of saypha® ChIQ™.
27. After use, treatment syringes and needles/cannula are biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.

C. Patient Instructions

Please also instruct your patients of the following:

- Patients should seek immediate medical help if they experience changes in vision, signs of stroke, white appearance of the skin or unusual pain during or shortly after treatment. Patients should seek medical advice as soon as any undesired side effects occur.
- Within the first 24 hours, patients should avoid strenuous exercise and extensive sun or heat exposure. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection site.
- Within the first 2 days, the patient should avoid massaging the treatment area as this increases the risk of implant mobility and impaired wound healing.
- If the treated area is swollen, an ice pack may be applied to the site for a short period.

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[2] Jones DH, Fitzgerald R, Cox SE, et al. Preventing and treating adverse events of injectable fillers: evidence-based recommendations from the American Society for Dermatologic Surgery Multidisciplinary Task Force. *Dermatol Surg*. 2021;47(2):214-226.

9. HOW SUPPLIED

saypha® ChIQ™ is supplied in individual treatment syringes with two 27G ½" needles for single patient use and ready for injection (implantation). The volume in each syringe is as stated on the syringe label and the carton. The contents of the syringe are sterile and non-pyrogenic. Do not re-sterilize. Do not use if package is opened or damaged.

As long as the syringe is stored in its originally sealed blister, the viscoelastic implant inside the intact syringe is guaranteed to be sterile until the use-by date printed on the folding box and the label on the syringe. A compromised sterile barrier may lead to a non-sterile implant that could cause bacterial infections associated with skin inflammation and irritation, erythema, pain, fever, and abscess. Therefore, do not use the syringe beyond the use-by date or if it is cracked or broken.

10. SHELF LIFE AND STORAGE

saypha® ChIQ™ must be used prior to the use-by date printed on the packaging and syringe label.

Store the device in the original blister and folding box at 5–25°C/ 41–77°F, in a dry place and protected from sunlight, heat and frost.

To place an order, contact *[placeholder for contact details].*

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Patents: See *[placeholder for website with patent information]*

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