CLINICAL INVESTIGATION PLAN (CIP)

Title of the clinical investigation:	**A randomized, subject- and evaluator-blinded, controlled, non-inferiority multicenter, parallel group comparison study to evaluate effectiveness and safety of saypha® VOLUME Lidocaine for midface augmentation in order to correct volume deficit**
Short title:	Volido
Investigation ID:	CPH-301-201417
IDE no.:	G210347
CIP version:	7.0
CIP version date:	15-MAY-2024
Sponsor:	CROMA-PHARMA GmbH Industriezeile 6, 2100 Leobendorf, Austria Phone: +43 2262 684 680; Fax: +43 2262 68468 165 E-mail: clinical.studies@croma.at; Web: www.croma.at
Investigation site(s):	Approximately 16 investigation sites located in the USA (an updated list of the sites, including names, addresses and positions of the corresponding Principal investigators, is kept separately from the CIP)
Other institutions involved:	[redacted] An updated list of institutions that are involved in project management, monitoring, data management and statistics is kept separately from the CIP
CONFIDENTIAL	This clinical investigation plan is the property of CROMA-PHARMA GmbH and must be kept strictly confidential. Any unauthorized disclosure, copy or use of this document, or information contained herein, is prohibited.

Approval and signature pages

Sponsor approval

CIP identifier: **CPH-301-201417**

Coordinating investigator agreement

CIP identifier: **CPH-301-201417**

I agree:

- To assume responsibility for the proper conduct of the clinical investigation at the site specified below, and to conduct the investigation in compliance with this Clinical Investigation Plan (CIP), including any amendments thereof, any other study conduct procedures provided by the sponsor or their authorized representatives, the principles of Good Clinical Practice (GCP), and applicable regulatory requirements.
- Not to implement any deviations from, or changes to, the CIP (including CIP amendments) without agreement from the sponsor, prior review and favorable opinion from the Ethics Committee, and approval from the Competent Authority, if applicable, except where necessary to eliminate an immediate hazard to the subject(s) or for administrative aspects of the clinical investigation (where permitted by all applicable regulatory requirements).
- That I am familiar with the appropriate use of the medical devices under investigation as described in this CIP and any other information provided by the sponsor including, but not limited to, Investigator´s brochure (IB) and the Instructions for Use (IFU).
- To ensure that all persons providing assistance during the clinical investigation are adequately informed about the medical devices under investigation and of their investigation-related duties and functions.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the product under investigation, and more generally about his/her financial ties with the sponsor. The sponsor will use and disclose this information solely for the purpose of complying with regulatory requirements.

Investigator's name: [redacted]

Investigation site: [redacted]

Address: [redacted]

Investigator's signature: _____

Date: _____

Principal investigator agreement

CIP identifier: **CPH-301-201417**

I agree:

- To assume responsibility for the proper conduct of the clinical investigation at the site specified below, and to conduct the investigation in compliance with this Clinical Investigation Plan (CIP), including any amendments thereof, any other study conduct procedures provided by the sponsor or their authorized representatives, the principles of Good Clinical Practice (GCP), and applicable regulatory requirements.
- Not to implement any deviations from, or changes to, the CIP (including CIP amendments) without agreement from the sponsor, prior review and favorable opinion from the Ethics Committee, and approval from the Competent Authority, if applicable, except where necessary to eliminate an immediate hazard to the subject(s) or for administrative aspects of the clinical investigation (where permitted by all applicable regulatory requirements).
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Investigation site: _____

Address: _____

_____

_____

_____

Principal Investigator's name: _____

Principal Investigator's signature: _____

Date: _____

Investigators and administrative structure of the clinical investigation

Investigators: This is a randomized, subject- and evaluator-blinded, controlled, non-inferiority multicenter, parallel group comparison study to evaluate effectiveness and safety of saypha® VOLUME Lidocaine for midface augmentation in order to correct volume deficit, which will be conducted in the USA.

An updated list of investigation sites and corresponding principal investigators will be kept separately from the CIP.

Sponsor: **CROMA-PHARMA GmbH**

The sponsor will be responsible for overall implementation and oversight of the clinical investigation.

Sponsor's address and other contact details are provided on the cover page.

Other institutions: [redacted]

This is a contract research organization (CRO), also called sponsor's representative elsewhere in this CIP. The address and other contact details of sponsor's representative are provided on the cover page.

Contact project management: [redacted]

Contact for reportable events is provided in a separate manual

An updated list of individuals responsible for various aspects of the investigation at sponsor's representative will be kept separately from the CIP.

An updated list of all key persons involved in the clinical investigation, including other institutions, if any, will be kept and maintained in the Trial Master File (TMF).

Synopsis

Investigation title	**A randomized, subject- and evaluator-blinded, controlled, non-inferiority multicenter, parallel group comparison study to evaluate effectiveness and safety of saypha® VOLUME Lidocaine for midface augmentation in order to correct volume deficit**
Short title	Volido
Investigation ID	CPH-301-201417
Phase of development	Pivotal (Phase 3)
Indication	Moderate to severe midface volume deficit (grades 2 or 3 on the 5-point Midface Volume Deficit Severity Scale (MVDSS))
PLANNED CLINICAL INVESTIGATION PERIOD	
Planned duration	Each subject will take part in the investigation for up to 92 weeks The total anticipated duration of the investigation, from the first-subject-first visit to the last-subject-last-visit, is around 114 weeks, based on expected recruitment period of about 22 weeks.
CLINICAL INVESTIGATION OBJECTIVES AND PURPOSE	
Objectives	**Primary objective:** To demonstrate non-inferiority in the effectiveness of saypha® VOLUME Lidocaine for midface augmentation in order to correct moderate to severe volume deficit versus [redacted] based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase and compared to baseline assessments. **Secondary effectiveness and other objectives:** The following general topics are applicable for all below defined objectives: • For the **initial treatment phase**: o all **secondary effectiveness objectives** will be evaluated for saypha® VOLUME Lidocaine versus [redacted] o evaluation in general will be assessed for Visits 4 to 9 (SV1): Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase • For the **repeat-treatment phase**: o **Other objectives** will be evaluated descriptively for saypha® VOLUME Lidocaine, only o evaluation will be assessed at Visits RT3 to Visit RT5 (Week 4, 12 and 24 after last injection of repeat-treatment phase) *Midface volume deficit and nasolabial fold improvement* • To further assess effectiveness of saypha® VOLUME Lidocaine 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) • To assess the effectiveness of saypha® VOLUME Lidocaine for correction of moderate to severe midface volume deficit based on the ***independent blinded photographic reviewer´s*** assessment (initial treatment phase only)

	• 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) • To assess the effect of midface treatment with saypha® VOLUME Lidocaine on the nasolabial folds based on the blinded evaluator´s live assessment *Global aesthetic improvement* • To evaluate global aesthetic improvement based on subject's assessments (initial treatment phase only) • To evaluate global aesthetic improvement based on the blinded evaluator's assessments (initial treatment phase only) *Subject's satisfaction with outcome and appearance appraisal* • To assess subject´s satisfaction with overall treatment outcome • To assess subject´s appearance appraisal after treatment *Subject's pain assessment and injection volume* • To evaluate subject's perception of pain after each treatment • To assess total injection volume needed for optimal correction **Safety objectives:** • To assess safety of saypha® VOLUME Lidocaine during the entire study period including subject complaints as recorded in the subject diaries • To evaluate long term safety of saypha® VOLUME Lidocaine after repeat-treatment • To assess safety of saypha® VOLUME Lidocaine when used in cross over treatment referring to initial and repeat treatment [redacted] in initial treatment phase switched to saypha® VOLUME Lidocaine in repeat-treatment phase)
CLINICAL INVESTIGATION DESIGN	
Clinical Investigation Type	Interventional
Control Type	Non-inferiority clinical investigation
Blinding/Masking	Subject- and evaluator-blinded
Design and Visit Overview	The clinical investigation is a randomized, subject- and evaluator-blinded, active treatment controlled, multicenter, clinical investigation. The clinical investigation will comprise two treatment groups as follows: • **Test device:** saypha® VOLUME Lidocaine • **Comparator device:** [redacted] Eligible subjects will be randomized at Baseline visit (Visit 2) in a 2:1 ratio to undergo bilateral treatment with saypha® VOLUME Lidocaine or [redacted], respectively. Baseline severity of midface volume deficit will be determined at Visit 1 by the blinded evaluator using the 5-point MVDSS. In addition, the subjects face will be photographed to document baseline condition for further assessments. At Visit 2, eligible subjects will be randomized and undergo bilateral midface augmentation treatment with either saypha® VOLUME Lidocaine or [redacted] (baseline treatment).

	If an optimal aesthetic correction has not been achieved after the baseline treatment, as evaluated by the treating investigator, a touch-up treatment may be performed at Week 2 (Visit 3) using the same device as initially applied at Visit 2. At Week 48 (Visit 9 (SV1)) after last treatment of the initial treatment phase, subjects of both treatment groups (test device and comparator device) may qualify for optional repeat-treatment, which will be done with saypha® VOLUME Lidocaine only. Screening visits for repeat-treatment will be every 4 weeks up to 12 weeks after Visit 9 (SV1). As soon as the subject is eligible in MVDSS score, a full eligibility assessment for repeat-treatment will be done. 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. Again, the blinded evaluator at the site decides, if subject is eligible for the repeat-treatment (regarding MVDSS). Visit SV4 (12 weeks after Visit 9 (SV1) at the latest) 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 for repeat-treatment and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment, Visit 9 (SV1), SV2 or SV 3 will be the end of study visit for the respective subject. Subjects who are eligible and willing to undergo optional repeat-treatment at Visit RT1 will enter the repeat-treatment follow-up phase. Follow-up visits on-site will occur at: • **Initial treatment phase:** Week 2 after baseline treatment, and 2, 4, 8, 16, 24, 36, 48 weeks after last treatment, i.e., baseline or touch-up treatment, respectively (Visits 3 to 9 (SV1)) • **Screening phase for repeat-treatment:** Week 4, 8 and 12 after Visit 9 (SV1) – (Visits SV2 to SV4) • **Repeat-treatment phase:** Week 2 after repeat-treatment, and 2, 4, 12 and 24 weeks after last treatment, i.e., repeat- or touch-up treatment, respectively (Visit RT2 to RT5) In addition to the on-site follow-up visits, 24-48 hours after each treatment the subjects will be contacted by phone for safety checkup. If applicable, the incidence, severity, seriousness and type of adverse events resulting from device injection will be determined and closely followed up until resolution. Midface volume deficit will be evaluated *(live* assessment) by the blinded evaluator at the site using the 5-point MVDSS during follow-up visits of the initial and repeat-treatment phases. A central independent blinded photographic reviewer will assess the MVDSS for the same time points of the initial treatment phase based on photographs taken during the subject´s visits. In addition, volume change measurements will be done on 3D photographs. Severity of nasolabial folds (NLFs) will be assessed using the 4-point Nasolabial Folds Severity Rating Scale (NLF-SRS) during intial and repeat-treatment phases, respectively, at each onsite visit by the blinded evaluator at the site *(live* assessment). Subject's pain perception during treatment and recovery from treatment will be evaluated by means of a numerical pain rating scale (NPRS) immediately and for 60 min (in 15 minutes intervals) after each device administration.

	Global aesthetic improvement will be evaluated by reviewing current photographs relative to photographs taken at the Baseline visit. Both – the blinded evaluator at the site and the subject – will assess the global aesthetic improvement (using the modified GAIS) at each on-site visit after last injection of the initial treatment phase. Subject´s satisfaction with the outcome of the treatment will be assessed with the FACE-Q™ questionnaires "Satisfaction with Outcome" and "Satisfaction with Cheeks" at each on-site visit after last injection of the initial and repeat-treatment phase, respectively. Subject´s "Satisfaction with Cheeks" will also be assessed at Visit 2 (Baseline visit) and Visit RT1. The safety will be evaluated based on occurrence of adverse events, which will be collected at each visit (on-site and telephone visits) throughout the clinical investigation, beginning after signature of the ICF until the last visit. In order to identify potential adverse events post-administration a safety evaluation after 15 minutes needs to take place). A subject diary will be used to 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 and repeat-treatment, respectively, and 6 weeks in case of touch-up treatment). In order to evaluate any potential vision changes, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) will be additionally performed at treatment visits (prior to- and 30 min after any treatment) and at all follow-up visits of the initial and repeat-treatment phase. A basic neurological examination (F.A.S.T) will be performed for all subjects who show signs of ophthalmic complications due to filler injection. Abnormal clinically significant changes in visual examination or experience neurological symptoms indicative of a vaso-occlusional event after any treatment will lead to withdrawal of the subject from further treatment(s) in case an eye specialist or neurologist confirm that the result is related to a vascular injection of the dermal filler. The subjects may remain in the study for at least safety assessments during the scheduled study visits. Pre-defined activities following a related vaso-occlusional event will be performed.
SUBJECT SELECTION AND ELIGIBILTY CRITERIA	
Number of investigation sites	Subjects will be recruited by approximately 16 investigation sites located in the USA
Number of subjects	Approximately 486 subjects in total will be randomized and treated resulting in 437 evaluable subjects for the primary endpoint. Randomization will be in a 2:1 ratio (test device: 324, comparator device: 162). Approximately 300 subjects are estimated to qualify for repeat treatment.
Eligibility criteria – Baseline treatment	
Inclusion criteria (baseline treatment)	A subject must meet **ALL** of the following criteria to be **ELIGIBLE** for this clinical investigation: 1. Male or female subjects aged 22 – 75 years (inclusive) of age at Screening 2. Subjects with bilateral, approximately symmetric moderate to severe midface volume deficit (severity scores of 2 or 3 on the 5-point Midface Volume Deficit Severity Scale), as assessed by the blinded evaluator at

	the site 3. 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). 4. Healthy skin in the midface area and free of diseases that could interfere in cutaneous aging evaluation 5. 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) 6. 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
Exclusion criteria (baseline treatment)	Subjects who meet **ANY** of the following criteria are **NOT** eligible for this study and must not be enrolled: 1. Females, who are pregnant and/or, lactating or planning to become pregnant during the clinical investigation 2. History of severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies 3. History of hypersensitivity to hyaluronic acid preparations, lidocaine or any amide-based anesthetic 4. Tendency to keloid formation and/or hypertrophic scars and/ or have pigment disorders 5. Known human immune deficiency virus-positive individuals 6. Presence of infectious, inflammatory or proliferative cancerous or pre-cancerous lesions in the treatment area 7. Re-current (three times a year over the last year) herpes simplex in the treatment area 8. History or presence of any autoimmune or connective tissue disease, or current treatment with immuno-modulating therapy 9. Uncontrolled (or unstable) Diabetes mellitus or systemic diseases as per investigator discretion 10. 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 11. Implantation of dermal fillers in the treatment area within the preceding 24 months prior to Visit 1 (Screening) and during the entire investigation 12. 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 13. Facial lipolysis, including submental fat treatments, within the previous

	12 months prior to Visit 1 (Screening) and during the entire investigation 14. Bariatric surgery within 12 months prior to Visit 1 (Screening) and during the entire investigation 15. History of bleeding disorder and/or use of anticoagulant, antiplatelet, thrombolytic medication, or anti-inflammatory drugs (oral/injectable corticosteroids or non-steroidal anti-inflammatory drugs, e.g.,[redacted] or other substances known to increase coagulation time (vitamins or herbal supplements, e.g.,[redacted], high doses of vitamin E supplements) from ten days pre- to seven days post injection (baseline treatment and touch-up treatment) 16. 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 17. Beard longer than three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator 18. 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. 19. 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) 20. Any medical condition prohibiting the inclusion in the study according to the judgment of the treating investigator 21. Previous enrollment in this clinical investigation 22. 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 23. Midface volume deficit due to a congenital defect, trauma, or abnormalities in facial adipose tissue distribution such as those associated with HIV related lipodystrophy 24. 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 25. 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). 26. 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.

Eligibility criteria – Touch-up treatments (TUP1 and TUP2)	
Inclusion criteria (touch-up treatments)	A subject must meet **ALL** of the following criteria to be **ELIGIBLE** each for **touch-up-treatment**: 1. Females of childbearing potential must have a negative urine pregnancy test
Exclusion criteria (touch-up treatments)	Subjects who meet **ANY** of the following criteria are **NOT** eligible for each **touch-up-treatment**: 1. Occurrence of a related Serious Adverse Event or Adverse Event of Special Interest (i.e., embolic events, with possible, probable, or causal relationship to an intravascular injection of the device, as changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke, skin necrosis, or impending necrosis) during or after the previous injections 2. Subjects who experienced visual changes considered abnormal clinically significant or other serious medical conditions during or after the previous injections 3. Subjects who have one of the following assessments during the visual examinations: Snellen acuity test worse than 20/40 (with corrective eyewear, if applicable), abnormal confrontational visual field test, or abnormal ocular motility test.
Eligibility criteria – Repeat-treatment	
Inclusion criteria (repeat-treatment)	A subject must meet **ALL** of the following criteria to be **ELIGIBLE** for **repeat-treatment:** 1. 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. The subject does not have to return to his baseline severity to be permitted to receive a repeat-treatment. 2. Subject has completed initial treatment phase up to Visit 9 (SV1) and is willing to attend the study visits of the screening phase for repeat-treatment and repeat-treatment phase 3. Females of childbearing potential must have a negative urine pregnancy test 4. Healthy skin in the midface area and free of diseases that could interfere in cutaneous aging evaluation
Exclusion criteria (repeat-treatment)	Subjects who meet **ANY** of the following criteria are **NOT** eligible for repeat-treatment: 1. Occurrence of a related Serious Adverse Event or Adverse Event of Special Interest (i.e., embolic events, with possible, probable, or causal relationship to an intravascular injection of the device, as changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke, skin necrosis, or impending necrosis) during or after the baseline injection and/or touch-up injections 2. Occurrence of a related Adverse Event that occurred during the initial treatment phase, and is ongoing at the time of the repeat treatment (i.e., relationship is classified as “possible”, “probable” or “causal

	relationship"; outcome is "not recovered / resolved", "recovering / resolving", "recovered / resolved with sequelae" or "unknown") 3. Subjects who experienced visual changes considered abnormal clinically significant or other serious medical conditions during or after the baseline or touch-up injections, respectively 4. Subjects who have one of the following assessments during the visual examinations: Snellen acuity test worse than 20/40 (with corrective eyewear, if applicable), abnormal confrontational visual field test, or abnormal ocular motility test 5. Subjects who became pregnant since start of the study or planning to become pregnant during the clinical investigation 6. Known human immune deficiency virus-positive individuals 7. Presence of infectious, inflammatory or proliferative cancerous or pre-cancerous lesions in the treatment area 8. Development of re-current (three times a year over the last year) herpes simplex in the treatment area since study start 9. Development of any autoimmune or connective tissue disease since study start, or current treatment with immuno-modulating therapy 10. Development of uncontrolled (or unstable) diabetes mellitus or systemic diseases since study start as per investigator discretion 11. Facial plastic surgery, tissue augmentation with silicone, fat or another non-absorbable substance (permanent fillers) and semi-permanent fillers (e.g., poly-L-lactic acid) in the area of device application and during the initial treatment phase of the investigation 12. Implantation of dermal fillers (other than the test and comparator device used in the investigation) in the treatment area during the initial treatment phase of the investigation 13. 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), or chemical peeling during the initial treatment phase of the investigation or is planning to undergo such procedures during the repeat-treatment phase of the investigation 14. Facial lipolysis, including submental fat treatments during the initial treatment phase of the investigation 15. Bariatric surgery during the initial treatment phase of the investigation 16. Development of bleeding disorder and/or use of anticoagulant, antiplatelet, thrombolytic medication, or anti-inflammatory drugs (oral/injectable corticosteroids or non-steroidal anti-inflammatory drugs, e.g., [redacted] 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 (repeat-treatment and touch-up treatment) 17. Planned dental/oral surgery or modification (bridge-work, implants) within four weeks prior to the injection and to a minimum of four weeks post injection 18. Any medical condition prohibiting the inclusion for repeat-treatment according to the judgement of the treating investigator 19. Beard longer than three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator

	20. Previous enrollment in initial treatment phase of this clinical investigation and early termination, or significant incompliance with the protocol requirements 21. Current or previous treatment with another investigational drug and/or medical device or participation in another clinical study 22. Midface volume deficit due to a trauma, or abnormalities in facial adipose tissue distribution such as those associated with HIV related lipodystrophy 23. Subjects who experienced weight change for a minimum of 10% since study start or subjects who have the intention to change eating habits that result in a weight gain or loss >10% during the entire investigation 24. 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 RT1

INVESTIGATIONAL DEVICE(S), DOSE AND MODE OF ADMINISTRATION	
Test device	saypha® VOLUME Lidocaine: Crosslinked hyaluronic acid (HA) 23 mg/mL + 0.3% lidocaine hydrochloride.
Comparator device	[redacted]: Crosslinked HA 20 mg/mL + 0.3% lidocaine hydrochloride
Dose and mode of administration	The respective device will be administered by subcutaneous and/or supraperiosteal injection. The injection technique used will be selected by the treating investigator. For injection, either a needle (27G ½") or cannula (25G 1½") may be used in the discretion of the treating investigator. A minimum of approximately 100 subjects randomized to the test device will be treated with either needle or cannula. The volume administered is at the discretion of the treating investigator and depends on the severity of the midface volume deficit to be corrected. However, the maximum volume (left and right side of the midface together) must not 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.
Treatment occasions	**Baseline treatment** will be administered at Visit 2 (Day 0). Each eligible subject will receive either saypha® VOLUME Lidocaine or [redacted] into the midface region, according to the randomization scheme. **Touch-up treatment** is optional and may be administered at • Visit 3 (Week 2; initial treatment phase: TUP1) and • Visit RT2 (Week 2 after RT1; repeat-treatment phase: TUP2) if an optimal aesthetic correction has not been achieved after baseline and / or repeat-treatment, respectively. Decision on touch-up treatment is in the discretion of the treating investigator, but none of the exclusion criteria must be met. Touch-up treatment may be performed on one or both sides of the midface. In any case, it must be performed using the same device (either test device or comparator device) which was initially applied to the subject. **Repeat-treatment** is optional and may be administered once during the clinical investigation at Visit RT1 in eligible subjects using the saypha® VOLUME Lidocaine only (even if the subject was treated with the comparator device before).

ENDPOINTS	
Effectiveness endpoints	*General information on effectiveness endpoints* • The subjects pain assessment, nasolabial folds, and the volumetric change measurement will be assessed and analyzed for the left and right side of the face separately. • All other endpoints will be assessed and analyzed globally (i.e., left and right side together / combined) • **For MVDSS:** Subjects are defined as a 'responder' if they are showing an ≥1 point improvement on the 5-point MVDSS, based on the respective score at a given visit relative to the respective baseline score. The grade assigned at the respective baseline visit (either Baseline visit or Visit RT1) will represent the baseline value for derivation of the responder status at a given visit during the initial treatment phase or repeat-treatment phase. Assessments will be evaluated by either the blinded evaluator at the site or by the central independent blinded photographic reviewer.
Primary effectiveness endpoint	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
Secondary effectiveness endpoints (initial treatment phase)	The effectiveness of the investigational device during initial treatment phase will be further evaluated using the following **secondary effectiveness endpoints:** *MVDSS, NLF-SRS and Volumetric Change measurement* • The percentage of responders on the 5-point MVDSS, based on the ***blinded evaluator´s live*** assessment at Week 4, 8, 16, 36, and 48 after last injection of initial treatment phase compared to the score at Baseline visit. • The percentage of responders on the 5-point MVDSS, based on the ***independent blinded photographic reviewer´s*** assessment by using Baseline photographs at Week 4, 8, 16, 24, 36 and 48 after last injection of initial treatment phase compared to the score at Baseline visit • Mean change in midface volume deficit measured on the 5-point MVDSS and 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 • 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 • Shift from baseline (Baseline visit) in nasolabial folds measured by NLF-SRS based on the blinded evaluator´s live assessment at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase

Secondary effectiveness endpoints (initial treatment phase)	*Global aesthetic improvement based on modified GAIS* • The percentage of subjects with a global aesthetic improvement over baseline (at Baseline visit) (subjects who have been rated as "much improved" or "improved"), based on ***subject´s*** assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment phase using the 5-point *modified* GAIS. • The percentage of subjects with a global aesthetic improvement over baseline (at Baseline visit) (subjects who have been rated as "much improved" or "improved"), based on the ***blinded evaluator`s*** assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment phase using the 5-point *modified* GAIS. *Subject's satisfaction with outcome and appearance appraisal based on FACE-Q™ assessments* • The extent of ***subject´s*** satisfaction with ***overall treatment outcome*** at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase as assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome". • The extent of ***subject´s appearance appraisal*** at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase as assessed by the FACE-Q™ questionnaire "Satisfaction with Cheeks" compared to Baseline visit. *Subject´s pain assessment and injection volume* • ***Subject*** evaluation of ***pain*** after each treatment (baseline and touch-up treatment) on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable • ***Injection volume*** required to achieve optimal aesthetic result at each treatment (baseline- and touch-up treatment together)
Other endpoints (repeat-treatment phase)	The investigational device during repeat-treatment phase (saypha® VOLUME Lidocaine) will be evaluated using the following ***other effectiveness*** endpoints: *MVDSS and NLF-SRS* • The percentage of responders on the 5-point MVDSS, based on the ***blinded evaluator´s live*** assessment at Week 4, 12 and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1 • Mean change in midface volume deficit measured on the 5-point MVDSS and based on the ***blinded evaluator´s live*** assessment at Week 4, 12, and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1 • Shift from baseline (Visit RT1) in NLF-SRS based on the ***blinded evaluator´s live*** assessment at Week 4, 12 and 24 after last injection during repeat-treatment phase

Other endpoints (repeat-treatment phase)	*Subject's satisfaction with outcome and appearance appraisal based on FACE-Q™ assessments* • The extent of ***subject´s*** satisfaction with ***overall treatment outcome*** at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome" • The extent of ***subject´s appearance appraisal*** at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the FACE-Q™ questionnaire "Satisfaction with Cheeks" compared to the score at Visit RT1 *Subject´s pain assessment and injection volume* • Subject evaluation of ***pain*** after each treatment (repeat and touch-up-treatment) on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable • ***Injection volume*** required to achieve optimal aesthetic result at each treatment (repeat and touch-up treatment together)
Safety endpoints	The safety of the investigational device will be evaluated by treatment group including cross-over group (in repeat-treatment) and by treatment phase using the following endpoints: • Occurrence and frequency of adverse events during the entire study period including repeat-treatment phase (long-term safety). Symptoms of interest will be recorded in subject diary during the first 4 weeks (28 days) after each treatment (i.e., either 4 weeks after baseline and repeat-treatment, respectively, and 6 weeks in case of touch-up treatment) and documented as AE by investigator. • 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 and repeat-treatment, respectively, and 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).

STATISTICAL ANALYSIS	
Sample size calculation	The primary outcome measures for effectiveness will be 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 response rate for saypha® VOLUME Lidocaine based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase, while pB is the corresponding response rate for [redacted] Thus, a negative value for this difference means that the response rate of saypha® VOLUME Lidocaine is lower than the response rate for [redacted] The non-inferiority margin is -10%. Further assumptions for sample size calculation: • Response rate at Week 24 for saypha® VOLUME Lidocaine is 85.6% • Response rate at Week 24 for [redacted] is 85.6% • Randomization ratio 2:1 Based on these assumptions, 437 subjects (saypha® VOLUME Lidocaine: n=291, [redacted]: n=146) will be necessary in order to achieve a power exceeding 83% with a one-sided α of 2.5%. Assuming 10% exclusion from PPS results in 486 subjects to be randomized. Adding 6% screen failures yields approximately 516 subjects to be enrolled. Concerning FAS, it is expected that only very few subjects will be regarded as non-responder due to missing data for the primary effectiveness endpoint. Response rates at Week 24 after last injection of the initial treatment phase may be slightly smaller than assumed above. Due to the increased sample size in the FAS (more than 10% compared to the PPS) it is expected that the power will be adhered as specified above. Sample size calculation was done using SAS® version 9.4.
Analysis sets	*Safety Analysis Set (SAF)* The SAF compromises all subjects who were randomized and received at least one treatment with device (test device or the comparator device). Subjects in the SAF will contribute to the evaluation “as treated” i.e., the subjects’ assignment to the treatment group will be based on the device administered. *Full Analysis Set (FAS)* The FAS consists of all randomized subjects who received at least one administration of the test device or the comparator device. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomized”. *Per-Protocol Set (PPS):* The PPS is defined as a subset of the subjects in the FAS without major protocol deviation(s) affecting the primary effectiveness endpoint and assessed as ‘major excluding from PPS’.

General Statistical Considerations and Planned Statistical Analysis	*General Statistical Considerations* Unless otherwise specified, all measurements will be summarized descriptively at each visit by treatment group . In general, continuous variables will be summarized using the following descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data will be described using absolute and relative frequencies by category. Shift tables will be provided, where appropriate. For assessments over time, mean values may be plotted to explore the trajectory over time. All descriptive summaries and plots will be based on in-trial data (i.e., without imputation) unless otherwise specified. In addition, estimated treatment differences will be presented together with two-sided confidence intervals and corresponding p-values, if appropriate. *Effectiveness analyses* The evaluation of the primary and secondary effectiveness endpoint(s) will be performed both in the PPS and in the FAS for the initial treatment phase, and only for the FAS for the repeat phase. • For the *primary effectiveness endpoint,* the PPS and the FAS will be both considered equally important for the primary analysis.The analysis of the *primary effectiveness endpoint* will be performed on the PPS (primarily) and FAS. Confirmatory testing will be performed in a hierarchical ordering. Non-inferiority is demonstrated only if the results are consistent for both analysis populations. Subjects with missing baseline MVDS score and / or missing MVDS score at Week 24 after last injection of the initial treatment phase will be considered as non-responders for the primary analysis on the FAS. To calculate the primary outcome measure, the improvement over Baseline in the MVDS score assessed live by the blinded evaluator at the site at Week 24 after last injection of the initial treatment phase by subtracting the Midface Scale grade obtained at Baseline. The proportion of subjects with MVDS score improvement of ≥1 point will be then calculated for each treatment group. The primary effectiveness endpoint will be evaluated by means of a one-sided two-group Farrington-Manning test of proportions with the following hypotheses: o H0: pA – pB ≤ d0 o H1: pA – pB > d0. At this, pA is the response rate for saypha® VOLUME Lidocaine and pB is the response rate for [redacted], and d0=-0.1. Thus, a negative value for this difference means that the response rate of saypha® VOLUME Lidocaine is lower than the response rate for [redacted]

	The non-inferiority margin is -10%. The study decision will be based on a Farrington-Manning-statistics with a one-sided type I error rate level of 0.025. *Sensitivity analyses* of the primary effectiveness endpoint will be performed on the FAS addressing the different reasons for non-adherence and covering the following aspects to underline the robustness of the results: o Complete case analysis: In this analysis only those subjects will be included for whom the primary endpoint could be calculated; o Subjects with non-allowed concomitant medication / treatments before Week 24 after last injection of the initial treatment phase may be regarded as non-responder. o Multiple imputation under MNAR assumption for imputing missing MVDS scores at Week 24 assessed live by the blinded evaluator. • All *secondary effectiveness endpoints* will be analyzed in an exploratory manner by means of descriptive statistics. The descriptive tables will show the statistics by time of assessments as well as for the changes from baseline (if applicable). Concerning the follow-up for initial treatment, the last measurements / assessments before first treatment are defined as baseline. Concerning the time after repeat-treatment, the measurements / assessments at Visit RT1 before first repeat-treatment are defined as baseline. *Safety analyses* Safety analyses will be based on the SAF. • Incidence of AEs will be summarized by Preferred Term and System Organ Class, and also by intensity (severity), causal relationship to the respective device or procedure, and seriousness. • The frequency and occurrence rate, maximum intensity, overall duration, and seriousness of injection site reactions within four weeks (28 days) after baseline treatment, after repeat-treatment injection, respectively, and 6 weeks in case of touch-up treatment will be summarized by device. *Analysis of subgroups* The primary analysis will be based on the total trial population. Besides the total study population, the following subgroups will be analyzed by descriptive statistical methods for the primary and the main secondary effectiveness endpoints: • Injection equipment: Needle versus cannula • Gender: Female versus male • Fitzpatrick skin type • Race and ethnicity • Age group In addition, incidence of AEs and injection site reactions in will be summarized by preferred term (PT) and system organ class (SOC) within all of the above-mentioned subgroups. Frequency and occurrence rate injection site reactions will be summarized within all of the above-mentioned subgroups.

	Interim analysis (IA) An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit 48 weeks after their last injection during the initial treatment phase (Visit 9 (SV1)).

A schedule of assessments for initial treatment phase is given in Table 1 (Visit 1 to Visit 9 (SV1)) for the screening phase for repeat-treatment (SV2 to SV4) in Table 2, and for optional repeat-treatment phase in Table 3 (Visit RT1 to Visit RT5).

Schedule of procedures and assessments

Table 1. *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
NLF-SRS –blinded evaluator at site [18]	X*			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												
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]								
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 (see section 6.3.5). 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 (see Table 3).
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 (see section 6.3.5) 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 2. *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 (see Table 3).
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 (see section 6.3.5). 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 (see section 6.3.5) 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 3. *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
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

List of abbreviations

ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AOI	Anatomical Areas of Interest
ATC	Anatomical Therapeutical Chemical
BDDE	1,4-butanediol diglycidyl ether
CDMS	Clinical Data Management System
CE	*Conformité Européene* (European conformity)
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
COVID-19	Corona Virus Disease of 2019
CRO	Contract Research Organization
CTR	Common treatment site responses
DCP	Data Cleaning Plan
DMP	Data Management Plan
DRM	Data Review Meeting
EC	Ethics Committee
eCRF	electronic Case Report Form
EU	European Union
ExC	Exclusion criterion
FAS	Full Analysis Set
FST	Fitzpatrick skin type
G	Gauge
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GDPR	General Data Protection Directive
HA	Hyaluronic acid
HIPAA	Health Insurance Portability and Accountability Act
IA	Interim analysis
IB	Investigator's brochure
ICF	Informed Consent Form
IDE	Investigational device exemption
IFU	Instructions for Use
IMD	Investigational medical device
IMDRF	International Medical Device Regulators Forum

IRB	Institutional Review Board
ISO	International Organization for Standardization
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MDD	Medical Device Directive
MDR	Medical Device Regulation
MedDRA	Medical dictionary for regulatory activities
MNAR	Missing not at random
MVDSS	Midface Volume Deficit Severity Scale
NLF-SRS	Nasolabial Folds Severity Rating Scale
NPRS	Numerical Pain Rating Scale
PPS	Per-Protocol Set
PT	Preferred term
RT	Repeat Treatment
SADE	Serious adverse device effect
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDV	Source data verification
SOC	System organ class
SOI	Symptoms of interest
SV	Screening Visit
TMF	Trial master file
TUP	Touch-Up Treatment
US(A)	United States (of America)
U(S)ADE	Unanticipated (serious) adverse device effect
WHO	World Health Organization
WOCBP	Women of childbearing potential
US(A)	United States (of America)
3D	Three-dimensional

Glossary

Definitions of terms used in this Clinical Investigation Plan are in accordance with ISO 14155:2020 if not indicated otherwise (e.g., study-specific definitions). Some of the definitions may be defined under national regulations. Therefore, there may be the need to check for definitions written down in regional / national guidance documents or regulations can:

Adverse Device *Effect* (ADE)	Adverse event related to the use of an investigational medical device. This definition includes - adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. - any event resulting from use error or from intentional misuse of the investigational medical device. - the 'comparator' if the comparator is a medical device.
Adverse *Event* (AE)	An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the test device (IMD) or comparator device and whether anticipated or unanticipated. This definition includes events related to the test device or the comparator and events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of test device or comparator device. Study-specific addition: AEs initially observed beyond baseline treatment or worsening of pre-existing AEs are defined as treatment-emergent AEs (TEAEs).
(serious or non-serious) - **Adverse Events of Special Interest (AESI)** (study-specific definition)	AESIs are defined as scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such events may require further investigation in order to characterize and understand them. Depending on the nature of the event, rapid communication by the sponsor to other parties may also be needed. AEs of special interest are defined in section 14.1.
Blinded evaluator at the site (study-specific definition)	Only responsible for live MVDSS, NLF-SRS and modified GAIS evaluations at the site. **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 until final database lock.
Blinding	Blinding is a procedure in which one or more parties to the clinical investigation are kept unaware of the treatment assignment(s). This clinical investigation is termed 'evaluator blind', i.e., at least the *primary endpoint* is assessed without knowledge of whether an IMD or *comparator* has been used to treat a subject.
Case Report Form (CRF)	A CRF is a set of printed, optical or electronic documents for each subject on which information to be reported to the sponsor is recorded, as required by the CIP.

Central independent blinded photographic reviewer (study-specific definition)	Person responsible for MVDSS evaluations; will be dislocated from the investigation sites and will not discuss any findings with the investigators during the investigation
Clinical Investigation	The terms ‘clinical trial’ or ‘clinical study’ are synonymous with ‘clinical investigation’.
Clinical Investigation Plan (CIP)	Document that states the rationale, objectives, design and pre-specified analysis, methodology, organization, monitoring conduct and record-keeping of the clinical investigation. Study-specific addition: For the purpose of this document “protocol” is synonymous with “CIP”.
Comparator (device)	Medical device, therapy (e.g., active treatment, normal clinical practice), used in the control group in a clinical investigation.
Coordinating Investigator (CI)	A Coordinating Investigator is appointed by the sponsor to assist in coordinating the work in a multicentre clinical investigation.
Concomitant Treatment (study-specific definition)	All medications taken and non-pharmacological procedures applied by a subject during the course of a clinical study. Further details see “Prior Treatment”.
Deviation	Instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP.
Device Deficiency	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the test device or the comparator device.
Effectiveness	Achievement of a clinically significant intended result in a defined portion of the target population when the investigational medical device is used within its intended uses and according to its instructions for use, the investigator’s brochure and the CIP, as determined by documented scientific evidence
Ethics Committee (EC)	The Ethics Committee (EC) is an independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation. For the purposes of this document, “ethics committee” is synonymous with “research ethics committee”, “independent ethics committee” or “institutional review board”. The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.
Independent	A person not involved in the development of the investigational device or the conduct of a clinical investigation, except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest.

Investigational Medical Device (IMD)	Medical device being assessed for clinical performance, effectiveness or safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated within their intended use in a post-market clinical investigation (interventional or non-interventional). Study-specific addition: For the purpose of this document “IMD” is synonymous with “test device”.
Investigator	An individual member of the investigation site team designated and supervised by the Principal Investigator at an investigation site to perform clinical-investigation-related procedures or to make important clinical investigation-related and medical treatment decisions. An individual member of the investigation site team can also be called ‘sub-investigator’ or ‘co- investigator’.
Investigator’s Brochure (IB)	Compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation.
Institutional Review Board (IRB)	See definition for Ethics Committee.
Investigation site	Institution or site where the clinical investigation is carried out. Note: “investigation site” is synonymous with “study site”.
Investigator site file (ISF)	Binder(s) maintained at the study site containing all regulatory and study specific documents.
Malfunction	Failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use, IB or CIP.
Medical History (study-specific definition)	Medical history includes prior and ongoing concomitant diseases and possibly recurring conditions. New concomitant diseases, not pre-existing at Screening visit or a worsening in the concomitant diseases will be documented as adverse event (AE).
Point of Enrollment	Time at which, following recruitment but before any clinical investigation-related procedures are undertaken, a subject signs and dates the informed consent form.
Principal Investigator (PI)	The Principal Investigator (PI) is a qualified person responsible for conducting the clinical investigation at an investigation site. If a clinical investigation is conducted by a team of individuals at an investigation site, the PI is responsible for leading the team. Whether this is the responsibility of an individual or an institution can depend on national regulations.

Prior Treatment (study-specific definition)	All medications (prescription and over-the-counter products) taken and non-pharmacological procedures applied prior to Screening Visit that was stopped before the first use of the device (at Baseline) is classified as 'prior treatment'. Treatments used at least once after the first use of a device are classified as 'concomitant treatment'. Note, that a treatment classified as 'concomitant' could already be taken prior to first application of device.
Randomization	Randomization is a process of assigning subjects to the test device or comparator device using an established recognized statistical method using an element of chance to determine the unforeseeable assignment in order to reduce bias.
Serious Adverse Device *Effect* (SADE)	A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a SAE.
Serious Adverse Event (SAE)	A SAE is an adverse event that led to any of the following a) death, b) serious deterioration in the health of the *subject,* users, or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function including chronic diseases, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE.
Serious health threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals (according to ISO 14155).
Source Data	Source data are all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. This includes electronic source data initially recorded in an electronic format.

Source Document	Source documents are printed, optical or electronic document containing source data. Examples include: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.
Source Records	Collection of source documents containing source data.
Sponsor	Is an individual, company, institution or organization taking responsibility and liability for the initiation and management of a clinical investigation, and arranging the financial setup.
Subject	Is an individual who is or becomes a participant in a clinical investigation either as a recipient of the test device or the comparator device.
Treatment (phase) (study-specific definition)	**Baseline treatment:** Treatment at Visit 2 is defined as “baseline treatment”; **Touch-up treatment 1:** Optional treatment at Visit 3 is defined as “touch-up treatment 1” (TUP1) **Initial treatment (phase):** Baseline treatment and touch-up treatment together are defined as “initial treatment”; The study phase between Baseline visit and Visit 9 (SV1) is defined as initial treatment phase. For initial treatment either saypha® VOLUME Lidocaine (test device) or the comparator device [redacted] are administered (according to randomization of the subject) **Repeat-treatment (phase):** Optional treatment (with saypha® VOLUME Lidocaine only) at Visit RT1 is defined as “repeat-treatment”. The study phase beginning with repeat-treatment at Visit RT1 and up to Visit RT5 is defined as repeat-treatment phase. **Touch-up treatment 2:** Optional treatment at Visit RT2 is defined as “touch-up treatment 2” (TUP2) For repeat-treatment only saypha® VOLUME Lidocaine (test device) is administered.
Treating (unblinded) investigator (study-specific definition)	Responsible for all study related assessments and procedures (except those allocated to the blinded evaluator at the site and the central independent blinded photographic reviewer).
Trial Master File (TMF)	Binder(s) maintained at the sponsor’s (CRO´s) office containing all regulatory and study specific documents including the essential documents according to the ISO-GCP Guideline.
Unanticipated Serious Adverse Device *Effect* (USADE)	An USADE is a serious adverse device effect which by its nature, incidence, severity (intensity) or outcome has not been identified in the current risk assessment and the current version of the Investigator´s brochure (adapted according to ISO 14155) Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

For the USA only: **Unanticipated Adverse Device *Effect* (UADE)**	The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity (intensity), or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (according to investigational device exemption (IDE) regulations / 21 CFR 812.3(s))
Use error	A user action or lack of user action while using the medical device that leads a different response than that intended by the manufacturer or expected by the user. Use error includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the subject is not by itself considered a use error: A malfunction of a medical device that causes an unexpected result is not considered a use error.

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1 Background

1.1 Dermal Fillers

Age is the most significant factor contributing to the overall change in the appearance of an individual's face over time. The young face is full and rounded, especially in the upper and middle parts, and perceived as healthy. Facial aging is a multifactorial process including thinning of the skin, decreased skin elasticity, collagen degradation, bone resorption, and fat pad atrophy. During the ageing process, midface tissues lose volume, the excess of cheek skin occurs and as a result flattening and furrowing of the mid-cheek is observed. The face is no longer perceived as young but as sad, heavy, and long.[1]

Perception of age and health is critical in the judgement of attractiveness. Forming an impression in other humans about facial attractiveness is fast, automatic and mandatory, and impacts impressions of other social traits of a person with real-world consequences.[2]

Attractiveness influences both the self-perception and behaviour toward others and is related to traits such as self-confidence and social acceptance. It is not surprising, therefore, that aesthetic interventions can improve the psychological well-being and quality of life in people who elect to undergo such procedures due to aging. Common positive changes include increased satisfaction with self-appearance, reduced depression or anxiety, improved emotional well-being and increased self-confidence.[3]

Dermal fillers are used for facial rejuvenation and correction of deep wrinkles (e.g., nasolabial folds) and also to correct midface volume deficits. These treatments provide desirable aesthetic outcomes with minimal invasiveness and without the downtime associated with surgery.

Hyaluronic acid

Hyaluronic acidis a naturally occurring glycosaminoglycan that consists of repeating non-sulfated disaccharide units of glucuronic acid and *N*-acetylglucosamine. It is an essential component of the animal and human extracellular matrix, present in all tissues, most abundantly in the skin. Hyaluronic acid has a considerable water-binding capacity, and by this mechanism it increases dermal volume and compressibility.[4] Furthermore, it stimulates collagen synthesis and up-regulation of elastin, possibly by mechanical stretching of the skin, which in turn leads to stretching and activation of dermal fibroblasts.[5] Hyaluronic acid is degraded by enzymatic depolymerization via hyaluronidases and oxidation by free radicals. Native chains have a short half-life of 24-48 h, which may be significantly extended by cross-linking of the chains. The most commonly used cross-linking agent is 1,4-butanediol diglycidyl ether (BDDE). The cross-linked hyaluronic acid is degraded via the same mechanisms as native chains, but at a much slower rate, extending the clinical effect of BDDE-cross-linked hyaluronic acid for up to one year.[6]

Hyaluronic acid dermal filler for aesthetic use

Soft tissue fillers are nowadays widely used for smoothing skin wrinkles and folds, and volumizing facial contours. Various fillers are available on the market, but hyaluronic acid (HA) gels are most popular because of their versatility, ease of administration, predictable effectiveness, safety track record established during decades of use, and quick subject recovery after administration.[1, 7]

Since the launch of the first BDDE-cross-linked hyaluronic acid dermal filler for aesthetic use in Europe in 1996, over 50 clinical studies have been conducted with this type of medical device, which included more than 9,000 subjects.[6] Hyaluronic acid gels are currently considered as the gold standard for dermal fillers and are widely used in aesthetic dermatology for facial rejuvenation and re-contouring, with a remarkable track record of performance and safety.[5] Over time, their use was extended to medical reconstructive purposes in the treatment of pathologic conditions such as facial lipoatrophy, morphologic asymmetry of the face, and depressed scars.

Lidocaine hydrochloride

In order to improve the comfort of filler injections, novel formulations containing a local anaesthetic, lidocaine hydrochloride, have been developed to reduce procedural pain and to bypass the need for additional anaesthesia.[8]

Lidocaine hydrochloride is a well-known local anaesthetic, which has been in clinical use for over 60 years. It is currently one of the most widely used local anaesthetics. Lidocaine exerts its anaesthetic effects by blocking fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons, which prevents depolarization and inhibits the generation and propagation of nerve impulses.[9]

When used for infiltrative anaesthesia, lidocaine hydrochloride has fast onset of action (< 2min) and moderate duration of effect lasting 1.5-2 h.[10] Absorbed lidocaine is metabolized in the liver and eliminated via the kidneys with a half-life of around 90 minutes.[11] Lidocaine is generally well tolerated and safe. Adverse reactions are rare and usually result from high plasma concentrations due to accidental intravascular injection, excessive dosage (>400 mg), or rapid absorption from highly vascular areas. Early symptoms of toxicity include a metallic taste, tinnitus, light-headedness, and confusion, and may be followed by tremors, shivering, seizures and, ultimately, respiratory arrest. Cardiovascular toxicity may be manifested by hypotension, bradycardia, arrhythmia and cardiac arrest.[10], [11]

In soft tissue fillers the addition of lidocaine hydrochloride reduces pain and distress and provides a more comfortable injection experience.[12] The performance and safety of hyaluronic acid dermal fillers supplemented with lidocaine hydrochloride have been studied in several randomized clinical trials, which were mostly designed as split face trials, where the same dermal filler was administered with and without ancillary lidocaine. A detailed analysis of nine randomized clinical trials with the equivalent devices [redacted] has confirmed a statistically significant reduction in pain with formulations which contained lidocaine. The pain reduction was consistent across the studies, and present irrespective of the dermal filler tested. The frequency and severity of adverse events (AEs) was not different for dermal fillers with or without lidocaine, indicating no incremental safety risk.[13]

saypha® VOLUME Lidocaine – the test investigational medical device (IMD) - is an injectable hyaluronic acid gel implant produced by CROMA-PHARMA GmbH in Austria. [redacted] (known as [redacted] with Lidocaine in Europe[14]) was chosen as comparator device.

The indication for saypha® VOLUME Lidocaine to be studied in this clinical investigation is correction of moderate to severe midface volume deficit. There are no known data for use of saypha® VOLUME Lidocaine for bilateral midface augmentation available yet. However, there have been a few studies published over the last 2 years using hyaluronic acid fillers aimed at restoring midface volume. Jung et al. investigated in a total of 88 subjects with moderate to severe age-related midface volume deficit to evaluate the efficacy and safety of [redacted] Volume Lidocaine compared to [redacted]. The results showed that [redacted] Volume Lidocaine was not inferior to [redacted] in temporarily restoring midface volume at 24 weeks after treatment with all ADEs being mild or moderate in severity.[15]

Jones et al. evaluated the safety and efficacy of large gel particle hyaluronic acid with lidocaine. Sixty subjects with mild to substantial loss of midface fullness were treated to optimal correction; improvement in the Global Aesthetic Improvements Scale (GAIS) were reported for the majority of subjects (≥98.3% for investigator-assessed and ≥91.5% for subject-assessed) for up to 16 weeks. At 8 weeks, the Medicis Midface Volume Scale responder rate was 100% and subject satisfaction scores (5/6 questions) in the FACE-Q™ were ≥91.5%. Only five AEs were reported in this study, with one being considered injection procedure-related (mild presyncope). No serious AEs were reported.[16]

Moreover, Huh et al. conducted a randomized, active-controlled, 52-week study of hyaluronic acid fillers [redacted] in one side and [redacted] for anteromedial malar region augmentation. The HA fillers injected maintained the volume well for up to 52 weeks in the anteromedial malar augmentation. Additionally, both [redacted] showed similar effectiveness and safety profiles.[17]

1.2 Indication and intended use

The saypha® VOLUME Lidocaine device is *not yet* approved in the US, while in *Europe* (and other countries worldwide) the label is stating the following (**approved labeling incl. EU**, dated 06/2020; [18]):

- The device saypha® VOLUME Lidocaine is indicated to correct moderate to severe nasolabial folds. It is indicated to be injected into the deep dermis or subcutis

- The intended purpose of the device is to create volume in order to correct wrinkles and folds and to correct moderate to severe nasolabial folds to treat signs of ageing.

Within this clinical investigation (CPH-301-201417) the device will be used for midface augmentation in order to correct moderate to severe volume deficit. Saypha® VOLUME Lidocaine is to be administered by injection into the zygomaticomalar region, anteromedial cheek region and submalar region. The device has to be administered by subcutaneous and/or supraperiosteal injection.[46]

[redacted] is indicated for injection for cheek augmentation to correct age-related volume deficit in the midface and for augmentation of the chin region to improve the chin profile in adults over the age of 21. The device is administered by deep (subcutaneous and/or supraperiosteal) injection.[14]

In this clinical investigation, both medical devices will only be used to treat midface volume deficit.

2 Identification and description of the investigational devices

2.1 saypha® VOLUME Lidocaine

The following text gives a summary on the characteristics of the test device. Refer to the saypha® VOLUME Lidocaine Investigator's brochure (IB) for detailed information on the test device.[46]

Note: saypha® VOLUME Lidocaine and Princess® Volume Lidocaine are the same product marketed under different brand names in different countries. For consistency, the brand name of saypha® VOLUME Lidocaine will be used in this CIP.

Device description

Table 4 shows the main characteristics of saypha® VOLUME Lidocaine and Table 5 tabulates the single components of saypha® Volume Lidocaine.

Table 4. *Description of saypha® VOLUME Lidocaine*

Saypha® VOLUME Lidocaine
• is a class III medical device [A] incorporating the ancillary medicinal substance lidocaine hydrochloride as an integral part • is a sterile, biodegradable, viscoelastic, clear, transparent, isotonic, and homogenized and injectable gel implant provided in pre-filled 1 mL glass syringes for subcutaneous and/or supraperiosteal injection • is designed for single use. No materials of human or animal origin are used during manufacture or as raw materials; Moreover, the non-animal origin reduces any potential for hypersensitivity. • In general, HA fillers are degraded. They may provide volume for a period of four to twelve months after treatment before undergoing degradation.[20] For the test device the lifetime is anticipated to last up to nine months after treatment.

[A] Classification according to its field of application (MDD 93/42/EEC, Annex IX; Class III rule 8: implantable device which is wholly or mainly absorbed; and rule 13: incorporating, as an integral part, an ancillary medicinal product. The conformity assessment route complies with MDD 93/42 Annex II.3. (Quality System) and Annex II.4. (Design Examination for Class III Medical Devices).

Table 5. *Main components of saypha® VOLUME Lidocaine.*

Component	Concentration	Description
Hyaluronic acid (HA) (Sodium hyaluronate)	23 mg/g (2.3%)	• HA, a natural polysaccharide, is obtained from *Streptococcus equi* bacteria is highly cross-linked using 1,4-Butanediol Diglycidyl Ether (BDDE) • BDDE covalently binds native HA molecules to each other with repeating bridges, creating a polymer 'network', transforming the viscous liquid into a gel. • Compared with native HA, the highly crosslinked HA gel is considerably more resistant against enzymatic and free radical breakdown, so that its tissue residence time is dramatically increased. • Native HA is added in order to adjust the rheological properties and injectability of the fillers. • HA is a natural component of human skin, hence the device is naturally absorbed and excreted by the liver.
Lidocaine hydrochloride	3 mg/g (0.3%)	• Lidocaine hydrochloride (a medicinal product) is a well-known local anesthetic; it is added to saypha® VOLUME Lidocaine as an ancillary substance for reduction of procedural pain and to improve the comfort of filler injections thus bypassing the need for additional anesthesia • Lidocaine hydrochloride is rapidly released from the implant and quickly eliminated from the body, with a half-life of around 90 minutes.[11]

Manufacturing of saypha® VOLUME Lidocaine

saypha® VOLUME Lidocaine is manufactured in compliance with applicable Regulatory Requirements according to MDD 93/42/EEC (see section 10 of the IB for complete listing [46]).

All steps of the device preparation (design, manufacture, primary packaging, secondary packaging, labelling inspection, final inspection, moist heat sterilization, and release) are performed at the facilities of CROMA-PHARMA GmbH, Industriezeile 6, 2100 Leobendorf, Austria, in accordance with EN ISO 13485:2016.

Needles and cannulas for application

- The device is delivered with two sterile single use needles (27G ½'') per syringe. The needles are Ethylene oxide sterilized; they are medical devices according to their field of application, under class IIa (MDD 93/42/EEC, Annex IX, rule 6). The CE manufacturer is [redacted].
- [redacted] 25G 1½" cannulas may be used (will be provided by the sponsor´s representative).

Regulatory status

- **EU:** saypha® VOLUME Lidocaine received the CE mark in 2016 in compliance with the COUNCIL DIRECTIVE 93/42/EEC (Medical Device Directive, MDD). Saypha® VOLUME is marketed in the European Union (EU).
- **USA:** saypha® VOLUME Lidocaine is *not* approved for use in the USA yet.

2.2 [redacted]

General information

[redacted] was chosen as comparator device. The following text gives a summary on the characteristics of the comparator device. Detailed information on the comparator device [redacted] is given in the current IFU (dated 06/2020).[14]

Table 6 shows the main components and main characteristics of [redacted]:

Table 6. *Main components of* [redacted]

[redacted] • 20 mg/mL crosslinked HA in a physiologic buffer; obtained from *Streptococcus equi* bacteria • 0.3% (w/w) lidocaine hydrochloride
[redacted] • is a class III medical device incorporating the ancillary medicinal substance lidocaine hydrochloride as an integral part • is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant pre-filled in 2x1 mL syringes (made of Cycloolefin-Copolymer [COC polymer]) and four 27G ½" needles • The contents of the syringe are sterile and non-pyrogenic.

Manufacturer

- [redacted]
- [redacted]

Needles and cannulas for application

- The device is delivered with four 27G ½" needles. The CE manufacturer is [redacted]
- [redacted] 25G 1½" cannula may be used (will be provided by the sponsor´s representative). **Note:** The safety and effectiveness of cannula injection of [redacted] has only been clinically evaluated with the [redacted] 25G 1½" cannulas

Note: The device may be injected with a 25G 1" needle according to the IFU.[14] However, use of other needles than 27G ½" is not allowed within this clinical investigation

Regulatory status

- **EU:** [redacted] is commercially available in the European Union (EU) known as [redacted] with Lidocaine, which is CE certified (CE 0549) in accordance with the Medical Device Directive (93/42/EEC).
- **USA:** [redacted] is commercially available in the United States (see section 1.2). It has been marketed in the USA since 2013. It is also approved for midface-injection via cannula.[14]

3 Justification for the design of the clinical investigation

3.1 Non-clinical data and biocompatibility

3.1.1 *saypha® VOLUME Lidocaine*

The chemical, physical and biological properties of saypha® VOLUME Lidocaine were characterized during development.

Nonclinical biocompatibility studies have been conducted with saypha® VOLUME Lidocaine *in vitro* and *in vivo* and have investigated genotoxity, cytotoxicity, as well as acute, subacute subchronic and chronic systemic toxicity and local effects after implantation (tolerability), skin sensitization, irritation and pyrogenicity (see IB [46] section 5.1) of saypha® VOLUME Lidocaine.

The studies confirmed that saypha® VOLUME Lidocaine was well tolerated and with only a slight reaction observed in the implantation study. Saypha® VOLUME Lidocaine was shown to be non-sensitizing, weakly cytotoxic, not systemically toxic, not mutagenic, and non-irritant.

[redacted]

Not applicable.

3.2 Clinical data

3.2.1 *saypha® VOLUME Lidocaine*

Until now, two clinical studies were conducted. Safety data are available from these studies and post-market surveillance (see Section 4.2.1). However, there are no known data for use of saypha® VOLUME Lidocaine for bilateral midface augmentation available yet.

Clinical data for saypha® VOLUME Lidocaine is available from two clinical studies (VINO and SAVINO; see below).

Post-market study (CPH-401-201258, VINO)

VINO (CPH-401-201258) was a prospective, open-label, multicentre, post-market study evaluating the performance and safety of saypha® VOLUME Lidocaine for the correction of nasolabial folds (NLF).

In total, 62 Caucasian subjects were screened and included in the investigation, 61 of whom completed the investigation. One subject terminated the investigation early after Week 4. The study showed that the device is effective in reducing NLFs.

At the primary endpoint (Week 24 assessment) 95.1% in the ITT population and 94.1% in the PP population demonstrated ≥1 grade improvement in their NLF severity based on the nasolabial folds severity rating scale (NLF-SRS) compared with the baseline status (Day 0). Similarly, the proportion of subjects (ITT) with a reduction (i.e., improvement) of ≥1 NLF severity grade was 95.1% (ITT) and 94.1% (PP) at Week 4 and 87.1% (ITT) and 86.3% (PP) at Week 36/ET.

In addition, the proportion of subjects (ITT) with an improvement of the NLF severity based on the NLF-SRS by ≥1 grade from Baseline to Week 24 was assessed by an independent reviewer of photographs as 98.4% in the ITT and 98.0% in the PP population.

Besides, the study investigated the aesthetic improvement using the GAIS, subject´s satisfaction with the treatment and pain rating assessed by the subject. Results are given in the IB and have been published.[46]

saypha® VOLUME Lidocaine was shown to be safe and well tolerated when used for correction of nasolabial folds (see section 4.2.1 for details).

SAVINO study (CPH-101-201477)

SAVINO (CPH-101-201477) was a prospective, randomized, multicenter study evaluating saypha® VOLUME Lidocaine for the correction of nasolabial folds (NLFs). It was administered into the deep dermis or supraperiosteally.

The performance of the investigational device was evaluated by the investigator by assessing severity of NLFs using NLF-SRS at Weeks 4 and 24 after the initial treatment, and in comparison, to Day 0 (Baseline).

Analysis of the primary performance endpoint was performed after all subjects completed the follow-up visit at Week 24. The performance results of saypha® VOLUME Lidocaine clearly showed an overall convincing performance in the correction of NLF as assessed by investigators and subjects. The investigator grading using the NLF-SRS showed that most of the subjects (whole population: 69%) were still responders with ≥1 point improvement over Baseline at the primary assessment visit Week 24. An improvement of ≥2 grades was assessed in 30% of these subjects. Besides, the study investigated the aesthetic improvement using the GAIS, subject´s satisfaction with the treatment and pain rating assessed the subject. Summary of results is given in the IB.[46]

Overall, the performance and safety results of this clinical investigation demonstrate the benefit of saypha® VOLUME Lidocaine correcting NLFs providing rejuvenation and an aesthetic effect lasting for a satisfactory duration of at least 24 weeks and the good tolerability (see section 4.2.1 for details regarding safety results).

Post-market surveillance

saypha® VOLUME Lidocaine is marketed in in the European Union (EU) and in several other countries outside of the EU (see IB, section 7 for details).

Since 2018 up to end of May 2022, a total of 1,892,174 units of saypha® VOLUME Lidocaine were sold, thereof 1,080,738 units from manufacturing site 'HQ' (the manufacturing site material used within the underlying investigation [CPH-301-201417]) as compared to 811,436 sold units from the original manufacturing line 'C1' (ratio 1:0,75).

In the same period 12 of 48 Adverse Event complaints (weighted ratio 1:4) and 31 of 56 Product Quality complaints (weighted ratio 1:2,41) were linked to products from the 'HQ' manufacturing line. For 4 Adverse Event complaints and one Product Quality complaint the manufacturing line was not identifiable due to the lack of reported lot number of the affected product.

This data suggests that product quality of saypha® VOLUME Lidocaine did not suffer from the introduction of the new manufacturing line, thus confirming the favorable benefit/risk ratio for the device. No new adverse reactions were found in the complaints listing from 2016 until end of May 2022.[46]

In addition, post-market surveillance and complaints from competent authority data were checked for adverse reactions and events not yet covered by descriptions in the scientific literature with no new adverse reactions and events were found in the complaints listings.[46]

[redacted]

Juvéderm® VOLUMA™ XC was shown to be safe and effective when used for cheek augmentation to correct age-related volume deficit in the midface.

The **pivotal study for** [redacted] was a multi-center, single-blind, randomized, no-treatment controlled pivotal clinical study was conducted to evaluate the safety and effectiveness of Juvéderm® VOLUMA™ XC for cheek augmentation to correct age-related volume deficit in the midface (zygomaticomalar region, anteromedial cheek region, and submalar region).

The **one-year post-approval study** was a statistical evaluation of safety data collected from the pivotal study for [redacted]. The safety data were analyzed for subjects who have undergone repeat-treatment with [redacted] as part of the pivotal study mentioned above.

Recently, an additional clinical study was conducted to evaluate the safety and effectiveness of [redacted] with **cannula** [redacted] 25G 1½" cannula) versus needle assessed to correct age-related midface volume deficit in the zygomaticomalar region of the cheek. Statistical non-inferiority of using the cannula was concluded.

In addition, [redacted] was evaluated in a randomized, controlled clinical trial to evaluate the safety and effectiveness for chin augmentation.

Details and results for all above-mentioned studies are summarized in the IFU.[14]

Post-market surveillance

Adverse events that were received during post-market surveillance are summarized in section 4.2.2. Details are given in the IFU.[14]

Literature

Several clinical data from published clinical studies confirmed the effectiveness and safety profile in treating midface volume deficit.[21, 22]

3.3 Justification for the clinical investigation

In the present clinical investigation, saypha® VOLUME Lidocaine (test device) and [redacted] (comparator device) will be used for correction of moderate to severe volume deficiency of the midface. There are no known data for use of saypha® VOLUME Lidocaine for bilateral midface augmentation available yet. However, depending on the following non-clinical and clinical data, the investigation is justified:

- Non-clinical biocompatibility studies have confirmed that saypha® VOLUME Lidocaine was well tolerated and with only a slight reaction observed in the implantation study (also see section 3.1.1 for details).
- saypha® VOLUME Lidocaine received the CE mark in compliance with the COUNCIL DIRECTIVE 93/42/EEC (Medical Device Directive, MDD) in 2016.
- Two clinical studies for the correction of nasolabial folds (CPH-401-201258, 'VINO' and CPH-101-201477, 'SAVINO') were conducted. Saypha® VOLUME Lidocaine was shown to be effective (i.e., indicating a general improvement in the NLF severity rating scale grading) and was deemed safe and well tolerated (see section 3.2.1 for details).
- Safety data are also available from post-market surveillance since market entry in 2016 confirming the favourable risk/benefit ratio for the device. No new adverse reactions were found in the complaints listing. In addition, post-market surveillance and complaints from competent authority data did not reveal new adverse reactions and events (see section 3.2.1 for details).

The comparator device, [redacted], has a well-established record of safety and effectiveness and is approved for marketing for correcting volume deficit in the midface and hence an appropriate comparator as a positive control in this non-inferiority study design (see section 3.1.2 and section 3.2.2 for summaries, and IFU [14] for details).

Overall, non-clinical and clinical data indicate that both devices are well established. In addition, the assessment is based on a sufficient number of treatments.

4 Risks and benefits of the devices and clinical investigation

4.1 Anticipated clinical benefits

The treatment with saypha® VOLUME Lidocaine may remove or reduce a distressing aesthetic defect in subjects with volume deficiency of the midface ("none/minimal" to "very severe" volume deficit of the midface, see section 6.4.13), thereby improving their psychological and social wellbeing.

This is achieved by a minimally invasive procedure with a short downtime. The treatment will correct volume in the midface area immediate and a long-lasting effect is anticipated to last up to nine months after treatment.[46]

The comparator device, [redacted] is approved by the FDA for the treatment of condition under investigation (including the use of cannula) and was shown to be effective and safe over years.[14]

4.2 Anticipated adverse device effects

In general, physicians must inform the subject that there are potential side effects and/or incompatibilities associated with implantation of this device, which may occur immediately or may be delayed.

4.2.1 *saypha® VOLUME Lidocaine*

The anticipated ADEs for saypha® VOLUME Lidocaine are given in the current version of the IB.[46]

Safety data are available from two clinical studies, post-market surveillance (given in section 3.2.1) and from observations with devices similar to saypha® VOLUME Lidocaine. These are summarized in the following paragraphs.

Post-market study (CPH-401-201258, VINO)

'VINO' (CPH-401-201258) was a prospective, open label, multicentre, post-marketing clinical follow-up study evaluating Princess® VOLUME Lidocaine[B] for the correction of nasolabial folds. Overall, 62 subjects were included in the investigation, 61 of whom completed the investigation. A total of twelve subjects (19.4%) reported 18 AEs.

All 18 reported AEs were mild, and none of the AEs were judged by the investigator to have a definite, probable, or possible relationship to the investigational medical device. Ten AEs reported by eight subjects (12.9%) had a definite (nine AEs) or probable (one AE) relationship to the procedure and were classified as adverse device effects (ADEs) according to the sponsor's assessment.

The reported ADEs included injection site hypoesthesia (six subjects), injection site pain (two subjects), injection site hematoma (one subject), and syncope (one subject). All ADEs were mild and had resolved within a maximum of 13 days of their onset. General disorders and administration site disorders were the most frequently reported AEs. Injection site hypoesthesia and injection site pain were the only AEs reported by more than one subject. No AEs were assessed as serious, and no deaths occurred in the investigation.

SAVINO study (CPH-101-201477)

SAVINO (CPH-101-201477) was a prospective, randomized, multicenter study evaluating saypha® VOLUME Lidocaine for the correction of NLFs.

A total of 39 TEAEs was reported in 30 of 109 subjects (28%). 3 of the TEAEs were SAEs (appendicitis, vertebral foraminal stenosis and intervertebral disc protrusion) which were considered to be not related to the device or procedure. All other TEAEs were non-serious, 15 of them were local TEAEs, mainly of mild intensity. 14 of the 15 TEAEs were considered to be related to IMD (definite N=2 and probable N=8) and/or to procedure (definite N=6 and probable N=6).

All local TEAEs belonged to the system organ class 'general disorders and administration site conditions' according to MedDRA. The most frequently patient reported terms according to MedDRA class were 'administration site pain' and 'injection site pain' (3%, each), followed by 'administration site hematoma' and 'administration site swelling' (1%, each). All non-local TEAEs were considered not related to IMD or procedure. Most of the TEAEs had 'resolved' at the end of the investigation. The low number of mainly mild local TEAEs, considered to be related to IMD and/or to procedure was clearly lower than generally described in the literature. No other clinically relevant observations related to safety raised any concerns and no specific risks or precautions were required to be mentioned over those already known and described.[46]

[B] **Note:** saypha® VOLUME Lidocaine and Princess® Volume Lidocaine are the same product marketed under different brand names in different countries.

Overview: Adverse effects of hyaluronic acid dermal fillers

Adverse effects of hyaluronic acid dermal fillers are described in detail in the IB for saypha® VOLUME Lidocaine [46] and are summarized in Table 7.

***Table 7**. Adverse effects of hyaluronic acid dermal fillers* [46]

Commonly reported treatment related AEs (also refer to Section 8.2.1 of the IB)	**Rare AEs** (also refer to Section 8.2.2 of the IB)	**Very rare (S)AEs** (refer to Section 8.2.3 of the IB)
• Bruise/contusion (incl. hematoma) • Hemorrhage/bleeding (incl. ecchymosis) • Hypoesthesia (incl. numbness) • Itching sensation • Medical device site induration (incl. firmness) • Pain (incl. discomfort, tenderness, sensitivity to hot/cold liquids and foods) • Skin discoloration (incl. discoloration, dyspigmentation, erythema, redness, telangiectasia) • Skin inflammation/irritation • Subcutaneous nodule (incl. implant site mass (beading, lumpiness) implant visibility) • Swelling/edema (incl. malar edema) • Tactile disorder These minor AEs are commonly reported after the treatment procedure and are typically managed with the application of ice. These events are typically mild in intensity and should resolve within one to two days after injection. For more details refer to section 8.2.1 of the IB.	• Angioedema • Device dislocation • Dizziness (incl. vasovagal reaction during injection) • Malaise • Nausea • Nerve damage • Paresthesia • Peeling • Puncture marks • Presyncope • Rash • Sebaceous hyperplasia • Skin burning sensation • Skin disorders (incl. scar sarcoidosis, scleroderma, scleromyxedema) • Vasculitis For more details refer to section 8.2.2 of the IB	• Abscess • Bacterial infection • Capsular contracture • Fever • Fibrosis • Granuloma • Headache • Physical asymmetry • Herpes simplex reactivation • Hypersensitivity/allergic reaction • Syncope/fainting • Vascular obstruction/occlusion (incl. changes in vision, stroke, skin changing color or crusty or scabby skin around the eyelids, vasospasm, white appearance (or blanching) of the skin) • Vasoconstriction The following very rare device-related serious AEs have been reported after use of the device or similar devices: • Necrosis • Vascular compromise/arterial occlusion • Retinal artery occlusion For more details refer to section 8.2.3 of the IB.

[redacted]

The following paragraphs give a summary of the anticipated ADEs for [redacted]. The detailed description of the studies and anticipated ADEs for [redacted] can be found in the current version of the IFU.[14]

Pivotal Study: Clinical Evaluation of [redacted] for Cheek Augmentation

For safety evaluation, subjects noted common treatment site responses (CTRs) in pre-printed daily diaries for 30 days after initial treatment are summarized in Table 8.

***Table 8**. Common treatment site responses after initial treatment with [redacted] as reported by the subjects (N=265) in the diary.*

Common Treatment Site Response	**% (n)**
Any Treatment Site Response	98.1 % (260/265)
Tenderness	92.1% (244/265)
Swelling	85.7% (227/265)
Firmness	82.3% (218/265)
Lumps/Bumps	81.1% (215/265)
Bruising	77.7% (206/265)
Pain	66.4% (176/265)
Redness	66.0% (175/265)
Discoloration	41.1% (109/265)
Itching	38.5% (102/265)
Ache, acne, bulge, bumps, cheek larger upon waking up, dry patch, fine wrinkles, injection/needle marks, numbness, pigmentation from treatment, puffiness, rash, scratch near injection point, soreness, tightness, and yellowness.	≤ 5% of subjects

N = number of subjects who recorded responses in the diaries after the initial treatment.
n = number of subjects who experienced responses after the initial treatment.

Treatment site responses rated by the subjects were predominantly mild (21.5%; (56/260)) or moderate (59.2%, (154/260)) in severity and lasted for 2 to 4 weeks.

For those treatment site responses evaluated as moderate or severe, the median duration as moderate or severe was 2 days. The median time to complete resolution was 6 days. The severity of CTRs following repeat-treatment was similar, with a reduced incidence and duration compared to initial treatment (based on available data from 120 subjects).

CTRs reported in subject diaries that lasted *longer than 30 days* were considered adverse events (AEs). Where applicable, AEs were also reported by the treating investigator at all follow-up visits. Device and injection-related AEs are summarized in Table 9.

***Table 9**. Device- and injection-related adverse events reported by treating investigator and subjects occurring in subjects treated with [redacted] (N = 270)*

Adverse Event	Treated Subjects % (n)
> 1% of subjects	
Treatment site mass	18.9% (51/270)
Treatment site induration	14.1% (38/270)
Treatment site swelling	7.0% (19/270)
Treatment site pain	5.9% (16/270)
Treatment site hematoma	3.7% (10/270)
Treatment site discoloration	2.2% (6/270)
Treatment site erythema	1.9% (5/270)
Treatment site reaction	1.5% (4/270)
≤ 1% of subjects	
Injection site hypertrophy, nodule	0.7% [each AE]
Inflammation, injection site anesthesia, injection site dryness, injection site erosion, mass, contusion and syncope	0.4 % [each AE]
N = number of subjects who device- and injection-related adverse events after the initial treatment. n = number of subjects treated.	

These AEs were seen more frequently in subjects that received injection volumes greater than 9 mL, and in subjects older than 60 years of age.

Two subjects (0.7%; 2/270) reported 3 serious adverse events (SAEs) that were considered to be related to the device (see IFU for details).

Among the 270 subjects treated, 32.6% (88/270) experienced device- and injection-related AEs following initial and touch-up treatment. Of these 99% (624/627) were reported at a treatment site. Information on AEs following repeat-treatment was collected as part of the post-approval study (see below).

Post-approval study: One-Year Post-Approval Study of [redacted] for Cheek Augmentation

Safety data from subjects who underwent repeat-treatment with [redacted] as part of the pivotal study were analyzed. Again, CTRs were reported by the subjects within the pre-printed subject´s diary for 30 days after repeat-treatment. Data are summarized in Table 10.

Table 10. *Common treatment site responses after repeat-treatment with* [redacted] *as reported by the subjects (N=167) in the diary (occurring in > 5% of subjects).*

Common Treatment Site Response	**% (n)**
Any Treatment Site Response	90.1% (146/162)
Tenderness	76.5% (124/162)
Swelling	67.9% (110/162)
Firmness	67.9% (110/162)
Bruising	62.3% (101/162)
Lumps/Bumps	58.0% (94/162)
Redness	56.8% (92/162)
Pain	54.9% (89/162)
Itching	32.7% (53/162)
Discoloration	26.5% (43/162)
N=number of subjects who recorded responses in the diaries after the repeat-treatment. n= number of subjects who experienced responses after the repeat-treatment.	

The incidence of treatment site responses after repeat-treatment was lower than the incidence after initial/touch-up treatment. The reported treatment site responses were generally less severe and shorter in duration after repeat-treatment compared to initial/touch-up treatment (usually resolved within 2 weeks).

Again, treatment site responses reported in subject diaries lasting longer than 30 days were considered AEs and, where applicable, other AEs were reported by the treating investigator at all follow-up visits. These device- and injection-related AEs are summarized in Table 11.

Table 11*. Device- and injection-related adverse events reported by treating investigator and subjects occurring in > 1% of subjects treated with* [redacted] *(N = 167).*

Adverse Event	**Treated Subjects % (n)**
Total	**8.4% (14/167)**
Injection site mass	4.2% (7/167)
Injection site induration	4.2% (7/167)
Injection site bruising	1.2% (2/167)
N = number of subjects who device- and injection-related adverse events after the repeat-treatment. n = number of subjects treated.	

Device/injection-related AEs were lower and less severe after repeat-treatment compared to initial/touch-up treatment. Most of those AEs resolved within three months. There were no device/injection-related SAEs after repeat-treatment.

Cannula study for cheek augmentation

At total of 60 subjects seeking correction of age-related midface volume deficit underwent treatment in a randomized, within-subject, controlled clinical trial to evaluate the safety and effectiveness of [redacted]C using a [redacted] 25G 1½" cannula in one cheek and a needle in the other cheek. Again, the subjects completed a pre-printed diary forms for 30 days after treatment. These device- and injection-related AEs are summarized in Table 12.

***Table 12**. Common treatment site responses after treatment with [redacted] as reported by > 5% the subjects (N = 60) in the diary.*

Common Treatment Site Response	Cannula % (n)	Needle % (n)
Any Treatment Site Response	100.0% (60/60)	100.0% (60/60)
Tenderness to touch	91.7% (55/60)	96.7% (58/60)
Firmness	83.3% (50/60)	90.0% (54/60)
Swelling	81.7% (49/60)	85.0% (51/60)
Lumps/Bumps	70.0% (42/60)	83.3% (50/60)
Pain after injection	66.7% (40/60)	83.3% (50/60)
Bruising	60.0% (36/60)	71.7% (43/60)
Redness	55.0% (33/60)	61.7% (37/60)
Discoloration	36.7% (22/60)	43.3% (26/60)
Itching	18.3% (11/60)	20.0% (12/60)
N=number of subjects who recorded responses in the diaries after the repeat-treatment. n= number of subjects who experienced responses after the repeat-treatment.		

All subjects reported experiencing a local treatment site response after treatment with [redacted]. Subjects rated treatment site responses as being mostly mild or moderate in severity (about 90% for cannula and needle, respectively). About 60% of the treatment site responses resolved within 2 weeks.

Post-Market Surveillance for [redacted] with *and* without *Lidocaine*

The events listed in Table 13 were received from post-market surveillance for [redacted] *with and without* lidocaine with a frequency ≥5 and were not observed in the clinical studies (during the 6-13 months that subjects were monitored in the chin and cheek studies, respectively); this includes reports received globally from all sources including scientific journals and voluntary reports. Note, that [redacted] without lidocaine has been marketed outside the USA since 2005.[14]

***Table 13**. Post-market surveillance for* [redacted] with *and* without *Lidocaine with a frequency ≥ 5 and were not observed in the clinical studies.*[14]

***Note:** AEs are listed in order of number of reports received.*

• Inflammatory reaction • Lack of correction • Infection • Migration • Allergic reaction • Abscess • Paresthesia • Vascular occlusion • Drainage • Necrosis • Vision abnormalities * • Malaise • Scarring • Nausea • Granuloma • Deeper wrinkle • Dyspnea
* Vision abnormalities have been reported following injection into the nose, glabella, periorbital area, and/or *cheek*, with a time to onset ranging from immediate to one week following injection. Reported treatments include anticoagulants, sympathomimetics, steroids, and surgery.

Outcomes ranged from resolved to ongoing at the time of last contact.

Note, that events requiring medical intervention, and events where resolution information is not available, were reported after injection in the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indication for use (see Warnings section in the IFU [14]).

General Warnings for [redacted]

- Introduction of [redacted] into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction.
- Treatment site reactions consist mainly of short-term inflammatory symptoms and generally resolve within 2 to 4 weeks.

In general, rare but serious adverse events associated with the intravascular **injection of soft tissue fillers** in the face have been reported and include [14]

  - temporary or permanent vision impairment
  - blindness
  - cerebral ischemia or cerebral hemorrhage
  - leading to stroke
  - skin necrosis
  - damage to underlying facial structures.

Please see IFU of [redacted] [14] and section 6.2.4.2 for further General Precautions and Warnings when using the comparator device.

4.2.3 *Lidocaine hydrochloride*

In order to improve the comfort of HA filler injections, the local anesthetic lidocaine hydrochloride (a medicinal product) [11] has been included in their formulation to reduce procedural pain and to bypass the need for additional anesthesia.

Randomized controlled clinical trials, many of which have been split face trials, have compared the same dermal filler with and without lidocaine. The studies have been designed appropriately, with suitable outcome measures and appropriate analysis and have confirmed that treatment with dermal fillers with lidocaine resulted in a statistically and clinically significant reduction in pain ($p < 0.0001$).

The collective data has demonstrated unequivocal clinical benefit for dermal fillers incorporating lidocaine with no additional risks, since the frequency and severity of AEs was not different for dermal fillers with or without lidocaine.[24, 25], [26]

4.3 Possible interactions with concomitant medical treatments

No studies on drug interactions with saypha® VOLUME Lidocaine have been conducted in humans.

- Both devices must not be used in subjects on immunosuppressive therapy (also see Exclusion Criterion (ExC) #8; section 6.3.3; ExC#9 in section 6.3.5).
- Use of anticoagulant, antiplatelet, nonsteroidal anti-inflammatory drugs or thrombolytic drugs may increase the risk of bleeding or bruising (such as acetylsalicylic acid, clopidogrel, ticagrelor, and warfarin, heparin, enoxaparin, or apixaban). The subject should be asked about use of such medications (also see ExC #15; section 6.3.3, ExC#16 in section 6.3.5).
- Sodium hyaluronate is incompatible with quaternary ammonium compounds such as benzalkonium chloride solutions, hence the device should never be placed in contact with these substances or with medical-surgical instruments that have been in contact with these substances.

4.4 Risk mitigation strategy

The risks will be mitigated by

- Careful selection of subjects and exclusion of those who may have an increased risk of developing certain types of adverse events (AEs) (see section 4.2 and section 6.3.3).
- Engagement of experienced investigators who are familiar with soft tissue fillers, and who are appropriately trained to ensure correct and safe application of the test and the comparator devices (including treatment of potential safety issues). The sponsor has chosen only board-certified specialists (dermatologists or plastic surgeons) as principal investigators for this investigation who in addition to board certification have years in experience with dermal fillers, both in clinical investigations as well as in daily routine activities. An updated list of investigation sites and corresponding principal investigators and their qualifications will be kept separately from the CIP.
- In particular, the investigators must be familiar with the signs and symptoms associated with vascular occlusion and have a plan detailing how to treat the subject in the event of vascular occlusion; this may include on-site treatment and/or immediate referral to another health care professional for specialized treatment. For instance, in the event of blindness, subjects have to undergo immediate evaluation by an ophthalmology specialist.

  Ophthalmology specialists near each investigational site who are able to immediately examine subjects should be identified and informed about the clinical investigation procedure.

  A board-certified ophthalmologist will do a training to the treating investigators at the sites. Additionally, a specific treatment protocol in case of unintended intravascular injection that is consistent with those recognized by national, professional societies should be in place at each investigational site.

Additionally, a basic neurological examination (F.A.S.T [27, 28]) will be performed in all subjects who show signs of ophthalmic complications due to filler injection to ensure patient safety (see sections 6.4.8 and 6.4.9).

Investigation sites will also be required to have an emergency plan in place and a minimum medication readily available to promptly react in case a suspected vascular occlusion or allergic reaction occurs (see section 6.2.5).

The subjects will be instructed to immediately contact the treating investigator in case of any health concern occurring between the scheduled visits including special focus on experience of any signs/symptoms of vision changes or stroke since the injection (see section 6.4.8).

- Evaluation of vision changes through visual examinations before and after treatment and protocols at each investigational site for immediate intervention in the event of unintended vascular injection.
- Regular follow-up of the subjects, which allows for timely recognition and management of potential AEs, including phone calls for safety follow-up. The subjects will be contacted by phone 24 to 48 hours after each treatment to check their health condition.
- Careful selection of the comparator device ([redacted]) that´s use, safety and effectiveness is very well established and that is approved for the indication investigated in the EU and in the USA including the use of cannulas for application (see section 3.2.2 and section 4.2.2).
- Ensuring the safety and ensuring the rights of participants, site personnel and other persons involved in conducting the study (e.g., the clinical monitors) also during the COVID-19 (coronavirus) pandemic is paramount. Guidance documents of the EMA [29, 30], the European Commission [31] and the FDA [32], national supplementary recommendations and laws, and guidance from IRBs/ECs regarding management of clinical studies during the COVID-19 pandemic will be followed in their respective current versions and as applicable.

  Mitigation measures already taken

  Several mitigation measures have already been taken:

  - An exclusion criterion referring to an infection with SARS-CoV-2 was included into the investigation design (see section 6.3.3.2).
  - To minimize the risk for the subjects, in this investigation design, the safety follow-up 24 to 48 hours after each device injection will be performed as phone contact. Only in case of an AE or an unbearable injection site reaction an unscheduled on-site visit should be performed (see section 6.5.17).
  - The number of study sites planned to be included in the study was increased during study-set-up to mitigate the risk of COVID-19.
  - Each site is required to carry out all procedures and to have their own process how to manage the subjects that come into their clinic in light of COVID-19 (e.g., social distancing needs as far as possible, particular attention to the specific sanitation rules).

    In addition, at time of each scheduled on-site visit post-screening the study site may take into consideration to ask subjects repeatedly (alternatively by phone contact prior to the respective on-site visit or as a first measure during the on-site visit) if he/she currently suffers from active COVID-19 disease, from common signs and/or symptoms of COVID-19**,** if he/she had close contact to a person with confirmed COVID-19 within the last 14 days or since the last visit, or if they had been in a currently designated risk area.

    In case of a suspected infection with SARS-CoV-2 at any time during the clinical investigation, it is recommended to ask subjects to perform a test on SARS-CoV-2. This should be done in an official Corona test center or at the subject's family physician and / or in line with national / local provisions. Until the negative test result is available, remaining assessments planned for the respective study visit will be postponed.

    Of note, depending on the respective national regulation, SARS-CoV-2, may be a notifiable infection. If infection with SARS-CoV-2 is suspected or diagnosed, the investigator or the

laboratory may be required to report this by name (not pseudonymized) to the responsible health authority.

Possible Mitigation Measures in Case of Restrictions During the Pandemic

It is possible that, with the escalation of the pandemic, local circumstances lead to a local change in risk assessment. Certain study procedures may need to be adapted to then existing pandemic situation, e.g., when study sites are not accessible to subjects or clinical monitors, or individual subjects are unable to attend single visits, e.g., due to current active infection with SARS-CoV-2 and related quarantine, movement restrictions, subject´s concerns or site closure. An overview about the possible mitigation measures in case of restrictions during the pandemic is outlined in an addendum to the CIP.

All decisions to adjust the conduct of the clinical investigation will be based on the risk assessment (see section 6.9). The sponsor will continuously re-assess risks with special focus on the COVID-19 pandemic. This risk assessment will be based on relevant parties' input and should be documented on an ongoing basis. Investigators involved should initiate and/or be involved in risk assessment and planning of mitigation measures.

All measures taken, their prospective impact and their outcomes will be documented as part of the study-specific risk management documentation. Necessary changes will be agreed with and communicated clearly to investigators and study sites. Study subjects will be informed by the investigator about the possible changes in the conduct of the clinical study relevant to them (cancellation of on-site visits, etc.). In general, information process will be in line with information given in section 13.

4.5 Risk-to-benefit rationale

Hyaluronic acid-based dermal fillers, such as saypha® VOLUME Lidocaine as well as [redacted], are generally considered very safe and effective (see sections 3.1 and 3.2, and sections 4.2.1 to 4.2.3 for details).

When using saypha® VOLUME Lidocaine, only a very low number of product quality and adverse event complaints compared to the total number of devices sold have been reported since its first market entry (see section 3.2.1). All adverse events are described in the IB as commonly reported after use of dermal fillers. Based on similarity to other crosslinked HA fillers and an acceptable non-clinical safety profile, saypha® VOLUME Lidocaine is expected to be as safe as other HA fillers including the comparator device.

The risk assessment for saypha® VOLUME Lidocaine has been performed according to ISO 14971. Results of the risk assessment are described in the IB (section 9). The overall residual design, manufacturing, and use risks, and the benefit-risk-ratio of the device when used on subjects by experienced and trained physicians, according to the manufacturer's instructions for use, are considered to be fully acceptable.[46]

The safety of the subjects is of primary importance, and challenges due to COVID-19, were weighed against anticipated benefit for the subjects and society and respective measures are to be taken as appropriate (see section 4.4). Overall, the study subjects are healthy persons who desire a filler injection procedure for correction of moderate to severe volume deficiency of the midface and are not considered to be at an increased risk for virus infections nor at increased risk for a severe course of a COVID-19 due to participation in the investigation. Based on the current knowledge and available information on risks associated with the COVID-19 pandemic, treatment of adult subjects enrolled in the study seems justified. Therefore, the overall Risk-to Benefit assessment in regard to COVID-19 and in regard to related assessments is considered to be acceptable in view of a potential spread of the virus.

It is reasonable to conclude that potential benefits of participation in the investigation, including treatment with either the test device or comparator device, outweighs potential risks described in section 4.2 when:

- considering the potential benefits of correction, in particular the immediate and long-lasting improvement of distressing aesthetic defect (see section 4.1), and
- taking into account the risk mitigation measures (see section 4.4).

In conclusion, the overall risk-benefit-ratio for subjects participating in the study is justified.

5 Purpose and objectives of the clinical investigation

5.1 Intended purpose of the clinical investigation

The purpose of the current clinical investigation is to evaluate the effectiveness, safety and long-term safety of saypha® VOLUME Lidocaine for the correction of age-related moderate to severe volume deficit in the midface (augmentation of midface volume deficit), and to demonstrate its non-inferiority to one of the devices approved for the same indication [redacted] In addition, the duration of the aesthetic effect after implantation will be studied.

5.2 Objectives

5.2.1 *Primary objective*

- To demonstrate non-inferiority in the effectiveness of saypha® VOLUME Lidocaine for midface augmentation in order to correct moderate to severe volume deficit versus [redacted] based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase and compared to baseline assessments.

5.2.2 *Secondary effectiveness and other objectives*

5.2.2.1 General Aspects

The following general topics are applicable for all below defined objectives:

- For the **initial treatment phase:**
  - all **secondary effectiveness objectives** will be evaluated for saypha® VOLUME Lidocaine versus [redacted]
  - evaluation in general will be assessed for Visits 4 to 9 (SV1): Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase
- For the **repeat-treatment phase:**
  - **Other objectives** will be evaluated descriptively for saypha® VOLUME Lidocaine, only
  - evaluation will be assessed at Visits RT3 to Visit RT5 (Week 4, 12 and 24 after last injection of repeat-treatment phase)

5.2.2.2 Objectives

Midface volume deficit and nasolabial fold improvement

- To further assess effectiveness of saypha® VOLUME Lidocaine 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)
- To assess the effectiveness of saypha® VOLUME Lidocaine for correction of moderate to severe midface volume deficit based on the ***independent blinded photographic reviewer´s*** assessment (initial treatment phase only)
- 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)
- To assess the effect of midface treatment with saypha® VOLUME Lidocaine on the nasolabial folds based on the blinded evaluator´s live assessment

Global aesthetic improvement

- To evaluate global aesthetic improvement based on ***subject's*** assessments (initial treatment phase only)
- To evaluate global aesthetic improvement based on the ***blinded evaluator's*** assessments (initial treatment phase only)

Subject's satisfaction with outcome and appearance appraisal

- To assess subject´s satisfaction with ***overall treatment outcome***
- To assess subject´s ***appearance appraisal*** after treatment

Subject's pain assessment and injection volume

- To evaluate subject's ***perception of pain*** after each treatment
- To assess total ***injection volume*** needed for optimal correction

5.2.3 *Safety objectives*

- To assess **safety** of saypha® VOLUME Lidocaine during the entire study period including subject complaints as recorded in the subject diaries
- To evaluate **long term safety** of saypha® VOLUME Lidocaine after repeat-treatment
- To assess safety of saypha® VOLUME Lidocaine when used in cross over treatment referring to initial and repeat treatment [redacted] in initial treatment phase switched to saypha® VOLUME Lidocaine in repeat-treatment phase)

5.3 Endpoints: Criteria for evaluation

5.3.1 *General information on effectiveness endpoints*

- The subjects pain assessment, nasolabial folds, and volumetric change measurement will be assessed and analyzed for the left and right side of the face separately.
- All other endpoints will be assessed and analyzed globally (i.e., left and right side together / combined)
- **For MVDSS in general:** Subjects are defined as a 'responder' if they are showing an ≥1 point improvement on the 5-point MVDSS, based on the respective score at a given visit relative to the respective baseline score. The grade assigned at the respective baseline visit (either Baseline visit or Visit RT1) will represent the baseline value for derivation of the responder status at a given visit during the initial treatment phase or repeat-treatment phase. Assessments will be evaluated by either the blinded evaluator at the site or by the central independent blinded photographic reviewer.

5.3.2 *Primary effectiveness endpoint*

The effectiveness of the investigational device will be evaluated using the following primary endpoint:

- 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

5.3.3 *Secondary effectiveness and other endpoints*

5.3.3.1 Initial treatment phase

The effectiveness of the investigational device during initial treatment phase will be further evaluated using the following **secondary effectiveness endpoints:**

MVDSS, NLF-SRS and Volumetric Change measurement

- The percentage of responders on the 5-point MVDSS, based on the ***blinded evaluator´s live*** assessment at Week 4, 8, 16, 36, and 48 after last injection of initial treatment phase compared to the score at Baseline visit.
- The percentage of responders on the 5-point MVDSS, based on the ***independent blinded photographic reviewer´s*** assessment by using Baseline photographs at Week 4, 8, 16, 24, 36 and 48 after last injection of initial treatment phase compared to the score at Baseline visit
- Mean change in midface volume deficit measured on the 5-point MVDSS and 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
- 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
- Shift from baseline (Baseline visit) in nasolabial folds measured by NLF-SRS based on the blinded evaluator´s live assessment at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase

Global aesthetic improvement based on modified GAIS

- The percentage of subjects with a global aesthetic improvement over baseline (at Baseline visit) (subjects who have been rated as “much improved” or “improved”), based on ***subject´s*** assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment phase using the 5-point *modified* GAIS.
- The percentage of subjects with a global aesthetic improvement over baseline (at Baseline visit) (subjects who have been rated as “much improved” or “improved”), based on the ***blinded evaluator`s*** assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment phase using the 5-point *modified* GAIS.

Subject’s satisfaction with outcome and appearance appraisal based on FACE-Q™ assessments

- The extent of ***subject´s*** satisfaction with ***overall treatment outcome*** at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase as assessed by the subject using the Face-Q™ Questionnaire “Satisfaction with Outcome”.
- The extent of ***subject´s appearance appraisal*** at Week 4, 8, 16, 24, 36, and 48 after last injection of initial treatment phase as assessed by the FACE-Q™ questionnaire “Satisfaction with Cheeks” compared to Baseline visit.

Subject´s pain assessment and injection volume

- ***Subject*** evaluation of ***pain*** after each treatment (baseline and touch-up treatment) on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable
- ***Injection volume*** required to achieve optimal aesthetic result at each treatment (baseline- and touch-up treatment together)

5.3.3.2 Repeat-treatment phase

The investigational device during repeat-treatment phase (saypha® VOLUME Lidocaine) will be evaluated using the following ***other effectiveness*** endpoints:

MVDSS and NLF-SRS

- The percentage of responders on the 5-point MVDSS, based on the ***blinded evaluator´s live*** assessment at Week 4, 12 and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1
- Mean change in midface volume deficit measured on the 5-point MVDSS and based on the ***blinded evaluator´s live*** assessment at Week 4, 12, and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1
- Shift from baseline (Visit RT1) in NLF-SRS based on the ***blinded evaluator´s live*** assessment at Week 4, 12 and 24 after last injection during repeat-treatment phase

Subject's satisfaction with outcome and appearance appraisal based on FACE-Q™ assessments

- The extent of ***subject´s*** satisfaction with ***overall treatment outcome*** at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome"
- The extent of ***subject´s appearance appraisal*** at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the FACE-Q™ questionnaire "Satisfaction with Cheeks" compared to the score at Visit RT1

Subject´s pain assessment and injection volume

- Subject evaluation of ***pain*** after each treatment (repeat and touch-up-treatment) on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable
- ***Injection volume*** required to achieve optimal aesthetic result at each treatment (repeat and touch-up treatment together)

5.3.4 *Safety endpoints*

The safety of the investigational device will be evaluated by treatment group including cross-over group (in repeat-treatment) and by treatment phase using the following endpoints:

- Occurrence and frequency of adverse events during the entire study period including repeat-treatment phase (long-term safety). Symptoms of interest will be recorded in subject diary during the first 4 weeks (28 days) after each treatment (i.e., either 4 weeks after baseline and repeat-treatment, respectively, and 6 weeks in case of touch-up treatment) and documented as AE by investigator.
- 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 and repeat-treatment, respectively, and 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).

5.4 Risks and anticipated adverse device effects that are to be assessed

Based on the equivalence of saypha® VOLUME Lidocaine with these products and available non-clinical and clinical safety data of the device under investigation, it is anticipated that it will share the same safety profile (details described in section 4).

Risks and anticipated ADEs for the test device are given in the current version of the IB.[46] All anticipated ADEs according to the IB section 8.2 have to be documented and reported as described in section 14.

For precautions to be taken to avoid occurrence of adverse events associated with the test device refer to section 6.2.4 and the current IB.[46]

6 Design of the clinical investigation

6.1 Design description

6.1.1 *Visit Overview*

This is a randomized, subject and evaluator-blinded, active treatment controlled, parallel group, non-inferiority, multicenter study with a dermal filler for the correction of moderate to severe midface volume deficit.

The clinical investigation will comprise randomization to two treatment groups:

- **Test device:** saypha® VOLUME Lidocaine
- **Comparator device:** [redacted]

Eligible subjects will be randomized at Baseline visit in a 2:1 ratio to undergo bilateral treatment with saypha® VOLUME Lidocaine or [redacted]^{TM} [redacted], respectively.

The Screening visit (Visit 1) will be performed within 2 weeks prior to randomization and will entail informed consent and screening assessments as specified in section 6.5.1. During this visit the treating investigator will determine eligibility of subjects based on study inclusion and exclusion criteria (see section 6.3.3). Screening and Baseline visit (Visit 2 / Day 0) can be combined and performed at one day.

Baseline severity of midface volume deficit will be determined at Visit 1 by the blinded evaluator using the 5-point MVDSS. In addition, the subjects face will be photographed to document baseline condition for further assessments.

At Visit 2, eligible subjects will be randomized and undergo bilateral midface augmentation treatment with either saypha® VOLUME Lidocaine or [redacted] (baseline treatment).

If an optimal aesthetic correction has not been achieved after the baseline treatment, as evaluated by the treating investigator, a touch-up treatment may be performed at Week 2 (Visit 3) using the same device as initially applied at Visit 2.

At Week 48 (Visit 9 (SV1)) after last treatment of the initial treatment phase, subjects of both treatment groups (test device and comparator device) may qualify for optional repeat-treatment, which will be done with saypha® VOLUME Lidocaine only.

Screening visits for repeat-treatment will be every 4 weeks up to 12 weeks after Visit 9 (SV1). As soon as the subject is eligible in MVDSS score, a full eligibility assessment for repeat-treatment will be done. 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 (see section 6.3.5). Again, the blinded evaluator at the site decides, if subject is eligible for the repeat-treatment (regarding MVDSS).

Visit SV4 (12 weeks after Visit 9 (SV1) at the latest) 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 for repeat-treatment and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment, Visit 9 (SV1), SV2 or SV 3 will be the end of study visit for the respective subject.

Subjects who are eligible and willing to undergo optional repeat-treatment at Visit RT1 will enter the repeat-treatment follow-up phase.

Follow-up visits on-site (see Figure 1.) will occur at:

- **Initial treatment phase:** Week 2 after baseline treatment, and 2, 4, 8, 16, 24, 36, 48 weeks after last treatment, i.e., baseline or touch-up treatment, respectively (Visits 3 to 9 (SV1))
- **Screening phase for repeat-treatment:** Week 4, 8 and 12 after Visit 9 (SV1) – (Visits SV2 to SV4)
- **Repeat-treatment phase:** Week 2 after repeat-treatment, and 2, 4, 12 and 24 weeks after last treatment, i.e., repeat- or touch-up treatment, respectively (Visit RT2 to RT5)

In addition to the on-site follow-up visits, 24-48 hours after each treatment the subjects will be contacted by phone for safety checkup. If applicable, the incidence, severity, seriousness and type of adverse events resulting from device injection will be determined and closely followed up until resolution.

Figure 1 displays an overview of the visits.

Figure 1. *Visit Overview.*

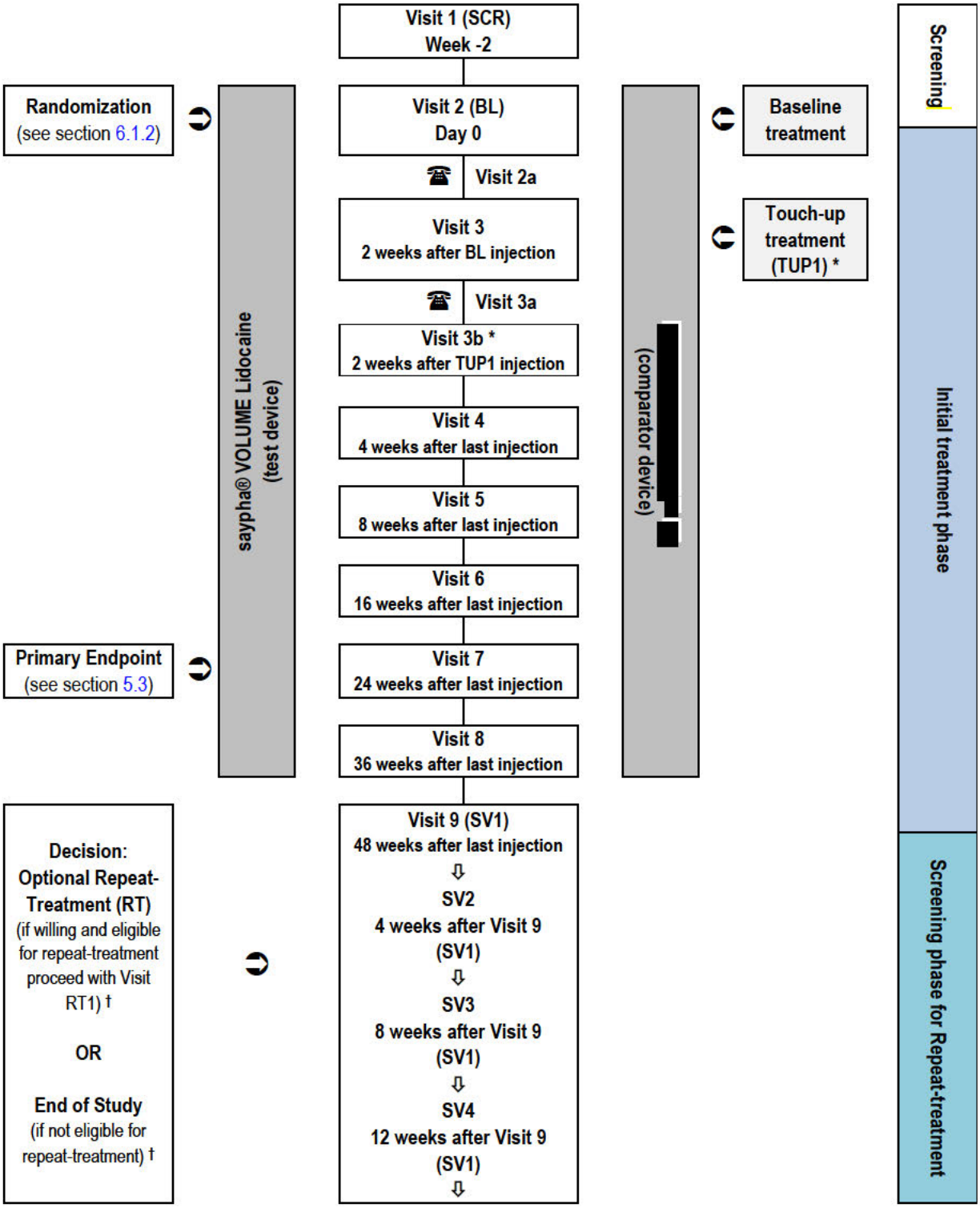
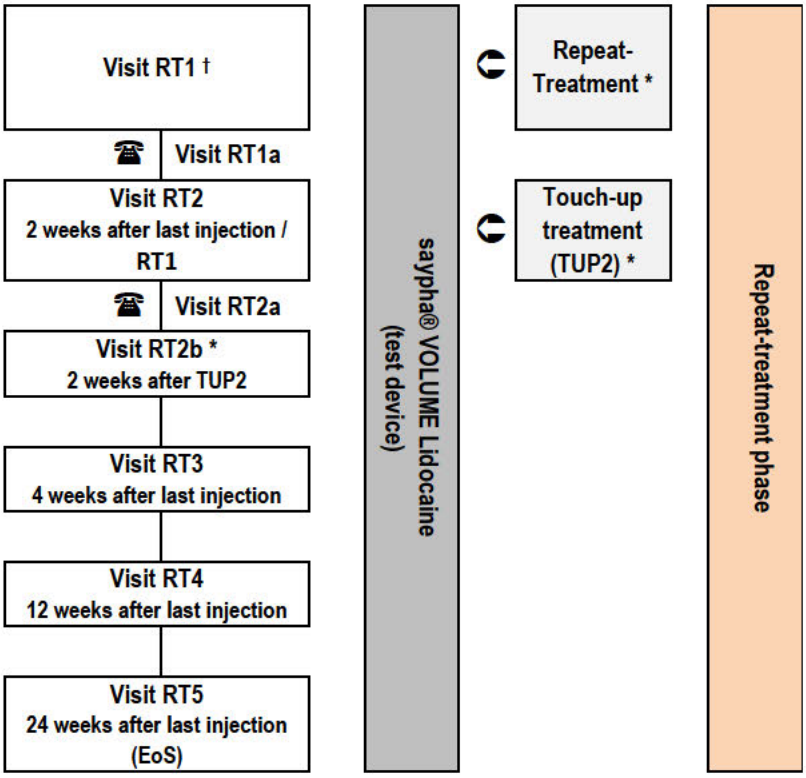


Figure 2. *Visit Overview (continued).*



Notes: *optional † May be combined with either Visit 9 (SV1), SV2 to SV4 (⇩: 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.
In case an inclusion criterion is not met / an exclusion criterion is met for repeat-treatment (see section 6.3.5) and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment, Visit 9 (SV1), SV2 or SV 3 will be the end of study visit for the respective subject.)
Abbreviations: SCR: Screening; BL: Baseline; SV: Screening Visit; RT: Repeat-Treatment ☎: Telephone Visit;

Midface volume deficit will be evaluated *(live* assessment) by the blinded evaluator at the site using the 5-point MVDSS during follow-up visits of the initial and repeat-treatment phase. A central independent blinded photographic reviewer will assess the MVDSS for the same time points of the initial treatment phase based on photographs taken during the subject´s visits (see section 6.4.13). In addition, volume change measurements will be done on 3D photographs (by Canfield Scientific, Inc., see section 6.4.12).

Severity of nasolabial folds (NLFs) will be assessed using the 4-point Nasolabial Folds Severity Rating Scale (NLF-SRS) during intial and repeat-treatment phases, respectively, at each onsite visit by the blinded evaluator at the site *(live* assessment).

Subject's pain perception during treatment and recovery from treatment will be evaluated by means of a numerical pain rating scale (NPRS) immediately and for 60 min (in 15 minutes intervals) after each device administration (see section 6.4.14).

Global aesthetic improvement will be evaluated by reviewing current photographs relative to photographs taken at the Baseline visit. Both – the blinded evaluator at the site and the subject – will assess the global aesthetic improvement (using the modified GAIS) at each on-site visit after last injection of the initial treatment phase (see section 6.4.16).

Subject´s satisfaction with the outcome of the treatment will be assessed with the FACE-Q™ questionnaires "Satisfaction with Outcome" (see section 6.4.17) and "Satisfaction with Cheeks" (see section 6.4.18) at each on-site visit after last injection of the initial and repeat-treatment phase, respectively. Subject´s "Satisfaction with Cheeks" will also be assessed at Visit 2 (Baseline visit) and Visit RT1.

The safety will be evaluated based on occurrence of adverse events, which will be collected at each visit (on-site and telephone visits) throughout the clinical investigation, beginning after signature of the ICF until the last visit. In order to identify potential adverse events post-administration a safety evaluation after 15 minutes needs to take place (see section 6.4.20).

In order to evaluate any potential vision changes, visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) will be additionally performed at treatment visits (prior to and 30 min after any treatment) and at all follow-up visits of the initial and repeat-treatment phase. A basic neurological examination (F.A.S.T) will be performed for all subjects who show signs of ophthalmic complications due to filler injection.

Abnormal clinically significant changes in visual examination or experience of neurological symptoms indicative of a vaso-occlusional event after any treatment will lead to withdrawal of the subject from further treatment(s) in case an eye specialist or neurologist confirm that the result is related to a vascular injection of the dermal filler. The subjects may remain in the study for at least safety assessments during the scheduled study visits. Further activities following a related vascular event are described in section 16.1.

A subject diary will be used to record injection site reactions, and symptoms of interest over the first four 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 – see section 6.4.19.

A detailed schedule of procedures is given in section 6.5 and the “Schedule of procedures and assessments”. Detailed descriptions of assessments and procedures can be found in section 6.4.

6.1.2 *Randomization*

The randomization will be performed at the Baseline visit (Visit 2), after final confirmation of subject’s eligibility. Treatment assignment will be pre-planned according to a computer-generated randomization schedule in a 2:1 ratio (test device : comparator device). The schedule will contain the following treatment assignments, which will be randomly allocated to sequential randomization scheme:

- **Test device:** saypha® VOLUME Lidocaine
- **Comparator device:** [redacted]

The randomization information will assign the subject to one of the treatment groups. In addition, a minimum of 100 subjects randomized to the test device will be treated with either needle or cannula.

Only *unblinded site staff* performs the randomization via a randomization function of the eCRF.

Neither the blinded evaluator at the site nor the central independent photographic reviewer will have access to the randomization system (see section 6.1.3 for details). The randomization number will be documented in the eCRF.

The exact procedure for obtaining a randomization number/treatment assignment for a subject will be provided to each investigational site before the study is initiated by training and will be described in a separate manual or other appropriate document.

6.1.3 *Blinding*

The blinded evaluator at the site, who will perform live assessments of treatment effectiveness, as well as the central independent blinded photographic reviewer will be blinded to the treatment administered.

Subjects will also be blinded to the treatments they received until finalization of Visit 9 (SV1). Measurements to keep the blinding are described below.

Subjects

- Subjects will be blinded to the treatment administered
    - Subjects will be blind-folded during treatment. Subjects might be unblinded via label or design of the syringe/backstop of both devices that are different in appearance. Before removing the blind-folds, the respective device (incl. all needles/cannulas used, the surrounding boxes/blisters, etc.) must be removed from the treating room or covered (e.g., with a

nontransparent box) before the sleep mask is removed). The way of blinding (e.g., goggles, masks, other) has to be documented in the subject's source record and in the eCRF.

- Also, the sites must ensure, that before, during and after the treatment there can be no specific information found in the clinical and especially the treating room (e.g., logos on the device or on the outer boxes; the subject must have no view on the computer screen during randomization process)
- The treating investigator and other site staff must not disclose the device injected to the subject

Blinded evaluator at the site

The blinded evaluator at the site will be independent of the study conduct and blinded against the randomization code of each subject until data base lock.[C] The following measures will be taken to ensure the blinded evaluator at the site throughout the clinical investigation:

- Each site has to install two types of study personnel:
  - Unblinded site staff (i.e., treating investigator, other site staff)
  - Blinded evaluator at the site.

  Of note, unblinded site staff as well as CRO staff (including Clinical Research Associates (CRAs)), data managers, medical monitor and biostatistician) and sponsor will be unblinded to the treatment group assignment.
- The treating investigator, all other unblinded site and CRO / sponsor staff must not disclose the blinded evaluator at the site the identity of the treatment group the subjects belong to. Especially the treating investigator must ensure that the blinded evaluator at the site is not inadvertently unblinded when evaluating the subjects.
- The blinded evaluator at the site will not be present during treating investigator's evaluation of the subject or vice versa.
- The treating investigator and the blinded evaluator at the site will not discuss any details or guesses about the treatment assignment, potential touch-up or repeat-treatment, or results of assessments in individual subjects during the course of the investigation and until the final database lock. The same applies to any discussions between blinded evaluators at the site.
- The treating investigator will explain to each subject that they should not discuss, any side-effects or complaints, nor personal views on treatment success with the blinded evaluator at the site, in order to assure scientific rigor and unbiased results of the trial.
- Results of ratings will be documented on Rating Sheets by the blinded evaluator at the site (see section 6.4.12 for details).
- The blinded evaluator at the site will not have access to the subject´s source records during the course of the investigation and until the final database lock. If this will not be technically feasible, e.g., in case of electronic source records, the blinded evaluator will commit to abstain from accessing these records and will maintain the list of prohibited medical files to avoid accidental access
- The blinded evaluator at the site will not have access to the eCRF to keep the blinding towards the treatment assignment of the subject. Results of the ratings will be transferred into the eCRF by an

[C] Note: The **blinded evaluator at the site** is *not* blinded for treatment allocation during the repeat-treatment phase. However, he/she will be blinded for the treatment a subject received during the initial treatment phase until final database lock.

unblinded team member. However, the blinded evaluator at the site will have an emergency access to the eCRF/IWRS for emergency unblinding (also see below).

- The blinded evaluator at the site will not have access to the data of the interim analysis or the interim clinical investigation report (iCIR).
- The site staff will be trained by the CRA on the required procedures to maintain the blinding of the blinded evaluator at the site.

In the event that the treatment group allocation for a subject becomes known to blinded evaluator at the site, the sponsor must be notified immediately (i.e., within 24 hours).

Unblinding a subject's treatment group to the blinded evaluator at the site must be recorded in the subject's source record, in the eCRF indicating the date and will be considered a protocol deviation. The evaluability of such subjects will be discussed at the data review meeting (DRM).

Central independent blinded photographic reviewer and volumetric change measurement

A central independent blinded photographic reviewer (see section 6.4.13) and staff at the photo provider conducting the volume changes measurement (see section 6.4.12) will:

- be dislocated from the investigation sites
- will have no access to randomization schedule / eCRF or information on treatment assignment, and
- will not discuss any findings with the treating investigators and blinded evaluators at the sites during the investigation until after the final study database lock.

Emergency unblinding

There will be no special procedure for emergency unblinding because the treating investigator and other study staff will be aware of the treatment allocation. In case, only the blinded evaluator at the site is available in case of an emergency situation, and an unblinding is required, he/she **should** contact the Medical Monitor or the Sponsor first before accessing the subject´s medical records for unblinding.

The subjects will know that they have received a hyaluronic acid dermal filler with lidocaine, which is, sufficient level of information needed in case of emergency. However, the subjects will receive a participant card with 24/7 emergency telephone numbers.

Any cases of unblinding will be documented by the site staff.

6.1.4 *Discussion of clinical investigation design*

This clinical investigation is undertaken to evaluate the effectiveness, safety and long-term safety of saypha® VOLUME Lidocaine for the correction of moderate to severe midface volume deficit, and to demonstrate its non-inferiority to one of the devices approved for the same indication [redacted]. In addition, the duration of the global aesthetic improvement and subject´s satisfaction after implantation will be assessed.

The investigation is designed to minimize potential bias during collection of clinical observations and to allow for interpretation of results in the context of available treatment options.

Approximately 486 subjects will be randomized in this investigation (324 test device and 162 comparator device) in order to get a sufficient number of evaluable subjects per treatment group (437 in total). The sample size selection is justified in section 7.1. The method of randomization is used to minimize the bias arising from the assignment of subjects to treatment groups (see section 6.1.2).

The primary and several secondary and other effectiveness endpoints (see section 5.3) are based on the 5-grade MVDSS, a validated instrument for semi-quantitative assessment of volume deficit in the midface as assessed live by the blinded evaluator at the site.[33] Blinded outcome assessment by a blinded rater is a common practice to reduce bias arising from the expectations of individuals collecting data. The sites will make their best efforts to assign the same blinded evaluator for evaluation activity throughout the clinical investigation to maintain consistency of effectiveness evaluation (see section 6.4.12).

In view of multicenter conduct of the investigation, the validated MVDSS assessment will be also evaluated centrally, by experienced independent blinded photographic reviewers.[34] This will allow for unified assessment of treatment responses across the sites and checking if any bias was introduced by inter-observer variability between the sites.

The rater blinding regarding treatment group in initial treatment will remain in effect until study data base lock. The blinded evaluator at the site will be trained on the MVDSS and NLF-SRS prior to start of the investigation during the investigator meeting, a live WebEx with a sponsor medical consultant, or through review of a recording of the WebEx. Open questions by on-site located raters will be answered during the pre-study visits; further training on the scale will be also performed during site pre-study visits, if needed. The independent blinded photographic reviewers will be trained on the MVDSS prior to their assessments of the photographs.

In addition, the improvement of midface volume deficit will also be evaluated centrally by using computerized volume change measurement based on the 3D photographic images. The quantified data of the volume change measurement provide additional evidence confirming the effectiveness of the test device for the indication to be treated (see section 6.4.12).

The time point for definition of the primary endpoint (Week 24 after last injection of the initial treatment phase) was selected based on clinical experience with other HA fillers and will be corroborated by earlier and later observations (see Table 1 and Table 3 for details). Difference of one grade on this scale is considered to be clinically meaningful since it can be visually recognized by various observers as demonstrated during validation of the scale.

The clinical relevance of the investigation will be also supported by several (other) secondary effectiveness endpoints (see section 5.3), related to global aesthetic improvement (by using the modified GAIS) [35] and subject's satisfaction with outcome (overall and the cheeks by using FACE-Q™ scales).[36, 37]

Information on occurrence of pain will be primarily obtained by collection of AEs, with additional insight into pain intensity being obtained directly after the injection using a semi-quantitative 11-point Numeric Pain Rating Scale (NRPS).[38].

Touch-up treatments are allowed in the investigation, and the treating investigator will determine the appropriate injection volume and injection technique and equipment (i.e., needle/cannula) based on his/her clinical experience (see sections 6.2). A minimum of 100 subjects randomized to the test device will be treated with either needle or cannula. Use of either needle or cannula is based on the treating investigator´s medical decision.

Finally, it is well known that in routine clinical practice many patients choose for repeating treatments with HA dermal fillers to maintain the aesthetic improvement achieved with the first one.[39-41] A repeat-treatment at one of the later time points (earliest Week 48 after baseline treatment) has been therefore added, not only to improve subject retention in the investigation, but also to collect safety data after repeated administration of the test device. This actually allows the sponsor to determine if subjects previously treated with a different device behave differently with exposure to saypha® VOLUME Lidocaine.

Safety and long-term safety of saypha® VOLUME Lidocaine for the correction of moderate to severe midface volume deficit will be monitored by documentation of safety parameters (AEs, injection site reactions and device deficiencies; see section 6.4.19).

Overall, the proposed design for this investigation is considered ethically and scientifically justified.

6.2 Handling and Administration of the medical devices

A description of both devices is given in section 2.

6.2.1 *Packaging, labelling and storage*

Labelling and traceability of the devices

The study labels will comply with appropriate information as mandated by applicable guidelines and national regulatory requirements, as appropriate.

Label text will be available into local languages and a copy will be filed in the TMF.

Study labels will include the batch number (lot number) and a kit number. Both devices are identified and tracked by those batch numbers. To ensure the traceability of each device, the batch numbers must be documented in the source medical record of the subject treated with the device.

Table 14. *Storage and packaging of the devices.*

	Saypha® VOLUME Lidocaine	[redacted]
Packaging	Per carton box (= one kit) • One prefilled syringe of 1.0 mL filler solution • two 27G ½" disposable sterile needles	Per carton box (= one kit) • Two prefilled syringes of 1.0 mL filler solution, each • four 27G ½" disposable sterile needles **Note:** The volume in each syringe is as stated on the syringe label and on the carton.
Optional / additional injection equipment	[redacted] 25G 1½" cannula	[redacted] 25G 1½" cannula
	Note: Cannulas will be provided by the sponsor´s representative.	
Batch number	Batch number will be on the study label	Batch number will be on the study label
Kit number	Kit number will be on the study label.	Kit number will be on the study label
Storage	Store at + 2 to + 25 °C/ +36 to +77 °F in a dry place in the original box and protected from light, heat and frost. Finished sterilized saypha® VOLUME Lidocaine product has a shelf life of 36 months at 2 to 25°C.	Store at room temperature (up to 25°C/77°F). DO NOT FREEZE. [redacted] injectable gel must be used prior to the expiration date printed on the label.
Note: The safety and effectiveness of cannula injection of [redacted] has only been clinically evaluated with the [redacted] 25G 1½" cannulas **Note:** [redacted] may be injected with a 25G 1" needle according to the IFU. However, use of needles other than 27G ½" is **not allowed** within this clinical investigation.		

6.2.2 *Administration (test and comparator devices)*

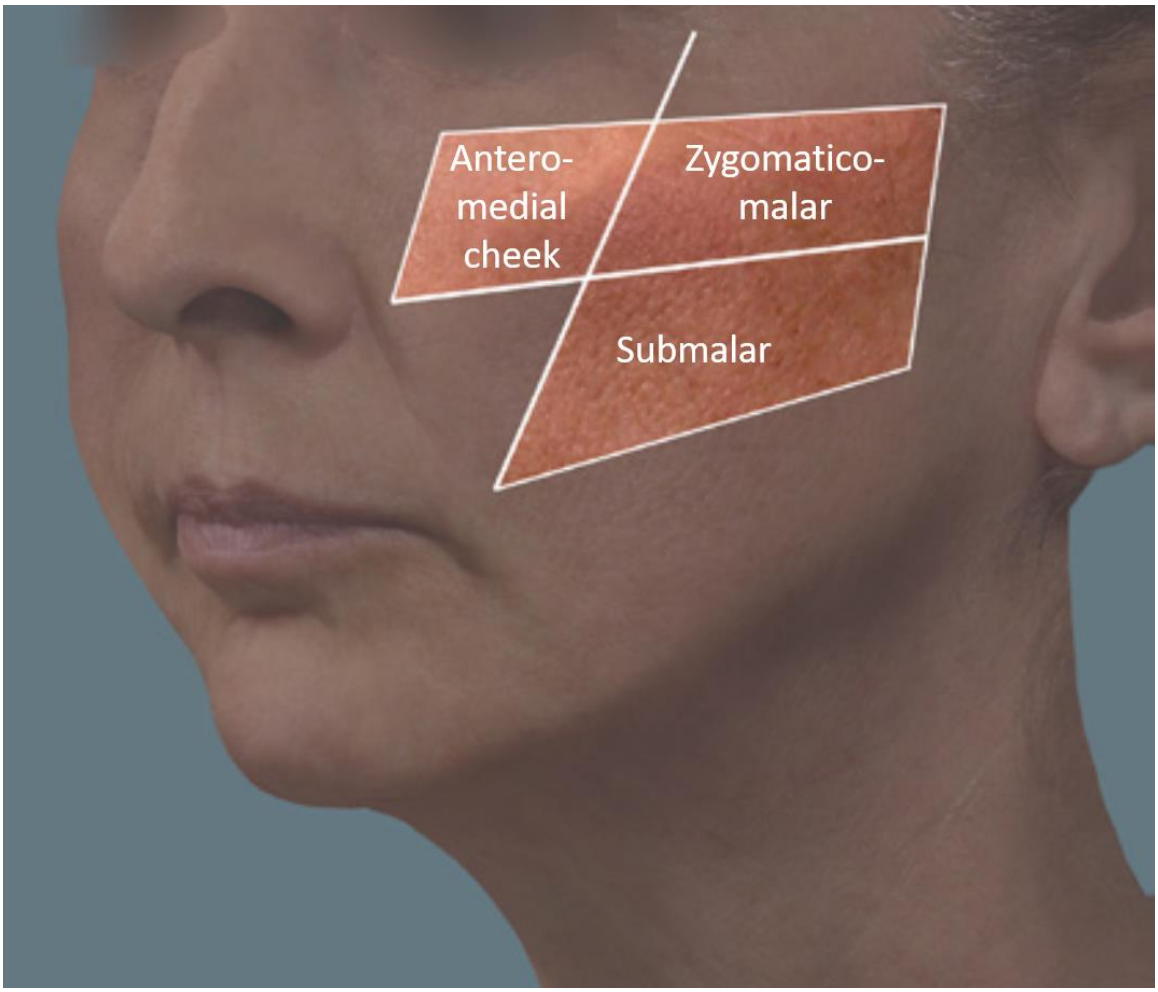
Anatomic areas of midface treatment

The anatomic areas of midface treatment are defined as follows:

- Anteromedial cheek (left and right)
- Submalar (left and right)
- Zygomaticomalar (left and right)

A visual depiction of the anatomic areas of midface treatment is given in Figure 3.

Figure 3. *Anatomic areas treated.*



Treatment occasions

Each subject may be treated on up to four occasions:

- **Baseline treatment** will be administered at Visit 2 (Day 0). Each eligible subject (see section 6.3.3) will receive either saypha® VOLUME Lidocaine or [redacted] into the midface region, according to the randomization scheme (see section 6.1.2).
- **Touch-up treatment after baseline treatment (optional)** may be administered at Visit 3 (2 weeks after baseline treatment)
- **Repeat-treatment (optional)** will be administered once during the clinical investigation, at Visit RT1, in eligible subjects (see section 6.3.5) using the saypha® VOLUME Lidocaine only even if the subject was treated with the comparator device before.
- **Touch-up treatment after repeat-treatment (optional)** may be administered at Visit RT2 (2 weeks after repeat-treatment)

In general, a touch-up treatment may be administered if an optimal aesthetic correction has not been achieved after baseline and / or repeat-treatment in the discretion of the treating investigator and if none of the exclusion criteria are met (see section 6.3.5).

The touch-up treatment may be performed on one or both sides of the midface. In any case, it must be performed using the same device (either test device or comparator device) which was initially applied to the subject.

Injection technique and injection equipment

Table 15 describes the injection techniques and injection equipment to be used in the investigation.

Table 15. *Description of injection technique and injection equipment used in the investigation*

Injection technique	**saypha® VOLUME Lidocaine** [46]	[redacted] **[also see IFU]** [14]
	For each treatment, the injection technique used will be selected by the treating investigator. The technique used is essential for the success of the treatment. The following injection techniques should be employed based on investigator's preference and characteristics of the defect under correction.	
	• Every injection technique may be selected within this clinical investigation	• Tunneling, fanning, crosshatching, and ferning techniques may be used with needle or cannula • Serial puncture may be used with a needle. Injection may be administered in an antegrade or retrograde fashion. • The injection technique for regard to the angle and orientation of the bevel, the depth (subcutaneous and/or submuscular/ supraperiosteal) of injection, and the quantity administered may vary depending on the area being treated. Injection of the filler too superficially (intradermally), or in large volumes over a small area, may result in visible and persistent lumps and/or discoloration.
Injection equipment	Either needle or cannula will be used (see below) in the discretion of the treating investigator. A minimum of 100 subjects randomized to the test device will be treated with either needle or cannula.	
	• 27G ½'' needle (provided with the syringe) • 25G 1 ½'' cannula [redacted] provided separately)	• 27G ½" needle (provided with the syringe) • 25G 1½" cannula [redacted] provided separately)

Administration of saypha® VOLUME Lidocaine and [redacted]

Table 16 gives detailed instructions how to administer the test device and the comparator device.

Table 16. *Administration of saypha® VOLUME Lidocaine and* [redacted]

Step	**saypha® VOLUME Lidocaine [also see current version of IB]**	[redacted] **[also see IFU]** [14]
Prior to administration	• The device must be injected into non-inflamed, disinfected, healthy skin • After ensuring that the subject has thoroughly washed the treatment area with soap and water, the area should be prepped with alcohol or another antiseptic. **Note:** IB for saypha® VOLUME Lidocaine (section 8.1.5 therein) and IFU for [redacted] [14] (section B. Health Care Professional Instructions #5) read that topical anaesthetic patch or cream or injectable anesthesia may be used to manage pain during and after injection. However, **injectable** anaesthesia is not allowed to manage pain during and after injection. Whenever possible (i.e., if the subject agrees) additional **topical** anaesthetic (patch or cream) should be avoided in this investigation to not falsify the pain assessment (as collected via Numerical Pain Rating Scale; see section 6.4.14). In case additional local anesthesia is used, this has to be documented as concomitant treatment in the subject's records and the eCRF.	
Preparation for administration	Instructions incl. visual illustration how to attach needle / cannula to the syringe is given in section 20.3.	Instructions incl. visual illustration how to attach needle / cannula is given in section 20.4 and in the IFU [14] **Note:** Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the [redacted] and needle hub connection. In such case follow instructions given in section 14.9.
Administration	The following applies to saypha® VOLUME Lidocaine and [redacted] (according to IFU of [redacted] [14]) • If the needle/cannula is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle/cannula • When using a cannula, an entry point is made in the skin, e.g., with a sharp needle of appropriate size • 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. • After the first small amount of material has been injected into the patient, wait a full 3 seconds to allow the lidocaine to take effect before proceeding with the rest of the injection. • Distribute in small aliquots (small boluses of 0.1 mL to 0.2 mL) over a large area to reduce the risk of persistent lumpiness. • With submuscular/supraperiosteal injection, the number of times the needle passes through the muscle should be minimized to reduce the risk of bruising. It is important to stop injecting before the needle tip reaches the level of the deep dermis to prevent material from being placed too superficially in the skin.	

Table 16. *Administration of saypha® VOLUME Lidocaine and* [redacted]

Step	**saypha® VOLUME Lidocaine [also see current version of IB]**	[redacted] **[also see IFU]** [14]
	• Correct to 100% of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.	
	• 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 the guidelines, which include hyaluronidase injection as given in section 6.2.5. Also see sections 6.3.6, 14.5.4 and 16.1. • The maximum volume to be applied per treatment and the overall investigation is given in section 6.2.3.	
Completion of administration	• After the injection, doctors may apply a light massage in order to distribute the product uniformly.	• The area of lost facial volume should be lifted by the end of the injection. When injection is completed, the treated site may be gently massaged to mold the product to the contour of the surrounding tissue and assure that it is evenly distributed and conforms to the contour of the surrounding tissues. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.
After administration	• After use, treatment syringes and needles may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements (please also see sections 6.2.6 and 6.2.7). • Pain intensity will be assessed immediately after injection, and at 15 min-intervals for 60 min post-treatment by using the NPRS (see section 6.4.14 for details). • In order to identify potential AEs (especially, to detect blanching caused by arterial occlusions) post-administration of device (baseline treatment, touch-up treatment and repeat-treatment) a safety evaluation 15 minutes after the administration needs to take place (see section 6.4.19). • Should any of the vision assessments (Snellen visual acuity, confrontational visual test field, or ocular motility – see section 6.4.76.4.8) suddenly worsen after the injection of the device, the treating investigator must examine the subject to exclude vascular injection and contact an eye specialist, if necessary. • A basic neurological examination (F.A.S.T) will be performed for all subjects who show signs of ophthalmic complications due to filler injection (see section 6.4.9). • Prior to discharge the subject should be advised to follow restrictions specified in section 6.3.8 and to inform their investigator as soon as possible about any unwanted event. • Details for each treatment will be documented in the subject's records and the eCRF with the same level of details (see section 6.4.10).	

6.2.3 *Applied volume of the devices*

The volume administered is at the discretion of the treating investigator and depends on the severity of the midface volume deficit to be corrected.

However, the maximum volume (left and right side of the midface together) must not 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.

A maximum of 6.0 mL on one side of the midface is allowed total per treatment phase (i.e., a maximum of 4.0 mL on the other side).

Table 17 gives an overview of the average volume of the devices administered in the clinical investigation.

Table 17. *Volume of the devices administered in the clinical investigation per treatment and overall*

Treatment Session	**saypha® VOLUME Lidocaine**	[redacted]
Initial treatment phase **per subject** (baseline treatment plus touch-up treatment)	Total volume must not exceed **10 mL** per 60 kg (130 lbs) body mass **in total** (baseline plus touch-up treatment; left and right side of the midface together)	Total volume must not exceed **10 mL** per 60 kg (130 lbs) body mass **in total** (baseline plus touch-up treatment; left and right side of the midface together)
Repeat-treatment phase **per subject** (repeat-treatment plus touch-up treatment)	Total volume must not exceed **10 mL** per 60 kg (130 lbs) body mass **in total** (repeat-treatment plus touch-up treatment; left and right side of the midface together)	Total volume must not exceed **10 mL** per 60 kg (130 lbs) body mass **in total** (repeat-treatment plus touch-up treatment; left and right side of the midface together)
Total volume per subject during the entire study	Total volume must not exceed **20 mL** per 60 kg (130 lbs) body mass in total	Total volume must not exceed **20 mL** per 60 kg (130 lbs) body mass in total
Note 1: 'Year' means rolling 365 days, starting with study start / baseline injection. **Note 2:** Based on preclinical studies and a toxicological risk assessment, subjects should be limited to 20 mL of [redacted] per 60 kg (130 lbs) body mass **per year**. The safety of injecting greater amounts has not been **established.** [14] **However, for this investigation, the above given limit must be followed for both devices.**		

After each administration, the actual volume of the device injected will be recorded in the subject´s source records and in the eCRF (also see section 6.4.10).

6.2.4 *Precautions and warnings for the investigator*

Only precautions and warnings that require a study-specific action during the investigation are listed below. For the complete list of precautions and warnings please refer to current IB [46] (section 8.1.5) for saypha® VOLUME Lidocaine and to the respective IFU of the comparator device.[14]

Each treating investigator has to familiarize himself / herself with the CIP and the detailed precautions and warnings in the above-mentioned documents.

6.2.4.1 saypha® VOLUME Lidocaine

Precautions and Warnings

- According to the IB (section 8.1.5), sensitive skin may be pre-treated using a local anesthetic patch or cream (also see section 6.2.2).

  Note: Whenever possible (i.e., if the subject agrees) additional topical anesthetic (patch or cream) should be avoided in this investigation to not falsify the pain assessment (see section 6.4.14). In case additional local anesthesia is used, this has to be documented as concomitant treatment in the subject's records and the eCRF.

- The device must not be used if the expiry date has lapsed, or if the integrity of the syringe cannot be verified, of if packaging or contents are damaged (open or shifted tip cap or in an opened or damaged blister, syringe is not stored in its originally sealed blister, needle with a damaged container). In such case follow instructions given in section 14.9.
- The device should only be used with the needles / cannulas and syringe provided by the manufacturer / sponsor´s representative (also see section 2.1 and section 6.4.19).
- Do not inject into blood vessels, bones, tendons, ligaments, nerves or muscles. Do not inject the device into naevi. In such cases, subjects should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur. Also see section 6.2.5 and section 14 for documentation and reporting obligations for AEs. Also see sections 6.3.6, 14.5.4 and 16.1.
- Subjects should be advised not to apply make-up for twelve hours after injection and to avoid prolonged exposure to sunlight and UV; also subjects should not use saunas or Turkish baths for one Week after the injection (also see section 6.3.8).
- Subjects should be advised not to massage the treatment site for a few days following the injection, to avoid the possible risk of product mobility (also see section 6.3.8).
- The device should never be placed in contact with quaternary ammonium compounds (such as benzalkonium chloride solutions) or with medical-surgical instruments that have been in contact with these substances (also see section 4.3).

6.2.4.2 [redacted]

Warnings

- The product must not be injected into blood vessels. Introduction of [redacted] 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.

  Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a subject exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure (see section 6.4.8 for information on visual examinations to be performed).

  Subjects should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur. Also see section 6.2.5 and section 14 for documentation and reporting obligations for AEs. Also see sections 6.3.6, 14.5.4 and 16.1.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled. The treating investigator must document subject´s temporary discontinuation and the reason in the subject's source records and on the electronic Case Report Form (eCRF).
- Treatment site reactions consist mainly of short-term inflammatory symptoms and generally resolve within 2 to 4 weeks (also see section 4.2.2).

Precautions

- [redacted] is packaged for single-patient use. Do not resterilize. Do not use if package is open or damaged. In such case follow instructions given in section 14.9.
- [redacted] injectable gel is a clear, colorless gel without particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe. In such case follow instructions given in section 14.9.
- [redacted] is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product. In such case follow instructions given in section 14.9.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety has been established for use in patients between 35 and 65 years of age for cheek augmentation. However, the filler is indicated for cheek augmentation to correct age related volume deficit in the midface in adults over the age of 21 (see InC#1 in section 6.3.3.1).
- Subjects may experience late onset nodules with use of dermal fillers, including [redacted] (see section 14 for documentation and reporting obligations for AEs).
- Subjects who experience skin injury near the site of [redacted] implantation may be at a higher risk for adverse events (see section 14 for documentation and reporting obligations for AEs).
- The safety of [redacted] with cannula for cheek augmentation has not been established in subjects with Fitzpatrick Skin Types V and VI. However, for this study, inclusion of subjects with Fitzpatrick Skin Types IV to VI is encouraged (see section 6.6).

6.2.5 *Rescue medication and emergency plan*

In case of any expected adverse event associated with the study treatment (e.g., vascular occlusion), the Expert Consensus Recommendations for treatment of Soft Tissue Filler Complications [42] or the ASDS guidelines of care: injectable fillers [43] should be followed in the discretion of the investigator. Both references are filed in the Investigator Site File.

The investigation sites will be required to have an emergency plan in place and a minimum medication readily available in case a suspected vascular occlusion or allergic reaction occurs. CRAs will control, if such an emergency plan is in place and the medication is available.

Any rescue medication / procedure applied should be documented in the subject´s source record and in the eCRF as concomitant treatment (see section 6.4.5).

6.2.6 *Device accountability*

Both devices (saypha® VOLUME Lidocaine and [redacted]) must not be used outside the context of this clinical investigation plan (CIP).

The devices must be handled in accordance with the sponsor's instructions (see section 6.2.1 to 6.2.4) and the current version of the IB of the test device [46] and the IFU of the comparator device [14], respectively.

Documentation of receipt, dispensing/use in individual subjects, and return of device must be maintained by the investigator or his/her designee. Appropriate forms will be provided by the sponsor or their representative to facilitate device accountability.

At the end of the investigation, all remaining clinical investigation material should be destroyed on site, following the site-specific destruction procedure after a monitor has verified all accountability documentation. If the site does not have an appropriate destruction process, the material must be returned to the sponsor designee.

Empty or used syringes will not be returned to the sponsor, but will be destroyed by the investigation site, in line with their routine procedure for medical waste disposal. Used needles/cannulas should be disposed immediately after the use as per routine procedure for medical waste disposal at the site.

According to the underlying monitoring plan (see also section 6.7) the monitor will regularly check study documentation and inventory of devices held by the investigator to verify accountability of all devices used.

6.2.7 *Handling of deficient devices*

Any device alleged to be deficient must not be used by the investigator and must be returned to the sponsor´s designee. In case of device deficiencies also instructions in section 14.9 must be followed.

6.3 Subjects

6.3.1 *Number of subjects and duration of the clinical investigation*

Up to 486 subjects are planned to be randomized in a 2:1 ratio (test device: 324, comparator device: 162) and treated. Approximately 516 subjects will need to be screened to reach 486 subjects randomized (accounting for a screening failure rate of approx. 6%) and to ensure that 437 subjects will be evaluable for the primary endpoint. Approximately 300 subjects are estimated to qualify for repeat treatment.

Inclusion of subjects is planned to be as equally distributed as possible between the sites. The clinical investigation is planned to be conducted at approximately 16 study sites with enrolment target of approximately 20 to 30 subjects per site. The maximum expected number of subjects to be enrolled per each site will be 45 but may be higher if agreed with the Sponsor.

Each subject will take part in the investigation for up to 92 weeks.

The total anticipated duration of the investigation, from the first-subject-first visit to the last-subject-last-visit, is around 114 weeks, based on expected recruitment period of about 22 weeks.

6.3.2 *Recruitment strategy*

Subjects will be recruited by sites located in the USA (a list of the sites, including names, addresses and positions of the corresponding Principal Investigators, is kept separately from the CIP).

The investigator may also offer participation in the study to potential candidates identified in their subject database. The investigation may be advertised as requested by the sites. In such case, the advertising strategy and materials will be submitted to the Institutional Review Board (IRB) / Ethics Committee (EC)for prior review and approval.

Every effort will be made to include individuals with all Fitzpatrick skin types (FST, see section 6.4.2 for details) in a proportional pattern adequately include patients of diverse skin colcor and background in this study.

The FST enrollment levels planned to be achieved are as follows:

- **FST I to III:** approximately 80% of subjects
- **FST IV to VI:** at least 20% of subjects
- **FST V and VI:** approximately 10% of subjects

These FST enrollment levels will not be seen in each investigation site, i.e., there will be over-representation at some sites and underrepresentation at other sites. However, enrollment of the different FST levels will be monitored during the enrollment period via the eCRF system (report) by the project management team at the CRO. Details how to monitor enrollment levels via the eCRF system will be described in the project management plan.

6.3.3 *Eligibility criteria – Baseline treatment*

6.3.3.1 Inclusion criteria

A subject must meet **ALL** of the following criteria to be **ELIGIBLE** for the study:

1. Male or female subjects aged 22 – 75 years (inclusive) of age at Screening
2. Subjects with bilateral, approximately symmetric moderate to severe midface volume deficit (severity scores of 2 or 3 on the 5-point Midface Volume Deficit Severity Scale), as assessed by the blinded evaluator at the site
3. Females of childbearing potential[D] must have a negative urine pregnancy test and must agree to use an effective[E] 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).
4. Healthy skin in the midface area and free of diseases that could interfere in cutaneous aging evaluation
5. 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)
6. 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

6.3.3.2 Exclusion criteria

A subject who meets **ANY** of the following criteria is **NOT** eligible for the study and must not be enrolled:

1. Females, who are pregnant and/or, lactating or planning to become pregnant during the clinical investigation
2. History of severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies
3. History of hypersensitivity to hyaluronic acid preparations, lidocaine or any amide-based anesthetic
4. Tendency to keloid formation and/or hypertrophic scars and/ or have pigment disorders
5. Known human immune deficiency virus-positive individuals
6. Presence of infectious, inflammatory or proliferative cancerous or pre-cancerous lesions in the treatment area
7. Re-current (three times a year over the last year) herpes simplex in the treatment area
8. History or presence of any autoimmune or connective tissue disease, or current treatment with immuno-modulating therapy
9. Uncontrolled (or unstable) Diabetes mellitus or systemic diseases as per investigator discretion

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[D] A woman is considered to be of childbearing potential (WOCBP) if fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[E] Effective methods of birth control include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion), vasectomized partner (provided that is the sole sexual partner of the subject and that the vasectomized partner has received medical assessment of the surgical success) and sexual abstinence (if in line with the preferred and usual lifestyle of the subject and defined as refraining from heterosexual intercourse during the entire period of the trial).

10. 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
11. Implantation of dermal fillers in the treatment area within the preceding 24 months prior to Visit 1 (Screening) and during the entire investigation
12. 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
13. Facial lipolysis, including submental fat treatments, within the previous 12 months prior to Visit 1 (Screening) and during the entire investigation
14. Bariatric surgery within 12 months prior to Visit 1 (Screening) and during the entire investigation
15. 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., [redacted]) 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)
16. 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)
17. Beard longer than three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator
18. 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.
19. 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)
20. Any medical condition prohibiting the inclusion in the study according to the judgment of the treating investigator
21. Previous enrollment in this clinical investigation
22. 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
23. Midface volume deficit due to a congenital defect, trauma, or abnormalities in facial adipose tissue distribution such as those associated with HIV related lipodystrophy
24. 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
25. 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).
26. 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.

6.3.4 *Eligibility criteria – Touch-up treatments (TUP1 and TUP2)*

6.3.4.1 Inclusion Criteria

A subject must meet **ALL** of the following criteria to be **ELIGIBLE** for each **touch-up-treatment**:

1. Females of childbearing potential must have a negative urine pregnancy test

6.3.4.2 Exclusion criteria

A subject who meets **ANY** of the following criteria is **NOT** eligible for each **touch-up treatment**:

1. Occurrence of a related Serious Adverse Event or Adverse Event of Special Interest (i.e., embolic events, with possible, probable, or causal relationship to an intravascular injection of the device, as changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke, skin necrosis, or impending necrosis) during or after the previous injections
2. Subjects who experienced visual changes considered abnormal clinically significant or other serious medical conditions during or after the previous injections
3. Subjects who have one of the following assessments during the visual examinations: Snellen acuity test worse than 20/40 (with corrective eyewear, if applicable), abnormal confrontational visual field test, or abnormal ocular motility test.

6.3.5 *Eligibility criteria – Repeat-treatment (with saypha® VOLUME Lidocaine only)*

The eligibility criteria given in section 6.3.5.1 and section 6.3.5.2 must be assessed for repeat-treatment.

6.3.5.1 Inclusion criteria

A subject must meet **ALL** of the following criteria to be **ELIGIBLE** for **repeat-treatment**:

1. 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. The subject does not have to return to his baseline severity to be permitted to receive a repeat-treatment.
2. Subject has completed initial treatment phase up to Visit 9 (SV1) and is willing to attend the study visits of the screening phase for repeat-treatment and repeat-treatment phase
3. Females of childbearing potential must have a negative urine pregnancy test
4. Healthy skin in the midface area and free of diseases that could interfere in cutaneous aging evaluation

6.3.5.2 Exclusion criteria

Subjects who meet **ANY** of the following criteria are **NOT** eligible for **repeat-treatment:**

1. Occurrence of a related Serious Adverse Event or Adverse Event of Special Interest (i.e., embolic events with possible, probable, or causal relationship to an intravascular injection of the device, as changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke, skin necrosis, or impending necrosis) during or after the baseline injection and/or touch-up injections
2. Occurrence of a related Adverse Event that occurred during the initial treatment phase, and is ongoing at the time of the repeat treatment (i.e., relationship is classified as “possible”, “probable” or “causal relationship”; outcome is “not recovered / resolved”, “recovering / resolving”, “recovered / resolved with sequelae” or “unknown”)
3. Subjects who experienced visual changes considered abnormal clinically significant or other serious medical conditions during or after the baseline or touch-up injections, respectively

4. Subjects who have one of the following assessments during the visual examinations: Snellen acuity test worse than 20/40 (with corrective eyewear, if applicable), abnormal confrontational visual field test, or abnormal ocular motility test
5. Subjects who became pregnant since start of the study or planning to become pregnant during the clinical investigation
6. Known human immune deficiency virus-positive individuals
7. Presence of infectious, inflammatory or proliferative cancerous or pre-cancerous lesions in the treatment area
8. Development of re-current (three times a year over the last year) herpes simplex in the treatment area since study start
9. Development of any autoimmune or connective tissue disease since study start, or current treatment with immuno-modulating therapy
10. Development of uncontrolled (or unstable) diabetes mellitus or systemic diseases since study start as per investigator discretion
11. Facial plastic surgery, tissue augmentation with silicone, fat or another non-absorbable substance (permanent fillers) and semi-permanent fillers (e.g., *poly*-L-*lactic* acid) in the area of device application and during the initial treatment phase of the investigation
12. Implantation of dermal fillers (other than the test and comparator device used in the investigation) in the treatment area during the initial treatment phase of the investigation
13. 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), or chemical peeling during the initial treatment phase of the investigation or is planning to undergo such procedures during the repeat-treatment phase of the investigation
14. Facial lipolysis, including submental fat treatments during the initial treatment phase of the investigation
15. Bariatric surgery during the initial treatment phase of the investigation
16. Development of bleeding disorder and/or use of anticoagulant, antiplatelet, thrombolytic medication, or anti-inflammatory drugs (oral/injectable corticosteroids or non-steroidal anti-inflammatory drugs, e.g., [redacted]) 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 (repeat-treatment and touch-up treatment)
17. Planned dental/oral surgery or modification (bridge-work, implants) within four weeks prior to the injection and to a minimum of four weeks post injection
18. Beard longer than three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator
19. Any medical condition prohibiting the inclusion for repeat-treatment according to the judgement of the treating investigator
20. Previous enrollment in initial treatment phase of this clinical investigation and early termination, or significant incompliance with the protocol requirements
21. Current or previous treatment with another investigational drug and/or medical device or participation in another clinical study
22. Midface volume deficit due to a trauma, or abnormalities in facial adipose tissue distribution such as those associated with HIV related lipodystrophy
23. Subjects who experienced weight change for a minimum of 10% since study start or subjects who have the intention to change eating habits that result in a weight gain or loss >10% during the entire investigation
24. 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 RT1

6.3.6 *Withdrawal criteria and procedures*

The subject **MUST** be withdrawn from the investigation for any of the following reasons:

1. Withdrawal of consent: At any time during the investigation and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

The subject **MAY** be withdrawn from the investigation for any of the following reasons:

1. Occurrence of an AE which requires a premature termination of the treatment or precludes follow-up of the subject (e.g., COVID-19)
2. A major CIP deviation, which may interfere with evaluation of the treatment outcome (e.g., additional aesthetic correction of the defect during the course of the investigation, use of prohibited medication, or similar)
3. Investigator's decision, triggered by safety, behavioural or administrative reasons
4. Pregnancy; **Note:** pregnant women **must** be withdrawn from **further treatment**; However, pregnant women may remain in the study for safety assessments during the scheduled study visits.
5. Subjects with abnormal clinically significant changes in visual examination after treatment **must** be withdrawn from **further treatment** in case an eye specialist confirms that the result is related to a vascular injection of the dermal filler (see section 6.4.8 and section 16.1).

   The subjects may remain in the study at least for safety assessments during the scheduled study visits.
6. Subjects who experience neurological symptoms indicative of a vaso-occlusional event after treatment **must** be withdrawn from **further treatment** in case a neurologist confirms that the result is related to a vascular injection of the dermal filler (see section 6.4.9, also see section 16.1).

   The subjects may remain in the study at least for safety assessments during the scheduled study visits.

Reasons, circumstances and findings related to early withdrawal should be fully described in the subject's source records and the eCRF respecting the subject's rights.

Attempts should be made to perform an early termination visit, which should consist of the assessments planned for Visit 9 (SV1), Visit SV2 to SV4 or Visit RT5 (depending on the study phase) – also see section 6.5.16. In the event that the withdrawal is caused by an AE, the procedures stated in section 14 must be followed.

Efforts should be made, however, to get in touch with subjects who did not attend a scheduled visit and clarify the reason for default. The two attempts with also sending a registered letter to subject must be made and documented to try and make contact. If the subject is unreachable, a corresponding note should be provided in the subject´s source record.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "withdrawal" (see section 6.3.11).

6.3.7 *Replacement of subjects*

Subjects withdrawn from the investigation or lost for follow-up will not be replaced.

No re-screening is allowed. An exception may be granted with prior approval of the sponsor in case that subjects are withdrawn due to restrictions that might occur in the context of the ongoing COVID-19 pandemic (e.g., in case conduction of the clinical investigation in a protocol-conformal manner is no longer possible due to a new pandemic situation comparable to the COVID-19 pandemic in spring 2020).

6.3.8 *Life-style and other restrictions*

Contraception

Women of childbearing potential participating should not be pregnant and should use effective contraception methods throughout the clinical investigation or avoid unprotected sexual intercourse. Any pregnancy occurring in study subjects should be reported and followed-up as described in section 14.

Note 1: A woman is considered to be of childbearing potential (WOCBP) if fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Note 2: Effective methods of birth control include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (provided that is the sole sexual partner of the subject and that the vasectomized partner has received medical assessment of the surgical success and sexual abstinence (if in line with the preferred and usual lifestyle of the subject and defined as refraining from heterosexual intercourse during the entire period of the trial).

Male subjects should use an effective contraceptive method as a reproductive damage on the seminal fluid cannot be ruled out. Male fertile participants need to ensure safe contraception to prevent their female partner of childbearing potential from becoming pregnant. Contraceptive methods include surgical sterilization or a physical barrier such as a condom when having penile-vaginal intercourse. This applies from throughout the clinical investigation. Males will be counseled to inform their female partner about the participation in the clinical investigation.

Other restrictions

The following restrictions apply to all subjects:

- Make-up should not be applied for 12 hours after each device injection
- Within the first 24 hours after each device injection, subjects 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 treatment sites.

  Note: If the treated area is swollen, an ice pack may be applied to the site for a short period.
- Prolonged exposure to sunlight or ultraviolet (UV) radiation must be avoided for one week after each device injection.
- To minimize the risk of product mobility, the subject should be advised to avoid massaging the treatment site or applying pressure to this area for one week following each device injection (exception: a light massage may be applied after injection of the device for uniform distribution of the filler by the investigator – see Table 15 in section 6.2.2)
- Use of saunas or Turkish baths is prohibited for one week after each device injection.
- Beard longer than three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator (see ExC#17 in see section 6.3.3 and ExC#18 in section 6.3.5)

6.3.9 *Prohibited treatments*

The following medications and treatments are **prohibited prior to start** of the investigation (Visit 1) and **during the entire investigation**, if not stated otherwise below (also refer to the respective ExC in section 6.3.3 to 6.3.5):

- History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy
- Previous facial plastic surgery, tissue augmentation with silicone, fat or another non-absorbable substance (permanent fillers) 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 and during the entire investigation
  - chemical peeling within the last three months prior to Visit 1 and during the entire

investigation,

or is planning to undergo such procedures during the 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
- Anticoagulant, antiplatelet, or thrombolytic drugs, or 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- until seven days after **each** injection of the device
- Planned dental/oral surgery or modification (bridge-work, implants) within four weeks prior to baseline and repeat-treatment device injection and to a minimum of four weeks post device injections
- Current or previous treatment with another investigational drug and/or medical device or participation in another clinical study (within 30 days of Visit 1 (Screening) and entire investigation)
- Change in eating habits that result in a weight gain or loss >10% during the entire investigation
- According to IB (section 8.1.5) and IFU for [redacted] [14] (section B. Health Care Professional Instructions #5) sensitive skin may be pre-treated using a local anaesthetic patch or cream or injectable anesthesia. However, **injectable** anaesthesia is **not allowed** to manage pain during and after injection in this investigation. Additional **topical** anaesthetic (patch or cream) is allowed but should be avoided possible (i.e., if the subject agrees) to not falsify the pain assessment (as collected via Numerical Pain Rating Scale; see section 6.4.14).

6.3.10 *Medical care upon termination of the clinical investigation*

The study participants will not receive any study-specific treatment after their final study visit. Any further treatment, if needed, will be proposed to the subject by the investigator at their discretion.

6.3.11 *Screening failures, withdrawals, and completer*

Initial treatment phase

- Subjects who have signed the ICF but are not randomized and are not treated for any reason will be considered as screening failures. Data for screening failures will be documented in appropriate forms (e.g., Subject Screening/Enrollment Log). Screening data for these subjects will be kept in the Investigator's File. The type of data to be entered in the eCRF, if any, will be defined in the eCRF Completion Guidelines.
- Subjects who prematurely discontinue the investigation after receiving at least one dose of the device and who are not screening failures will be defined as withdrawals / dropouts.
- Subjects who complete the initial treatment phase (incl. Visit 9 (SV1)) but do not participate in the optional repeat-treatment phase are defined as completer (initial treatment phase).

Optional repeat-treatment phase including screening phase for repeat-treatment

- Subjects who enter the screening phase for optional repeat-treatment and
    - who are not eligible for the repeat-treatment phase and who are not treated for any reason during repeat-treatment phase will be considered as screening failures for repeat-treatment (SV1, SV2, SV3, SV4, RT1)
    - who are eligible but do not participate in the optional repeat-treatment phase will be considered as completer (initial treatment phase)
- Subjects who prematurely discontinue the investigation after receiving at least one dose of the device at Visit RT1 will be defined as withdrawals / dropouts.

- Subjects who complete the repeat-treatment phase (incl. Visit RT 5) are defined as completer (repeat-treatment phase).

6.3.12 *Subject identification, privacy and confidentiality*

Subjects' privacy and data confidentiality will be protected in line with the principles of Good Clinical Practice (GCP), the European General Data Protection Directive (GDPR), Health Insurance Portability and Accountability Act (HIPAA) and other applicable international and national requirements. Personal subject data transferred to CROMA-PHARMA GmbH in Austria should be in compliance with the European GDPR. Subjects will provide authorization for use of their personal data in accordance with the applicable regulations regarding privacy and data protection.

A unique numerical subject identification code will be assigned to each subject at screening. The format of the codes will be defined in the CRF Completion Guidelines. The investigator will assign the codes in ascending order, in line with the order of the informed consent date and time.

The investigator must ensure that anonymity of the subjects will be maintained and that their identities are protected from unauthorized parties.

In the eCRF or any other document submitted to the sponsor or sponsor's representative, subjects must be identified only by their identification codes; use of names, initials, complete birthdates, addresses, telephone numbers, electronic addresses or similar information is prohibited.

The investigator will keep the Subject Identification Log (including complete name, date of birth, and contact details of each subject). The investigator must maintain these documents in strict confidence.

For GCP compliance, all subjects will be informed and consented regarding the access to their personal investigation-related data by the monitors, auditors and inspectors of the clinical investigation, as well as transmission of their coded data to the sponsor or sponsor's representative and data retention for the duration defined in section 8.4. Professionals with access to subjects' data for monitoring, audits and inspections are bound to preserve strict confidentiality.

This CIP, other investigation-related documentation, collected data and all other information generated will be held in strict confidence. No information concerning the clinical investigation, nor the data collected will be released to any unauthorized third party without prior written approval of the sponsor.

Clinical photography

Besides *live* assessments by the blinded evaluator at the site, midface volume deficit will additionally be assessed by a central independent blinded photographic reviewer using photographs (see section 6.4.13). In addition, the photographs will be used for volumetric change measurement (see section 6.4.12) and modified GAIS assessment by the blinded evaluator at the site and subject (see section 6.4.16).

All photographs are submitted to the photo provider in a non-masked manner. During the study, all photographs will be stored in the data base of the photo provider in a non-masked and a masked version, respectively, to allow for review and assessments as required. Image masking will occur during the monitoring process and a 100% quality check will be completed by the photo provider to ensure all images are de-identified before they are forwarded to the sponsor. Details will be given in a separate manual.

Photographs used for publication purposes will *not* reveal the subject´s identity. For this purpose, subject's eyes will either not appear on the photographs or will be masked with e.g., a black bar; other attributes visible on the photographs that could identify a subject (e.g., characteristic scars, tattoos).

Subjects will be explicitly informed about these matters when obtaining written informed consent.

6.4 Assessments and procedures

Assessments and procedures that will be performed during the investigation are described below. The exact timing of each assessment is indicated in Table 1 to Table 3 and in section 6.5.

It is the treating investigator's obligation to assure documentation of all relevant data in the subject's source record and the eCRF, such as medical history and concomitant diseases, date of enrollment into the clinical investigation, visit dates, results of examinations, application of the device, AEs and device deficiencies.

All subject questionnaires assessing improvement and satisfaction with appearance and outcome (i.e., modified GAIS, FACE-Q™) should preferably be done at the beginning of the respective visit to avoid potential influence of investigator's comments on subject's perception during the visit.

Important note: The assessments and procedures described in the following sections must ONLY be conducted by the treating investigator (or trained site staff, if applicable), except for the MVDSS, NLF-SRS and modified GAIS rating, that will be done by the blinded evaluator at the site. The central independent blinded photographic reviewer will conduct MVDSS assessment (see section 6.4.13).

To ensure consistency of effectiveness assessments over the study duration, it is preferred that the same person performs the same assessments on the same subject across all visits.

Treatment-related procedures are described in section 6.2.2, AE and device deficiency collection procedure in section 14.9. All other assessments and procedures are described below.

Actions during ongoing COVID-19 pandemic

During COVID-19 pandemic situation, special risk mitigation procedures need to be performed to protect the safety of subjects, site personnel and other persons involved. Possible mitigation measures to be taken into consideration by the study sites are described in section 4.4.

In addition, a separate CIP addendum (see section 4.4) gives detailed information about the possible mitigation measures and alternative procedures in case of restrictions during the pandemic.

If the conduct of visits or assessments of a specific subject is affected by the COVID-19 situation this should be documented in the subject´s source records.

6.4.1 *Demographic data*

Information on subject's year of birth, gender, race and ethnicity will be collected. All demographic data will be documented in the subject´s source record and in the eCRF.

6.4.2 *Fitzpatrick skin types*

The Fitzpatrick skin type (FST) scale [44] is a widely used numerical classification scheme for human skin color shown in Table 18.

Table 18. *Fitzpatrick skin types.*

Skin type	Characteristics
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	Rarely burns, tans very well (moderate brown)
VI	Never burns, deeply pigmented

Skin type of the subject will be documented in the subject´s source record and in the eCRF.

Note: Enrollment levels for subjects of all FST is encouraged (see section 6.3.2 for details).

6.4.3 *Body weight measurement*

For body weight measurement, the subject must stand barefoot and wear light indoor clothing. Body weight will be recorded to the nearest kilogram in the subject´s source record and the eCRF.

Any findings in the body weight measurement at Screening (Visit 1) will be recorded in the subject´s source record and in the eCRF as medical history (see section 6.4.5).

Any changes of clinical relevance (*significant* weight loss or weight gain) compared to the Screening (Visit 1) measurement may represent an AE. The Investigator will evaluate if the change is due to a medical reason (e.g., an accompanying disease like metabolism disorders or cancer, unintended appetite gain/loss, edema), and - if medically reasonable - will record the diagnosis in the subject´s source record and document in the eCRF as an AE (see section 14).

6.4.4 *Pregnancy test*

In females of childbearing potential, including women who are postmenopausal for less than twelve months, urine pregnancy tests will be performed using a dipstick test. The result will be recorded in the subject's source record and the eCRF.

In case of positive test result at Screening (Visit 1) the subject must not be enrolled. Any female subject who becomes pregnant while participating in the investigation must be withdrawn from the study (also see section 6.3.6).

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Pregnancy needs to be reported and followed-up as described in section 14.5 and section 14.5.5.

6.4.5 *Medical history*

Relevant medical history findings (including major surgeries) will be collected at Screening (Visit 1) from subject interview and source records (if available). An update will be collected at Baseline (Visit 2).

Special attention should be paid to diseases and conditions assessed in exclusion criteria (see section 6.3.3), especially findings of clinical significance in visual examinations prior to the first treatment at Baseline visit (Visit 2) (see section 6.4.7).

Any medical condition / disease that is still present (ongoing) at Screening (Visit 1) should also be considered as concomitant disease. If such condition, however, deteriorates after Screening (Visit 1), at any time during the investigation, it should be documented as an AE (see section 14).

Medical history findings will be documented in the subject´s source record and in the eCRF by diagnosis and time of diagnosing (start date and end date, if applicable).

6.4.6 *Aesthetic history*

Aesthetic history is defined as aesthetic findings limited to procedures on the face.

Aesthetic history will be collected at Screening (Visit 1) from subject interview and source records (if available). An update will be collected at Baseline (Visit 2). Special attention should be paid to aesthetic procedures relevant for exclusion criteria (see section 6.3.3).

Findings will be documented in the subject´s medical record and in the eCRF by diagnosis and time of diagnosing (start date and end date, if applicable).

6.4.7 *Prior and concomitant treatments (medication and non-pharmacological procedures)*

All medications (prescription and over-the-counter products) taken and non-pharmacological procedures applied from 10 days prior to Screening (Visit 1) up to the End of Study Visit will be documented in the subject´s source record and in the eCRF.

Medications will be classified by drug generic name / trade name or active substance (in case no generic name is available).

Prohibited concomitant medications and non-pharmacological procedures (including surgeries or aesthetic procedures, see section 6.4.6) are listed in section 6.3.9.

6.4.8 *Visual examinations*

Visual examinations (including Snellen visual acuity, confrontational visual fields and ocular motility) will be performed at the study site by treating investigator or authorized designee as indicated in the "Schedule of procedures and assessments" (Table 1 and Table 3).

If device is administered during a visit, the examination will be performed both before and 30 min after each injection.

Overview of visual examinations

- **Snellen acuity test:** Visual acuity is the eye's ability to detect subtle details and is the measure of the eye's ability to see a sharp image at a specific distance. Visual acuity is determined by using a letter board.
- **Confrontational visual field test:** A confrontation visual field test is a quick and easy way to measure overall field of vision. This diagnostic test is also commonly known as the finger counting exam because the examiner may use his own fingers during the test. In general, human vision is divided into 4 quadrants (superior, inferior, nasal and temporal) in brain. The examiner will check the field of vision in each quadrant.

  In normal individuals

  - Superior field extends 55 to 60 deg from fixation
  - Nasal field extends from 60 to 65 deg from fixation
  - Inferior field extends from 70 to 75 deg from fixation
  - Temporal field extends 90 to 95 deg from fixation
- **Ocular motility:** Normal ocular motility is considered as the conjugate, full and painless movements of both eyes in all directions. It includes the study of 12 extra-curricular muscles and their impact on eye movement. To be more specific each eye has 6 muscles, four recti and two obliques, which when functioning normally allow the eyes to work together in a wide range of gaze. Restriction of movement in particular gaze ↑ ↓ ← → ↖ ↗ ↙ ↘ signifies the involvement of a specific muscle.

All visual examination results and the use of corrective eyewear (i.e., glasses/contact lenses) will be documented in the subject´s source record and in the eCRF.

Note: The subject should wear the same corrective eyewear (i.e., glasses/contact lenses) at each assessment, if appropriate. Details how to conduct visual examinations will be given in a separate manual.

Abnormal Visual Examinations at Baseline (Visit 2)

Any abnormal findings in visual examinations *prior to the first treatment at Baseline visit (Visit 2)* will be recorded as medical history (see section 6.4.5) in the subject´s medical record and in the eCRF. Special attention should be paid to ExC#18 (see section 6.3.3).

The following results from visual examinations at Baseline (Visit 2) will be considered abnormal and will exclude the subject from participation in the study:

- **Snellen acuity test**: Abnormality is defined as any result worse than 20/40 (with corrections, if applicable)
- **Confrontational visual field test**: Any abnormality at baseline will be considered if the subject fails to identify or count the finger(s)
- **Ocular motility**: Any deviation in the eye movement from the above given normal is considered as abnormal at baseline.

Abnormal Visual Examinations after Baseline visit (Visit 2)

Any clinically significant change *compared to prior each device application* will be recorded as AE according to section 14 in the subject´s source record and the eCRF. Special focus must be on the

Adverse event of special interest (AESIs) as defined in section 14.1.Any of the following changes in visual examinations after respective Baseline result will be considered **abnormal clinically significant**:

- **Snellen acuity test**: Any worsening of 2 lines or more in best corrected visual acuity (i.e., with glasses/contact lenses)
- **Confrontational visual field test**: Any change to the peripheral vision
- **Ocular motility**: Any change in the normal ocular motility

Respective Baseline results are defined as follows:

- Results at each visit will be compared to the results prior to first injection of each treatment phase, i.e., Visit 2 for initial treatment phase and Visit RT1 for repeat-treatment phase.
- At treatment visits, visual examinations will be performed before the injection and 30 min after the injection. The result post-injection (30 min after) *w*ill be compared to the results prior the injection.

If any of the above changes occur at any assessment, the treating investigator must refer the subject to an eye specialist to evaluate if the result is related to a vascular injection of the dermal filler. If the eye specialist confirms that the result is related to a vascular injection of the dermal filler, the subject must be withdrawn from **further treatment(s)** (see section 6.3.6) and further activities following a related vascular event will be reviewed (see section 16.1).

The subjects may remain in the study at least for safety assessments during the scheduled study visits.

6.4.9 *Neurological examination (F.A.S.T)*

The "F.A.S.T" examination is a basic neurological examination that will be performed by treating investigator (or authorized designee) according the instructions given in Table 19 for all subjects who show signs of ophthalmic complications due to filler injection.[27, 28]

Table 19. *F.A.S.T. Warning Signs and Instructions for Use (adapted per [27, 28])*

Symptom	Instructions for Use
F - Facial drooping	Ask the patient to smile or show teeth. Look for lack of symmetry. Does one side of the face droop or is it numb? Is the person's smile uneven?
A - Arm weakness	Lift the patient´s arms together to 90° if sitting; 45° if supine and ask him/her to hold the position for 5 seconds then let go. Or ask the person to raise both arms. Is one arm weak or numb? Does one arm drift downward or fall rapidly?
S - Speech difficulty	Look for disturbance of speech. Look for slurred speech. Look for word-finding difficulties. This can be confirmed by asking the patient to name commonplace objects that may be nearby, such as a cup, chair table, keys, pen. If there is a severe visual disturbance, place an object in the patient´s hand and ask him/her to name it.
T - Time	Time to call emergency services

More ways to spot a stroke [27]

- Sudden weakness or numbness of face, arm or leg, especially on one side.
- Sudden confusion, trouble speaking or understanding.
- Sudden trouble seeing in one or both eyes.
- Sudden trouble walking, dizziness, loss of balance or coordination.
- Sudden, severe headache with no known cause.

If any of the symptoms above are showing, time is of the essence; call the emergency services and redirect the patient to the hospital / acute stroke unit immediately.

Any clinically significant change compared to prior of each device application will be recorded as AE according to section 14 in the subject´s source record and the eCRF. Special focus must be on the AESIs as defined in section 14.1.

If any of the above changes occurs at any assessment, the treating investigator must refer the subject to a neurologist to evaluate if the result is related to a vascular injection of the dermal filler.

If the neurologist confirms that the result is related to a vascular injection of the dermal filler, the subject must be withdrawn from further treatment(s) (see section 6.3.6) and further activities following a related vascular event will be reviewed (see section 16.1). The subjects may remain in the study at least for safety assessments during the scheduled study visits.

6.4.10 *Injection volume, injection technique and injection equipment*

The following information will be documented in the subject´s source record and the in eCRF:

- Injection volume (see section 6.2.3 for details)
    - the volume injected will be calculated by the investigator based on the number of syringes used and the estimated amount of the gel remaining in each of the syringes used)
    - the injection volume will be documented separately
        - for right and left side of the midface
        - for each anatomical area of the midface (see section 6.2.2 for details)
        - per each treatment (i.e., for baseline- and repeat treatment and each touch-up treatment (if applicable)
- Kit numbers of kits used (see section 6.2.1 for details)
- Injection technique (see section 6.2.2 for details)
- Injection equipment used (i.e., needle or cannula (see 6.2.2 for details). **Note:** A minimum of 100 subjects randomized to the test device will be treated with either needle or cannula. Use of either needle or cannula is based on the treating investigator´s medical decision. Details how to monitor enrollment levels via the eCRF system will be described in the project management plan.
- Exact start time and end time of injection

For detailed instructions on administration of the devices refer to section 6.2.2.

6.4.11 *Clinical photography*

Photographs of the subject´s full face subject´s and neck will be taken by the investigator or designee using a digital 3D (three-dimensional) camera (provided by [redacted] the photo provider).

> **Note:** In addition to clinical photography (3D photos), another baseline photo (2D) should be taken on-site at Visit 1 (for details refer to a separate photography manual). This 2D photo will be used as baseline photo to evaluate the global aesthetic improvement (see below) in case of restrictions during the COVID-19 pandemic. Details are outlined in an addendum to the CIP.

If device is administered at the respective visit, photography must be conducted *before* the application of the device.

The photographs will be used

- for publication purposes (see section 6.3.12)
- for volume change measurements (see section 6.4.12)
- for evaluation of severity of midface volume deficiency using the 5-point MVDSS by a central independent blinded photographic reviewer (see section 6.4.13)

- for assessment of global aesthetic improvement using the modified GAIS by the blinded evaluator at the site and subject (see section 6.4.16)

Any excessive or distracting make-up has to be removed before photos are taken. A standardized procedure will be applied to ensure consistency of the background, camera settings, lighting, and subject position between the visits and across the sites.

Details will be given in a photography manual provided by [redacted].

6.4.12 *Volume change measurements*

Computerized volume change measurements ([redacted] will be used to evaluate the volume changes following injection of the device.

The volume changes quantified by measuring the difference between the 3D photography images taken at follow-up visits as indicated in the "Schedule of procedures and assessments" (post-treatment) relative to baseline pre-treatment pictures (taken at Visit 1) in the specified areas of interests (AOIs).

The anatomical areas of interest (AOIs) are given below and shown in Figure 4:

- Anteromedial cheek (left and right)
- Submalar (left and right)
- Zygomaticomalar (left and right)

The analysis script will produce measurements of positive, negative, and total volume change in comparison to the Screening (Visit 1) image for each AOI and for the combined AOIs of the left and right sides of the face. The left and right midface will be evaluated separately.

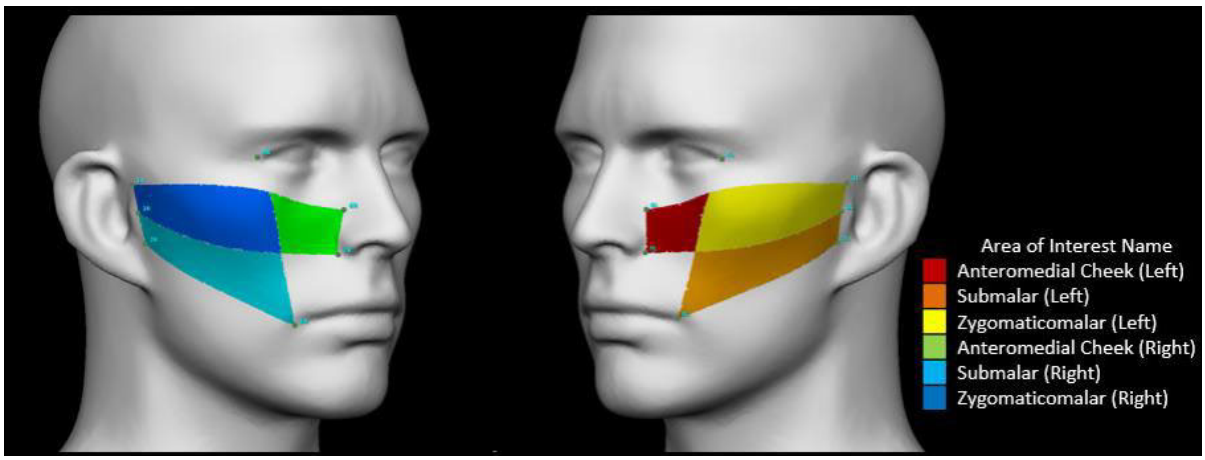


Figure 4. *Anatomical areas of interest (AOI) for volume change measurements.*

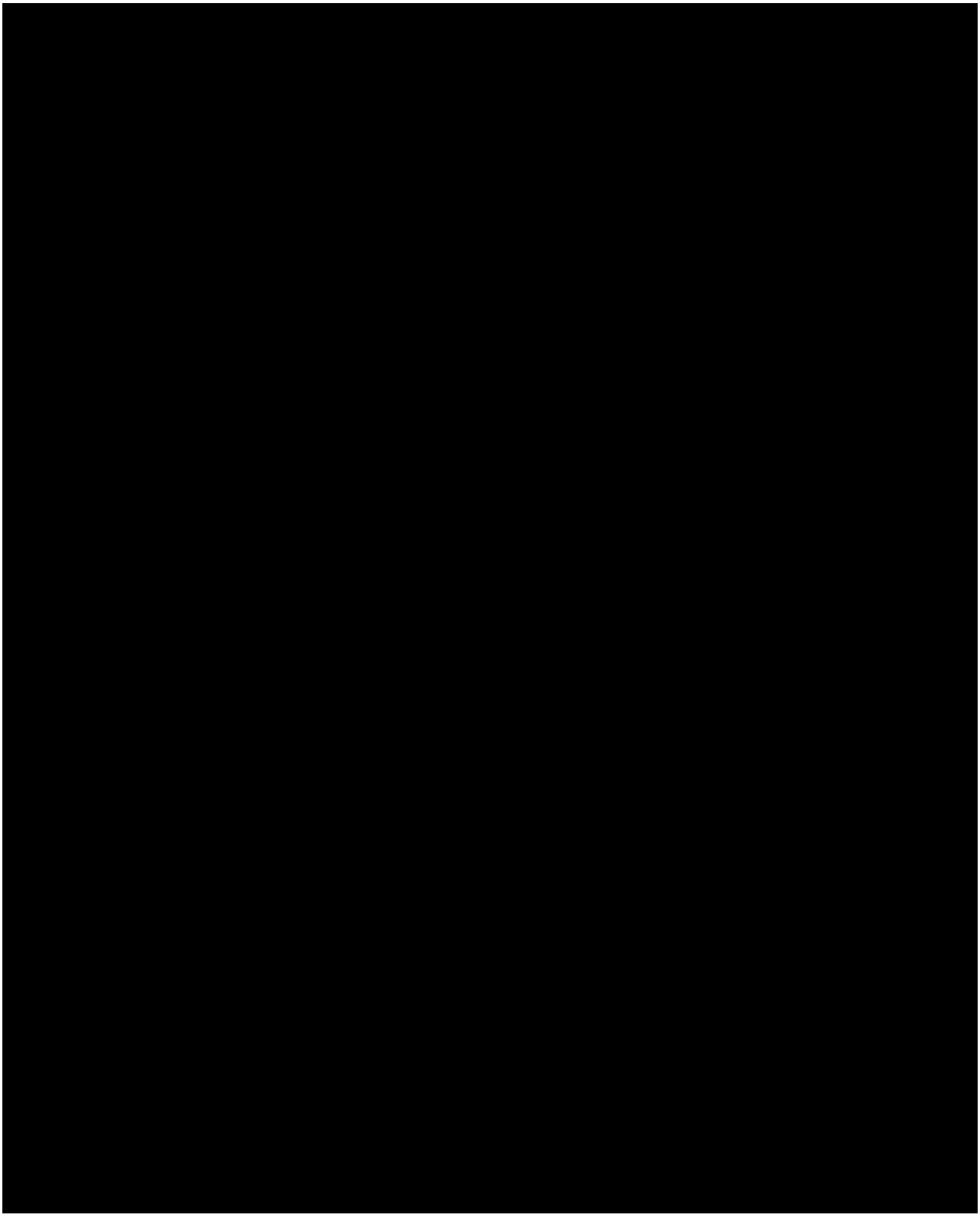
Once the photography images are received at the photography provider at the end of the initial treatment phase (i.e., all subjects have completed Visit 9 (SV1)), they will be analyzed based on scripts and procedures unique to the underlying application.

6.4.13 *Midface Volume Deficit Severity Scale (MVDSS) - Grading of midface volume deficiency*

The severity of midface deficit will be evaluated based on the Midface Volume Deficit Severity Scale (MVDSS), which is a validated 5-point rating scale ranging from grade 0 (none/minimal) to grade 4 (very severe).

The scale is briefly described in Table 20. The detailed MVDSS is provided in section 20.1.

Table 20. *Croma - Midface Volume Deficit Severity Scale (MVDSS)*



Note: No separate assessments will be performed for the *right and left* midface region. Only subjects with approximately symmetrical deficit will be included into the study (see InC#2 in section 6.3.3), so the left and the right cheek will *not* be graded separately. If asymmetry emerges during follow-up, which is unlikely, the grade will be assigned according to the side with a larger deficit, and asymmetry will be

recorded as an AE. If InC#2 is violated and asymmetry is already present at Day 0, the grade will also be assigned according to the side with the larger deficit. The same applies to eligibility for repeat-treatment (see InC#1 in see section 6.3.5).

Blinded evaluator at site:

- The **blinded evaluator** at the site will perform a *live* assessment of midface volume deficit based on the MVDSS **before each treatment and at each follow up visit** (see Table 1 and Table 3)

The assessments of the blinded evaluator will be documented in a MVDSS Rating Sheet indicating:

- the date and visit of the assessment
- the subject ID

The MVDSS Rating Sheets will be filed in the subject´s source record and results will be transferred in the eCRF by an unblinded member of the investigation site (see section 6.1.3).

Central independent blinded photographic reviewer

The severity of volume deficiency will additionally be assessed by central independent blinded photographic reviewers using MVDSS *on photographs* (see section 6.4.11) before **baseline treatment** and at **each follow up visit of the initial treatment phase** (see Table 1).

This assessment is performed after the photo has been uploaded and after all subjects have completed Visit 9 (SV1). The central independent blinded photographic reviewer will be dislocated from the investigation sites and will not discuss any findings with the investigators during the investigation. Further details will be described in a separate manual.

Note: For both, the blinded evaluator at the site and the central independent blinded photographic reviewer, the rater blinding regarding treatment group in initial treatment phase will remain in effect during the repeat-treatment phase until study data base lock.

6.4.14 *Nasolabial Folds Severity Rating Scale (NLF-SRS)*

The severity of nasolabial folds (NLFs) will be assessed using the Nasolabial Folds Severity Rating Scale (NLF-SRS). The NLF-SRS is a 5-point rating scale ranging from grade 0 (none/minimal) to grade 4 (extreme). Separate assessments will be performed for the *right and left* NLFs.

The scale is briefly described in Table 21. The detailed NLF-SRS is provided in section 20.2.

Table 21. *Croma - Nasolabial Folds Severity Rating Scale (NLF-SRS)*

The **blinded evaluator** at the site will perform a *live* assessment of nasolabial folds severity based on the NLF-SRS **before each treatment and at each follow up visit** (see Table 1 and Table 3).

The assessment of the blinded evaluator will be documented in the NLF-SRS Rating Sheet indicating:

- the date and visit of the assessment
- the subject ID

The NLF-SRS Rating Sheets will be filed in the subject´s source record and results will be transferred in the eCRF by an unblinded member of the investigation site (see section 6.1.3).

6.4.15 *Numeric Pain Rating Scale (NPRS) - Pain assessment*

After each treatment with the device, the subject will be asked by the treating investigator to quantify the pain associated with the procedure by means of a semi-quantitative 11-point Numeric Pain Rating Scale (NPRS), where "0" corresponds to no pain, and "10" to the worst pain imaginable.[38] Separate pain assessments will be performed for the right and left midface area treated.

Pain intensity will be assessed immediately after injection (approx. +3 min), and at 15 min-intervals (approx. ±3 min) after end time of the device administration for 60 min post-treatment by asking the subject one of the following questions, as appropriate:

- *"How would you rate the pain you have felt during the treatment, if "0" is no pain at all, and "10" is the worst pain you can imagine?"*
- *"How would you rate the pain you have felt during recovery from the treatment, if "0" is no pain at all, and "10" is the worst pain you can imagine?"*

Subject's response will be recorded on the Pain Assessment Form. If additional local anesthesia is used, this has to be documented on the Pain Assessment Form as well. The subject will be provided with the appropriate questionnaire in local language.

Completed subject's Pain Assessment Form will be considered as source documents and archived in the subject's source record. The results will be transferred into the eCRF.

6.4.16 *Modified Global Aesthetic Improvement Scale (GAIS) - "Global aesthetic improvement"*

The global aesthetic improvement after correction of midface volume deficit will be independently evaluated by the blinded evaluator at the site and the subject using the modified Global Aesthetic Improvement Scale (modified GAIS; based on [35]), a widely-used instrument presented in Table 22.

Table 22. *Modified Global Aesthetic Improvement Scale (GAIS)*

[redacted]

Subject

The subject will be asked to evaluate the global aesthetic improvement by reviewing the photographs taken at the current visit relative to photographs taken at the Baseline visit. For the assessment, the subject will answer the modified GAIS shown in Table 22 in local language.

Completed subject's modified GAIS will be considered as source documents archived in the subject's source record. The results will be transferred into the eCRF.

Blinded evaluator at the site

The blinded evaluator at the site will evaluate the global aesthetic improvement by reviewing the photographs taken at the current visit relative to photographs taken at the Baseline visit. Results will be recorded using the modified GAIS rater form (to be filed in the subject´s source record) transferred into the eCRF (see section 6.1.3).

6.4.17 *FACE-Q™ Questionnaire – "Satisfaction with overall outcome"*

Subject's satisfaction with the overall treatment will be assessed using the FACE-Q™ Questionnaire "Satisfaction with Outcome" (Patient experience scale: Outcome) in order to evaluate the performance of the devices and consistency in alignment with subject expectation.

The questionnaire is a validated instrument for evaluation of subject´s satisfaction with the overall outcome of the treatment.[36, 37] It comprises 6 positively worded items that ask the subjects to indicate how they feel about the result of their most recent facial aesthetic procedure.

Four response options are provided (i.e., 'definitely agree', 'somewhat agree', 'somewhat disagree', and 'definitely disagree'). For each statement, the subject may circle only one answer. The scale is described in Table 23 below.

Table 23. *FACE-Q™ Questionnaire – "Satisfaction with outcome"*

The subject will be provided with the appropriate questionnaire in local language.

Completed questionnaires will be considered as source documents and archived in the subject's source records. The results will be transferred into the eCRF.

6.4.18 *FACE-Q™ Questionnaire – "Satisfaction with Cheeks"*

Subject's satisfaction with overall midface augmentation will be evaluated using the respective FACE-Q™ Questionnaire (Appearance appraisal scale: Cheeks).

The scale is a validated instrument for evaluation of subject´s satisfaction with cheeks. It comprises 5 items. The scale measures the appearance of cheeks (side of the face below cheekbones) with items that ask about fullness, symmetry and attractiveness.[37]

Four response options are provided (i.e., 'very dissatisfied, 'somewhat dissatisfied', 'somewhat satisfied', and 'very satisfied'). For each statement, the subject may circle only one answer. The scale is described in Table 24 below.

Table 24. *FACE-Q™ appearance appraisal scale – "Satisfaction with cheeks".*

The subject will be provided with the appropriate questionnaire in local language.

Completed questionnaires will be considered as a source document and archived in the subject's source records. The results will be transferred into the eCRF.

6.4.19 *Subject diary: Injection site reactions and symptoms of interest*

The subjects will be asked to document predefined injection site reactions and symptoms of interest in a web-based electronic diary (eDiary).

Access to the eDiary needs to be initiated by site staff for each subject at the end of the initial and repeat-treatment session. Site staff will thoroughly train the subjects on completing the eDiary. Details on handling of the eDiary (e.g., initiation of accounts, training and instruction for the subjects, cancel access rights) will be provided to the site staff in a separate manual.

All injection site reactions / symptoms of interest documented by the subject in the eDiary will be directly available in the eCRF. The treating investigator (or designated staff) at the site will thoroughly review the entries for completeness at the next on-site visit after each treatment. Subjects who are non-compliant will be counseled and re-trained. The subjects will receive detailed instructions for completion and handling of the eDiary in local language.

To confirm that entries have been reviewed at a respective on-site visit, the treating investigator (or designated site staff) needs to document the review in the subject´s source record and in the eCRF.

All data will be considered as a source document.

Injection site reactions

The subjects will be asked to record injection site reactions 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). Injection site reactions include:

- Redness
- Pain after injection
- Tenderness to touch
- Firmness
- Swelling
- Lumps/Bumps
- Bruising
- Itching
- Discoloration (not redness or bruising)
- Other (other symptoms at the injection site not listed above) [with possibility to answer 'Yes' or 'No' and a free-text field to add a symptom at the injection site if answered 'Yes']

The presence and intensity of these symptoms per side of the midface (left and right side of the midface) will be documented and scored by the subject using a 5-grade scale for the left and right side separately on a daily basis within the diary (see Table 25).

Table 25. *Injections site reactions assessment by the subject.*

Score	Intensity code	Definition
0	No reaction	No injection site reaction
In case there is an injection site reaction the rating is as follows (left and right side of the midface):		
1	None	No observation.
2	Mild	Symptoms barely noticeable and does not cause discomfort. No influence on performance or functioning. Treatment of symptoms is not needed.
3	Moderate	Symptoms very noticeable and/or causes discomfort. Performance of daily activities is influenced. Treatment of symptoms may be needed.
4	Severe	Symptoms cause severe discomfort. Performance of daily activities is compromised. Treatment of symptoms is needed.

In case, the injection site reaction is not resolved after 4 weeks (28 days) it must be documented and reported (if applicable) as an AE as described in section 14. Note, that injection site reactions that are considered **serious** (see section 14) will be collected and processed as AE regardless of the occurrence date (see section 14).

Injection site reactions the subject is **not** specifically asked about in the subject diary (i.e., 'Other' symptoms at the injection site not listed above) need to be assessed and documented by the treating investigator:

- If an 'Other' symptom at the injection site is synonymous to one of the injection site reactions listed above, the treating investigator needs to document this fact in the subject´s source record. The synonymous 'Other' symptom at the injection site does not need to be transferred to the eCRF.
- If the 'Other' symptom at the injection site does not meet one of the injection site reactions listed above, it should be further assessed by the treating investigator and documented as AEs in the subject´s source record and in the eCRF (in English language) as described in section 14.

Symptoms of interest

Furthermore, the subjects will be asked if they have experienced any of the following symptoms of interest (SOIs) potentially associated with the unintended intravascular injection of the device during the first four 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):

Table 26. *Symptoms of interest to be assessed by the subject*

Symptoms of interest (diary term)

• Changes in vision:
  ○ loss of vision
  ○ blurriness
  ○ double vision
  ○ pain in or around your eye
  ○ blindness
  ○ blind spots
  ○ problems moving the eyes
• Skin changing color around the eyelids
• Crusty or scabby skin around the eyelids
• Headache
• Fever
• Dizziness
• Confusion
• Weakness or numbness in the arms or legs
• Changes to consciousness or alertness
• Difficulty speaking/speech impairment
• Face droop
• Changes to chewing and drinking
• Discomfort with palpation
• Sensitivity to hot/cold liquids and foods

SOI(s) documented by the subject in the eDiary will be directly available in the eCRF. The study site will closely monitor the SOI(s) in the eCRF between the on-site visits and - if deemed necessary – proactively contact the subject for safety reasons. If required, an unscheduled on-site visit may be performed (see section 6.5.17). The eDiary will include specific instructions for the subject to seek immediate medical attention if any of the above symptoms or signs are observed.

At each visit during eDiary period, the SOI(s) documented by the subject in the eDiary will be discussed with the subject.

All SOI(s) should be carefully verified by the investigator for their clinical significance (see section 14.2). If clinical significance is verified, the investigator will attempt to establish a diagnosis based on SOIs documented by the subject in the eDiary and/or additional clinical information the subject may report (see section 20.5.2). The diagnosis will be documented and assessed as AE(SI) rather than single SOI(s). If no diagnosis can be established the SOI term should be only documented and assessed as AE(SI). See sections 14.3 and 14.4 for details regarding documentation and assessment of AE(SI)s.

Note: SOIs that turn out to be not clinically significant due to any reason (see section 20.5.1) are not considered as AE(SI) and need not to be documented as AE(SI) in the eCRF. However, the investigator should add a statement in the subject's source records why the SOI was not considered clinically significant / as AE(SI).

Note: All AESIs (serious and non-serious, see section 14.1 for definition) and any other embolic event (regardless of seriousness and / or relationship to device or procedure) resulting from SOI assessment have to be reported by the investigator to the sponsor's representative within 24 hours of awareness of the event (see section 14.5).

6.4.20 *Safety monitoring*

The safety of the subjects will be monitored throughout the investigation, from Screening (Visit 1) until their End of Study visit. The follow-up period will be prolonged outside the investigation, if a related AE

is ongoing and not stabilized after 24 weeks after last injection of the repeat-treatment phase (see section 14.6 for details).

The subjects will be instructed to immediately contact the investigator by phone in case of occurrence of any untoward event between the visits (including visual examinations after treatment visits).

In order to identify potential AEs immediately post-administration a safety evaluation 15 min after each treatment needs to take place. Furthermore, subject diaries will be provided to the subjects, and they will be instructed to note injection site reactions, and symptoms of interest (see section 6.4.19).

Any subject with an (S)AE or clinically significant abnormal test result will be evaluated by the treating investigator and will be treated and/or followed up as per local clinical practice. Where appropriate, medical tests and examinations may be performed to ensure that an AE has fully resolved.

The procedure for collection, recording and reporting of AEs and device deficiencies is described in section 14. Device deficiencies will be documented as well at each device treatment (see section 14.9).

6.5 Schedule of procedures

The “Schedule of procedures and assessments” in Table 1 to Table 3 gives an overview of study procedures during study conduct. The following sections tabulate the procedures to be performed by visit.

Actions during ongoing COVID-19 pandemic

During COVID-19 pandemic situation, special risk mitigation procedures need to be performed to protect the safety of subjects, site personnel and other persons involved. Possible mitigation measures to be taken into consideration by the study sites are described in section 4.4.

In addition, a separate CIP addendum (see section 4.4) gives detailed information about the possible mitigation measures and alternative procedures in case of restrictions during the pandemic.

If the conduct of visits or assessments of a specific subject is affected by the COVID-19 situation this should be documented in the subject´s source records.

6.5.1 *Visit 1 – Screening (Day -14 up to Day 0)*

Note: Screening visit (Visit 1) and Baseline visit (Visit 2) may be performed as one visit.

- Provide subject information / Obtain written informed consent (see section 13)
- Assign the subject number by entering subject data into eCRF (see CRF Completion Guidelines)
- Collect demographic data (see section 6.4.1)
- Define Fitzpatrick skin type of the subject (see section 6.4.2)
- Perform body weight measurement (see section 6.4.3)
- Women of child-bearing potential:
  - Urine dipstick pregnancy test (see section 6.4.4)
  - Instruction about [highly] effective methods of contraception (see section 6.3.8)
- Record relevant medical history (i.e., prior and concomitant diseases, incl. major surgeries) (see section 6.4.5)
- Record relevant aesthetic history (i.e., information on prior facial aesthetic procedures) (see section 6.4.6)
- Record AEs from signature of the ICF onwards (see section 14)
- Record prior and concomitant treatments (see section 6.4.7)
- Midface volume deficit severity scale (MVDSS) – blinded evaluator at the site (see section 6.4.13)
- NLF-SRS – blinded evaluator at site (see section 6.4.14)
- Review and evaluate eligibility criteria (see section 6.3.3) including wash out periods for prohibited treatment (see section 6.3.8)

- Perform clinical photography (2D and 3D photos) (see section 6.4.11)
  - Upload the 3D photos for independent blinded photographic reviewer (MVDSS) (see section 6.4.13) and volumetric change measurement (see section 6.4.12)
  - Upload the 2D photo (see section 6.4.11)
- Schedule an appointment for the next on-site visit.

6.5.2 *Visit 2 – Baseline (Day 0)*

- Record any new AE or changes of AEs (see section 14). **Note:** this includes AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7), medical and aesthetic history (see section 6.4.5 and 6.4.6)
- Perform visual examinations prior to device administration (see section 6.4.8) with special focus on eligibility criterion on visual examinations (ExC #18, see section 6.3.3.2)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4) – prior to device administration
- FACE-Q™ - Satisfaction with cheeks (see section 6.4.18) – prior to device administration
- Re-assess and evaluate eligibility criteria (see section 6.3.3)
- For eligible subjects perform randomization (see section 6.1.2)
- Device administration (baseline treatment):
  - See section 6.2.2 to section 6.2.4 for detailed instructions for injection
  - Document information on injection (see section 6.4.9)
- Record any device deficiencies (see section 14.9)
- Pain assessment (during treatment) using the NPRS by subject immediately (approx.+3 min) after end time of device administration (see section 6.4.14)
- Pain assessment (during recovery from treatment) using the NPRS by subject every 15 min (approx. ±3 min) after end time of the device administration for 60 min post-treatment (see section 6.4.14)
- Perform visual examinations approximately 30 min after device administration (see section6.4.8).
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- Initiate access to eDiary and explain diary use incl. documentation of injection site reactions / symptoms of interest to the subject (see section 6.4.19)
- Advise the subject prior to discharge to follow restrictions specified in section 6.3.8.
- Schedule an appointment for the telephone visit and the next on-site visit.

6.5.3 *Visit 2a - Telephone Visit (24 to 48 hours (±4 hours) after baseline treatment)*

Note: The time of the telephone call has to be documented; it has to be conducted 24 to 48 hours (±4 hours) after the end of injection at Visit 2 (see section 6.4.9)

- Ask for any changes in AEs and new AEs (see section 14) including AESIs (see section 14.1)

  In case of an AE including vision changes, neurological issues, or an unbearable injection site reaction an unscheduled on-site visit must be performed (see section 6.5.17)
- Ask for changes in concomitant treatments (see section 6.4.7)
- Remind the subject to document injection site reactions / symptoms of interest in the diary (see section 6.4.19)

6.5.4 *Visit 3 – Week 2 (after baseline injection) ± 3 days*

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7)

- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4) – prior to device administration
- Review subject diary regarding injection site reactions / symptoms of interest; confirm review (see section 6.4.19)
- Perform visual examinations prior to device administration (see section 6.4.8) and review respective exclusion criteria (see section 6.3.5)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- MVDSS –blinded evaluator at the site (see section 6.4.13) – prior to device administration
- NLF-SRS – blinded evaluator at site (see section 6.4.14) – prior to device administration

Subjects not receiving the optional touch-up treatment:

- Remind subject regarding further documentation of injection site reactions / symptoms of interest in the diary (see section 6.4.19)
- Schedule an appointment for the next on-site visit.

Optional touch-up treatment:

Note: The touch-up treatment may be conducted if an optimal aesthetic correction has not been achieved after baseline treatment (i.e., at Visit 2) in the discretion of the treating investigator (see section 6.2.2 for criteria).

The touch-up treatment is optional and must only be conducted if the respective exclusion criteria are not met (see section 6.3.4).

The following assessments must be conducted for the respective subjects:

- Device administration (touch-up treatment)
  - See section 6.2.2 to section 6.2.4 for detailed instructions for injection
  - Document information on injection (see section 6.4.9)
- Record any device deficiencies (see section 14.9)
- Pain assessment (during treatment) using the NPRS by subject immediately (approx.+3 min) after end time of device administration (see section 6.4.14)
- Pain assessment (during recovery from treatment) using the NPRS by subject every 15 min (approx.±3 min) after end time of the device administration for 60 min post-treatment (see section 6.4.14)
- Perform visual examinations approximately 30 min after device administration (see section 6.4.8)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- Explain again diary use to the subject and documentation of injection site reactions / symptoms of interest (see section 6.4.19)
- Advise the subject prior to discharge to follow restrictions specified in section 6.3.8.
- Schedule an appointment for telephone visit and the next on-site visit.

6.5.5 *Visit 3a - Telephone Visit (24 to 48 hours (±4 hours) after touch-up treatment)*

Only in case of touch-up treatment at Visit 3

Note: The time of the telephone call has to be documented; it has to be conducted 24 to 48 hours (±4 hours) after the end of injection at Visit 3 (see section 6.4.9)

- Ask for any changes in AEs and new AEs (see section 14) including AESIs (see section 14.1)

  In case of an AE including vision changes, neurological issues, or an unbearable injection site reaction an unscheduled on-site visit should be performed (see section 6.5.17).
- Ask for changes in concomitant treatments (see section 6.4.7)

- Remind the subject to document injection site reactions / symptoms of interest in the diary (see section 6.4.19)

6.5.6 *Visit 3b – Safety follow-up (2 weeks (±3 days) after touch-up treatment)*

Only in case of touch-up treatment at Visit 3

- Record any changes in AEs and new AEs (see section 14) including AESIs (see section 14.1)
  In case of an AE including vision changes, neurological issues, or an unbearable injection site reaction an unscheduled on-site visit should be performed (see section 6.5.17).
- Record changes in concomitant treatments (see section 6.4.7)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4)
- Review subject diary regarding injection site reactions / symptoms of interest; confirm review (see section 6.4.19)
- Perform visual examinations (see section6.4.8) and review respective exclusion criteria (see section 6.3.5)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)

6.5.7 *Visit 4 to 8 – Week 4 to Week 36 (after last injection)*

Through the follow-up phase of the initial treatment phase the following visits will be performed:

- Visit 4 – Week 4 (± 5 d) after last injection
- Visit 5 – Week 8 (± 5 d) after last injection
- Visit 6 – Week 16 (± 7 d) after last injection
- Visit 7 – Week 24 (± 7 d) after last injection
- Visit 8 – Week 36 (± 7 d) after last injection

Note: Last injection refers to either

- **Visit 2** for subjects **without** touch-up treatment, or
- **Visit 3** for subjects **with** touch-up treatment (i.e., TUP1)

The following assessment will be performed:

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4)
- Review subject diary regarding injection site reactions / symptoms of interest; confirm review (see section 6.4.19) – only Visit 4
- Perform body weight measurement (see section 6.4.3)
- Perform visual examinations (see section 6.4.8)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- Perform clinical photography (see section 6.4.11)
- MVDSS –blinded evaluator at the site (see section 6.4.13)
- NLF-SRS –blinded evaluator at site (see section 6.4.14)
- Upload the photos for independent blinded photographic reviewer (MVDSS) (see section 6.4.13) and volumetric change measurement (see section 6.4.12).
- Modified GAIS assessment –blinded evaluator at the site (see section 6.4.16)
- Modified GAIS assessment – subject (see section 6.4.16)
- FACE-Q™ – Satisfaction with overall outcome of treatment (see section 6.4.17) – subject

- FACE-Q™ – Satisfaction with cheeks (see section 6.4.18) – subject
- Schedule an appointment for the next on-site visit.

6.5.8 *Visit 9 (SV1) – Week 48 (after last injection) ±7days*

Note: Last injection refers to either

- **Visit 2** for subjects **without** touch-up treatment or
- **Visit 3** for subjects **with** touch-up treatment

The following assessment will be performed:

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4) – prior to device administration
- Perform body weight measurement (see section 6.4.3) – prior to device administration
- Perform clinical photography (see section 6.4.11) – prior to device administration
- Perform visual examinations prior to device administration (see section 6.4.8) with special focus on eligibility criteria on visual examinations (see section 6.3.5)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- MVDSS – blinded evaluator at the site (see section 6.4.13)
  Note:
  - If the subject already qualifies for optional repeat-treatment with regards to MVDSS at this visit proceed with Visit RT1 (see section 6.5.10).
  - In case it is already known at this Visit that an inclusion criterion will be not met / an exclusion criterion will be met for repeat-treatment (see section 6.3.5) and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment, Visit 9 (SV1) will be End of Study visit for the respective subject.
- NLF-SRS –blinded evaluator at site (see section 6.4.14)
- Upload the photos for independent blinded photographic reviewer (MVDSS) (see section 6.4.13) and volumetric change measurement (see section 6.4.12).
- Modified GAIS assessment – blinded evaluator at the site (see section 6.4.16)
- Modified GAIS assessment – subject (see section 6.4.16)
- FACE-Q™ – Satisfaction with overall outcome of treatment (see section 6.4.17) – subject
- FACE-Q™ – Satisfaction with cheeks (see section 6.4.18) – subject

6.5.9 *Visit SV2 to SV4 – Week 4 to Week 12 after Visit 9 (SV1)*

Through the screening phase for optional repeat-treatment following visits will be performed:

- Visit SV2 – Week 4 (± 7 d) after Visit 9 (SV1)
- Visit SV3 – Week 8 (± 7 d) after Visit 9 (SV1)
- Visit SV4 – Week 12 (± 7 d) after Visit 9 (SV1)

The following assessment will be performed:

- MVDSS – blinded evaluator at the site (see section 6.4.13).
  Note:
  - If the subject qualifies for optional repeat-treatment with regards to MVDSS at one of the visits, proceed with Visit RT1 (see section 6.5.10).
  - SV4 is 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 for repeat-treatment (see

section 6.3.5) and further follow up in screening is not useful because the subject will apparently not qualify for repeat-treatment, either Visit SV 2 or SV 3 will be End of Study visit for the respective subject.

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7)
- Schedule an appointment for the next on-site visit

6.5.10 *Visit RT1 - Up to 12 weeks after Visit 9 (SV1) ±7days*

For optional repeat-treatment only saypha® VOLUME Lidocaine will be used.

The optional repeat-treatment must only be conducted if the respective eligibility criteria are fulfilled (see section 6.3.5).

The following assessments will be performed:

Note: In case the subject qualifies for optional repeat-treatment the following assessments do not need to be done twice at the respective visit:

- Visit 9 (SV1): pre-treatment assessments
- Visits SV2 to SV4: MVDSS by blinded evaluator, concomitant treatments, adverse events

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7) MVDSS –blinded evaluator at the site (see section 6.4.13) – prior to device administration
- NLF-SRS –blinded evaluator at site (see section 6.4.14) – prior to device administration
- Perform visual examinations prior to device administration (see section 6.4.8) with special focus on eligibility criterion on visual examinations (ExC #3 and 4, see section 6.3.5.2)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- Perform body weight measurement (see section 6.4.3)
- Women of child-bearing potential:
  - Urine dipstick pregnancy test (see section 6.4.4)
  - Re-Instruction about [highly] effective methods of contraception (see section 6.3.8)
- FACE-Q™ – Satisfaction with overall outcome of treatment (see section 6.4.17) – subject – prior to device administration
- FACE-Q™ – Satisfaction with cheeks (see section 6.4.18) – subject – prior to device administration
- Re-assess and evaluate eligibility criteria (see section 6.3.5); **Note:** In case an inclusion criterion is not met / an exclusion criterion is met, Visit RT1 will be End of Study visit for the respective subject.
- Device administration (repeat-treatment):
  - See section 6.2.2 to section 6.2.4 for detailed instructions for injection
  - Document information on injection (see section 6.4.9)
- Record any device deficiencies (see section 14.9)
- Pain assessment (during treatment) using the NPRS by subject immediately (approx.+3 min) after end time of device administration (see section 6.4.14)
- Pain assessment (during recovery from treatment) using the NPRS by subject every 15 min (approx.±3 min) after end time of the device administration for 60 min post-treatment (see section 6.4.14)
- Perform visual examinations approximately 30 min after treatment (see section 6.4.8)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- Initiate access to eDiary and explain diary use incl. documentation of injection site reactions / symptoms of interest to the subject (see section 6.4.19)

- Advise the subject prior to discharge to follow restrictions specified in section 6.3.8.
- Schedule an appointment for the telephone visit and the next on-site visit.

6.5.11 *Visit RT1a - Telephone Visit (24 to 48 hours days (±4 hours) after repeat-treatment)*

Note: The time of the telephone call has to be documented; it has to be conducted 24 to 48 hours (±4 hours) after the end of injection at Visit RT1 (see section 6.4.9)

- Ask for any changes in AEs and new AEs (see section 14) including AESIs (see section 14.1)

  In case of an AE including vision changes, neurological issues, or an unbearable injection site reaction an unscheduled on-site visit must be performed (see section 6.5.17).
- Ask for changes in concomitant treatments (see section 6.4.7)
- Remind the subject to document injection site reactions / symptoms of interest in the diary (see section 6.4.19)

6.5.12 *Visit RT2 – Week 2 (after repeat-treatment injection) ± 3 days)*

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4) – prior to device administration
- Review subject diary regarding injection site reactions / symptoms of interest; confirm review (see section 6.4.19)
- Perform visual examinations prior to device administration (see section 6.4.8) and review respective exclusion criteria (see section 6.3.5)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- FACE-Q™ – Satisfaction with overall outcome of treatment (see section 6.4.17) – subject – prior to device administration
- FACE-Q™ - Satisfaction with cheeks (see section 6.4.18) – subject – prior to device administration
- MVDSS –blinded evaluator at the site (see section 6.4.13) – prior to device administration
- NLF-SRS – blinded evaluator at site (see section 6.4.14) – prior to device administration

Subjects not receiving the optional touch-up treatment (TUP2):

- Remind subject regarding further documentation of injection site reactions / symptoms of interest in the diary (see section 6.4.19)
- Schedule an appointment for the next on-site visit.

Optional touch-up treatment:

Note: The touch-up treatment may be conducted if an optimal aesthetic correction has not been achieved after repeat-treatment (i.e., at Visit RT1) in the discretion of the treating investigator (see section 6.2.2 for criteria).

The touch-up treatment is optional and must only be conducted if the respective exclusion criteria are not met (see section 6.3.4).

The following assessments must be conducted for the respective subjects:

- Device administration (touch-up treatment)
  - See section 6.2.2 to section 6.2.4 for detailed instructions for injection
  - Document information on injection (see section 6.4.9)
- Record any device deficiencies (see section 14.9)

- Pain assessment (during treatment) using the NPRS by subject immediately (approx.+3 min) after end time of device administration (see section 6.4.14)
- Pain assessment (during recovery from treatment) using the NPRS by subject every 15 min (approx. ±3 min) after end time of the device administration for 60 min post-treatment (see section 6.4.14)
- Perform visual examinations approximately 30 min after device administration (see section 6.4.8)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- Explain again diary use to the subject and documentation of injection site reactions / symptoms of interest (see section 6.4.19)
- Advise the subject prior to discharge to follow restrictions specified in section 6.3.8.
- Schedule an appointment for telephone visit and the next on-site visit.

6.5.13 *Visit RT2a - Telephone Visit (24 to 48 hours (±4 hours) after touch-up treatment)*

Only in case of touch-up treatment at Visit RT2

Note: The time of the telephone call has to be documented; it has to be conducted 24 to 48 hours (±4 hours) after the end of injection at Visit RT2 (see section 6.4.9)

- Ask for any changes in AEs and new AEs (see section 14) including AESIs (see section 14.1)

  In case of an AE including vision changes, neurological issues or an unbearable injection site reaction an unscheduled on-site visit should be performed (see section 6.5.17).
- Ask for changes in concomitant treatments (see section 6.4.7)
- Remind the subject to document injection site reactions / symptoms of interest in the diary (see section 6.4.19)

6.5.14 *Visit RT2b – Safety follow-up (2 weeks (±3 days) after touch-up treatment)*

Only in case of touch-up treatment at Visit RT2

- Record any changes in AEs and new AEs (see section 14) including AESIs (see section 14.1)

  In case of an AE including vision changes, neurological issues, or an unbearable injection site reaction an unscheduled on-site visit should be performed (see section 6.5.17).
- Record changes in concomitant treatments (see section 6.4.7)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4)
- Review subject diary regarding injection site reactions / symptoms of interest; confirm review (see section 6.4.19)
- Perform visual examinations (see section 6.4.8) and review respective exclusion criteria (see section 6.3.5)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)

6.5.15 *Visit RT3 to RT5 - Week 4 to Week 24 (after last injection)*

Through the follow-up phase after repeat-treatment the following visits will be performed:

- Visit RT3 – Week 4 (± 5 d) after last injection
- Visit RT4 – Week 12 (± 7 d) after last injection
- Visit RT5 – Week 24 (± 7 d) after last injection

  Note: Last injection refers to either
  - **Visit RT1** for subjects **without** touch-up treatment, or
  - **Visit RT2** for subjects **with** touch-up treatment (i.e., TUP2)

The following assessment will be performed:

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)

- Record changes in concomitant treatments (see section 6.4.7)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4)
- Perform visual examinations (see section 6.4.8)
  - If applicable: Perform basic neurological examination (F.A.S.T) (see section 6.4.9)
- Review subject diary and documentation of injection site reactions / symptoms of interest; confirm review (see section 6.4.19) – only Visit RT3
- Perform body weight measurement (see section 6.4.3)
- MVDSS – blinded evaluator at the site (see section 6.4.13)
- NLF-SRS –blinded evaluator at site (see section 6.4.14)
- FACE-Q™ – Satisfaction with overall outcome of treatment (see section 6.4.17) – subject
- FACE-Q™ – Satisfaction with cheeks (see section 6.4.18) – subject
- Schedule an appointment for the next on-site visit – Visits RT3 and RT4 only

6.5.16 *Early Termination Visit*

At Early Termination Visit all attempts should be made to perform the assessments described for

- Visit 9 (SV1) if withdrawn during initial treatment phase (see section 6.5.8)
- Visit SV2 to SV4 if withdrawn during screening phase for repeat-treatment (see section 6.5.9)
- Visit RT5 if withdrawn during repeat-treatment phase (see section 6.5.15)

The following assessments are recommended to be completed at a minimum:

- Record any new AE or changes of AEs (see section 14) including AESIs (see section 14.1)
- Record changes in concomitant treatments (see section 6.4.7)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4)
- Perform visual examinations (see section 6.4.8)
  - If applicable perform neurological examination (F.A.S.T) (see section 6.4.9)
- MVDSS – blinded evaluator at the site (see section 6.4.12)

Only in case of Early Termination Visit during initial treatment phase (i.e., prior to Visit 9 (SV1)):

- Perform clinical photography (see section 6.4.11)
- Upload the photos for independent blinded photographic reviewer (MVDSS) (see section 6.4.13) and volumetric change measurement (see section 6.4.12)

6.5.17 *Unscheduled Visit*

An unscheduled visit may be performed at any time during the study if judged necessary by the treating investigator, such as

- severe or serious injection site reactions
- clinically significant AE including AESIs (see section 14.1)
- suspected or confirmed pregnancy.

In case the unscheduled visit results in early termination of the subject, the assessments for the Early Termination Visit should be performed (see section 6.5.16). Details of the event are to be recorded in the subject's records and in the eCRF.

6.6 Factors that may compromise the outcome

There are no foreseeable factors that may significantly compromise the outcome.

Subject eligibility criteria and prohibition of concomitant treatments and aesthetic procedures that may affect the outcome are carefully defined.

A substantial body weight change during the investigation period could possibly affect the results in individual subjects. This may obscure the effectiveness of the device at individual level. This factor will be controlled by monitoring body weight throughout the investigation (see section 6.3.8).

Beard longer than three-day beard, or excessive facial hair as well as prolonged exposure to sunlight or ultraviolet (UV) radiation and may affect the assessments. Subjects will be advised to avoid and to use daily skin care with UV protection in face throughout the entire clinical investigation (see section 6.3.8).

It is possible that women will prevail in the study population because they still more often seek facial aesthetic procedures than men. This potential gender imbalance will reflect common practice and is not considered relevant since available data on soft tissue fillers do not indicate any gender-related effect on treatment outcomes.

It may also happen that persons of color are enrolled in less numbers. When selecting the study sites, however, care was taken to ensure that adequate numbers of subjects with Fitzpatrick Skin Types (FST) IV, V, or VI will be enrolled to evaluate the safety profile for the subjects with the darkest skin types. To avoid disproportionate enrollment patterns with potential influence on the results FST enrollment levels were implemented (see section 6.3.2). In any case, every effort possible will be taken to enroll males and all Fitzpatrick Skin Types.

Changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information for protocol-specified procedures. The sponsor will implement measurements to prevent an influence on the outcome measures due to COVID-19 pandemic, as appropriate (see section 4.4). However, if changes are unavoidable, specific information will be captured in the subject´s source records and in the eCRF that explains the relationship to COVID-19 for missing protocol-specified information. The information will be summarized in the clinical investigation report (see section 8.5) or in a separate study-specific document, as applicable.

6.7 Monitoring and Monitoring plan

The conduct of this clinical investigation will be monitored by the sponsor’s representative, who will appoint one or more monitors. The extent of monitoring and source data verification will be specified in the Monitoring plan.

Prior to initiation of the clinical investigation at any of the investigation sites, the Monitor will discuss the CIP, the eCRF and other investigation-related documents and forms with the investigator and their staff, and verify that all prerequisites for the initiation are met. No subject should be enrolled into the investigation before this site initiation visit.

During the investigation, further monitoring visits will be performed according to GCP, the applicable standard operating procedures, and local regulations. At each visit the monitor will check the progress of enrolment, will review source data for adherence to the CIP, review eCRFs against source data for completeness, accuracy and consistency, and will also check if the device has been stored, dispensed and accounted for according to respective specifications.

The monitor will inform the investigator or their authorized designee on any error in the eCRF and will ensure that appropriate data corrections or clarifications are made in appropriate manner. In case of any other observed default, the monitor will inform the investigator and, when appropriate, the sponsor as well. The monitor will discuss and agree with the investigator suitable corrective actions and will follow-up their implementation.

Upon completion of the investigation, the monitor will ensure that all investigator's records are accurate and complete, all documents needed for the sponsor's files are retrieved, the remaining investigation supplies, including the device, are disposed of, and that all previously identified issues have been resolved.

The investigator and their institution must permit the monitoring of the investigation and must provide the monitor a direct access to those portions of the subject's source records, which directly concern this clinical investigation. Furthermore, key personnel at the site involved in the investigation must be available to assist the monitor during the monitoring visits.

6.8 Audits and inspections

The investigator will permit study related audits, IRB/EC review, and regulatory inspections, providing direct access to source data / documents.

Audits of the clinical investigation may be conducted by the sponsor or external organizations designated by the sponsor to evaluate compliance with the CIP, written procedures, GCP and the applicable regulatory requirements.

A risk-based approach will be used for selection of investigator sites for an audit. The following criteria may be used as a guide for site selection (including but not limited to):

- Study specific requirements.
- Sites with high and/or rapid enrolment.
- Negative outcome from regulatory inspections (e.g. Form FDA 483 issued).
- Level of professional experience of the assigned Site Monitor/CRA.
- Input from other sources (e.g., CROs, CRAs, project team members, centralized Monitoring findings, etc.).
- Previous experience with the investigator and/or site, including, but not limited to:
    - Performance and/or regulatory history
    - Sites with high volume of clinical studies currently active
    - Sites with less experience in clinical studies
    - Sites with high incidences of (Serious) Adverse Events (S)AEs)
    - Sites without or low incidence of SAEs and/or AEs when SAEs and/or AEs are expected
    - Sites with high enrollment and no SAEs/AEs
    - Investigator sites in countries that Croma has not conducted studies previously
    - Frequency of deviations/violations
    - Sites with a high frequency of CRA turn-over or backlog of monitoring visits.
- Sites that have not been the subject of other audits or inspections (e.g., Co-Visit Audit, Sponsor Site Audits, Regulatory Inspections) within the prior 6 months.
- Sites with an adequate number of enrolled subjects to ensure sufficient data for review during the audit.

A visit may be arranged by the sponsor or sponsor's representative in order to audit the investigation site and the investigation documents, which originate there. The auditor(s) will usually be accompanied by the monitor or the project manager. The investigator will be informed about the outcome of the audit.

In addition, inspections by health authority representatives, including foreign authorities, are possible at any time. The investigator should notify the sponsor and/or sponsor's representative [redacted]) of any such inspection immediately.

6.9 Quality and risk management

The sponsor will implement a system to manage quality throughout all stages of the study process in accordance with GCP, applicable regulations, and sponsor's / CRO's procedures (e.g., written SOPs).

The system implemented will focus on study activities essential to ensure human subject protection and the reliability of study results. The methods used to assure and control the quality of the investigation should be proportionate to the risks inherent in the investigation and the importance of the information collected. All aspects of the study should be operationally feasible and should avoid unnecessary complexity, procedures, and data collection. During Clinical Investigational Plan development processes and data that are critical to ensure human subject protection and the reliability of trial results were identified.

In general, risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., study design, data collection, informed consent process).

The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Predefined quality tolerance limits will be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Quality management activities must be documented and communicated to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

Details and consequences resulting from the ongoing risk management process are dealt with in the study specific risk management plan filed in the TMF.

7 Statistical considerations

Planned statistical analyses are briefly summarized below. Data analyses will be described in detail in the Statistical Analysis Plan (SAP).

7.1 Sample size and hypothesis

The primary outcome measures for effectiveness will be 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® VOLUME Lidocaine based on the blinded evaluator´s live assessment at Week 24 after last injection of initial treatment phase, while pB is the corresponding response rate for [redacted]. Thus, a negative value for this difference means that the response rate of saypha® VOLUME Lidocaine is lower than the response rate for [redacted].

The non-inferiority margin is -10%.

Further assumptions for sample size calculation:

- Response rate at Week 24 for saypha® VOLUME Lidocaine is 85.6%
- Response rate at Week 24 for [redacted] is 85.6%
- Randomization ratio 2:1

Based on these assumptions, 437 subjects (saypha® VOLUME Lidocaine: n=291, [redacted]: n=146) will be necessary in order to achieve power exceeding 83% with a one-sided α of 2.5%. Assuming 10% exclusion from PPS results in 486 subjects to be randomized. Adding 6% screen failures yields approximately 516 subjects to be enrolled.

Concerning FAS, it is expected that only very few subjects will be regarded as non-responder due to missing data for the primary effectiveness endpoint. Response rates at Week 24 after last injection of the initial treatment phase may be slightly smaller than assumed above. Due to the increased sample size in the FAS (more than 10% compared to the PPS) it is expected that the power will be adhered as specified above.

Sample size calculation was done using SAS® version 9.4.

Approximately 300 subjects are estimated to qualify for repeat treatment.

7.2 Analysed data sets

Safety Analysis Set (SAF)

The SAF comprises all subjects who were randomized and received at least one treatment with device (test device or the comparator device). Subjects in the SAF will contribute to the evaluation “as treated” i.e., the subjects’ assignment to the treatment group will be based on the device administered.

Full Analysis Set (FAS)

The FAS consists of all randomized subjects who received at least one administration of the test device or the comparator device. The statistical evaluation of the FAS will follow the intention-to-treat (ITT) principle and subjects will contribute to the evaluation “as randomized”.

Per-Protocol Set (PPS):

The PPS is defined as a subset of the subjects in the FAS without major protocol deviation(s) affecting the primary effectiveness endpoint and assessed as ‘major excluding from PPS’.

The relevance of protocol deviations will be assessed at the interim and final Data Review Meetings (DRMs). Protocol deviations will be assessed as either “minor” or “major”. Major protocol deviations that could directly interfere with analysis of the primary effectiveness endpoint will be further assessed as either ‘major *excluding* from PPS´ or `major *not* excluding from PPS´. Randomization errors will be considered ‘major excluding from PPS’.

The criteria for this assessment will be defined before analysis in Protocol Deviation Manual. Listings will be prepared to assess the eligibility of all subjects during the (i)DRM.

All effectiveness analyses for the initial treatment phase will be conducted using the PPS and the FAS. The effectiveness analysis for the repeat treatment phase will be conducted using the FAS only. Safety analyses will be based on the SAF.

7.3 Methods of analysis

The evaluation of the primary and secondary effectiveness endpoint(s) will be performed both in the Per-Protocol Set (PPS) and in the Full Analysis Set (FAS) for the initial treatment phase, and only for the FAS for the repeat phase.

Unless otherwise specified, all measurements will be summarized descriptively at each visit by treatment group.

In general, continuous variables will be summarized using the following descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data will be described using absolute and relative frequencies by category. Shift tables will be provided, where appropriate. For assessments over time, mean values may be plotted to explore the trajectory over time. All descriptive summaries and plots will be based on in-trial data (i.e., without imputation) unless otherwise specified.

In addition, estimated treatment differences will be presented together with two-sided confidence intervals and corresponding p-values, if appropriate. A statistical analysis plan (SAP) will be written in

addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalized before database lock.

7.3.1 *Interim analysis*

An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit 48 weeks after their last injection during the initial treatment phase (Visit 9 (SV1)).

Summary tables and subject data listings will be provided for the SAF and the FAS and all variables that are outlined in detail in the IA section of the final SAP.

The SAP has to be finalized prior to the IA database lock. The IA database will be cleaned and a data base lock prior to export for data analysis will be done.

7.3.2 *Final analysis*

Final analysis will be done after completion of the investigation (i.e., Visit RT5) by all subjects.

7.3.3 *Subject disposition*

Summary tables will be provided for the following subject characteristics:

- Number of subjects, both screened and received at least one administration of device, included in the study.
- Number of subjects by visit.
- Number of subjects included in the SAF, FAS and PPS.
- Number of subjects withdrawn from the study and the reason for withdrawal

Subjects who prematurely discontinue the investigation after receiving at least one dose of device will be defined as dropouts, see section 6.3.11.

7.3.4 *Demographics and baseline characteristics*

Summary statistics for demographic and baseline characteristics, including age, gender, race/ ethnicity, and other relevant study entry criteria will be prepared for the SAF. In addition, demographic and baseline characteristics including age, gender, race/ ethnicity as well as injection equipment will be presented by study site.

7.3.5 *Medical and aesthetic procedures history*

Medical history (incl. concomitant diseases) and aesthetic procedures history will be encoded using the Medical Dictionary for Regulatory Activities (MedDRA) system. These data will be presented for the SAF using frequency tables.

7.3.6 *Prior and concomitant treatments*

Prior and concomitant treatments (medication / non-pharmacological procedures) will be coded using MedDRA and the WHO DRUG Global, respectively. These data will be presented for the SAF using frequency tables.

7.3.7 *Effectiveness endpoints*

Primary effectiveness endpoint

The PPS and the FAS will be both considered equally important for the primary analysis.The analysis of the primary endpoint will be performed on the PPS (primarily) and FAS. Confirmatory testing will be performed in a hierarchical ordering. Non-inferiority is demonstrated only if the results are consistent for both analysis populations.

Subjects with missing baseline MVDS score and / or missing MVDS score at Week 24 after last injection of the initial treatment phase will be considered as non-responders for the primary analysis on the FAS.

To calculate the primary outcome measure, the improvement over Baseline in the MVDS score assessed live by the blinded evaluator at the site at Week 24 after last injection of the initial treatment phase by subtracting the Midface Scale grade obtained at Baseline. The proportion of subjects with MVDS score improvement of ≥1 point will be then calculated for each treatment group.

The primary outcome measure for effectiveness will be evaluated by means of a one-sided two-group Farrington-Manning test of proportions with the following hypotheses:

- H0: pA – pB ≤ d0
- H1: pA – pB > d0.

At this, pA is the response rate for saypha® VOLUME Lidocaine and pB is the response rate for [redacted], and d0 equals to -0.1. Thus, a negative value for this difference means that the response rate of saypha® VOLUME Lidocaine is lower than the response rate for [redacted] In addition to this, the response rates for both treatment groups along with their Clopper-Pearson exact 95% CIs will be tabulated.

The study decision will be based on a Farrington-Manning-statistics with a one-sided type I error rate level of 0.025.

In addition, ***sensitivity analyses*** of the primary effectiveness endpoint will be performed on the FAS addressing the different reasons for non-adherence and covering the following aspects (among others) to underline the robustness of the results:

- Complete case analysis: In this analysis only those subjects will be included for whom the primary endpoint could be calculated;
- Subjects with non-allowed concomitant medication / treatments before Week 24 after last injection of the initial treatment phase may be regarded as non-responder.
- Multiple imputation under MNAR assumption for imputing missing MVDS scores at Week 24 assessed live by the blinded evaluator.

Secondary effectiveness endpoints

All secondary effectiveness endpoints (see section 5.3.3) will be analyzed in an exploratory manner by means of descriptive statistics.

The descriptive tables will show the statistics described at the top of section 7.3 by time of assessments as well as for the changes from baseline (if applicable).

Concerning the follow-up for initial treatment, the last measurements / assessments before first treatment are defined as baseline. Concerning the time after repeat-treatment, the measurements / assessments at Visit RT1 before first repeat-treatment are defined as baseline.

Assessments on the MVDSS (see section 6.4.13) as well on the modified GAIS (see section 6.4.16) will be presented for each possible category. In addition, shift tables from baseline will be provided for the assessments on the MVDSS.

Concerning nasolabial folds measured by NLF-SRS based on the blinded evaluator's live assessment, shift tables from baseline will be presented for Week 4, 8, 16, 24, 36, and Week 48 after last injection of initial treatment phase.

Volume change measurements will be presented for each of the specified areas of interest (left side, right side, and total) at each time of assessment including change from baseline (see section 6.4.12).

The subject's satisfaction with overall treatment outcome will be evaluated based on the scores for 6 positively worded items that ask the subjects to indicate how they feel about the result of their most recent facial aesthetic procedure (FACE-Q™ "Satisfaction with Outcome", see section 6.4.17).

Correspondingly, the subject's satisfaction with overall midface augmentation will be evaluated based on the scores for 5 items concerning the appearance of cheeks (FACE-Q™ "Satisfaction with Cheeks", see section 6.4.18).

Concerning each injection, the subject's assessment of pain intensity on the Numeric Pain Rating Scale will be described at each time of assessment (immediately after the injection and after 15-minute intervals up to 60 minutes post-treatment) (see section 6.4.14).

The injection volume applied (right midface, left midface, and total), the duration of each injection as well as the injection technique and details concerning the injection equipment will be summarized for each injection time point and treatment group (see section 6.4.9).

In addition, at least the following main secondary effectiveness endpoints will be compared between the treatment groups by means of 95% confidence intervals for the differences in

- proportion of subjects with response on the MVDSS as assessed by the blinded evaluator at the site
- proportion of subjects with response on the MVDSS as assessed by the independent blinded photographic reviewer
- mean change in midface volume deficit measured on the 5-point MVDSS and based on the blinded evaluator´s live assessment
- proportion of subjects with global aesthetic improvement (in modified GAIS) as assessed by the subject
- proportion of subjects with global aesthetic improvement (in modified GAIS) as assessed by the blinded evaluator

This will be done for each time of assessment during follow-up for initial treatment.

The resulting 95% confidence intervals for proportions will be presented in forest plots and the boundaries of the confidence intervals evaluated with respect to their clinical relevance in an exploratory manner.

The investigational device during repeat-treatment phase (saypha® VOLUME Lidocaine) will be evaluated descriptively using the following other endpoints:

- The percentage of responders on the 5-point MVDSS, based on the ***blinded evaluator´s live*** assessment at Week 4, 12 and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1
- Mean change in midface volume deficit measured on the 5-point MVDSS and based on the blinded evaluator´s live assessment at Week 4, 12, and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1
- Shift from baseline (Visit RT1) in NLF-SRS based on the blinded evaluator´s live assessment at Week 4, 12 and 24 after last injection during repeat-treatment phase
- The extent of subject´s satisfaction with overall treatment outcome at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the subject using the Face-QTM Questionnaire "Satisfaction with Outcome"

- The extent of subject´s appearance appraisal at Week 4, 12 and 24 after last injection of repeat-treatment phase as assessed by the FACE-QTM questionnaire “Satisfaction with Cheeks” compared to the score at Visit RT1
- Subject evaluation of pain after each treatment (repeat and touch-up-treatment) on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable
- Injection volume required to achieve optimal aesthetic result at each treatment (repeat and touch-up treatment together)

7.3.8 *Safety endpoints*

AEs will be encoded using the MedDRA thesaurus in the most recent version available at the beginning of the study. This version will be used throughout the entire study. Updates of the MedDRA thesaurus will not be applied afterwards.

All AEs will be listed by subject, user or other persons, date and time since last treatment. Incidence of AEs will be summarized by preferred term (PT) and system organ class (SOC), and also by intensity, duration causal relationship to the device or procedure, and seriousness.

The frequency and occurrence rate, maximum intensity, overall duration, and seriousness of injection site reactions within four weeks (28 days) after baseline treatment, after repeat-treatment injection, respectively, and 6 weeks in case of touch-up treatment, will be summarized by device.

The number and percentage of subjects, user or other persons with at least one device deficiency will be summarized. Details concerning device deficiencies will be listed by treatment group and subject.

Urine pregnancy tests will be listed only.

The data will be presented for the SAF using frequency tables.

7.3.9 *Multicentre trial*

This study will take place in approximately 16 investigation sites. Inclusion of subjects is planned to be as equally distributed as possible between the sites (see section 6.3.1 for details).

Possible country (or geographical cluster) and study site effects will not be included in the primary analysis, but will be evaluated on an exploratory level by tabulation of the primary and key secondary endpoints by country (or geographical cluster) and study site, respectively.

Any pooling of study sites with few subjects as well as pooling of countries in geographical clusters will be agreed and specified in the SAP before database lock.

7.3.10 *Analysis of subgroups*

The primary analysis will be based on the total trial population. Besides the total study population, the following subgroups will be analyzed by descriptive statistical methods for the primary and the main secondary effectiveness endpoints:

- Injection equipment: Needle versus cannula
- Gender: Female versus male
- Fitzpatrick skin type
- Race and ethnicity
- Age groups

In order to gather information on potential heterogeneity of treatment effects between the different subgroups, an exploratory analysis will be performed using logistic regression models with subgroup as covariate and a treatment by subgroup interaction. 95% confidence intervals will be calculated for the treatment difference in each subgroup and presented in a forest plot.

In addition, incidence of AEs will be summarized by preferred term (PT) and system organ class (SOC) within all of the above-mentioned subgroups. Frequency and occurrence rate of injection site reactions will be summarized within all of the above-mentioned subgroups.

The detailed statistical analysis of subgroups will be described in the statistical analysis plan (SAP).

7.4 Subject data listings

All recorded data will be presented in subject data listings.

7.5 Missing data

Adverse events with unknown onset times will be counted as post device administration AEs. AEs with missing relationship to device will be counted as related AEs (ADEs).

Concerning statistical evaluation of the primary effectiveness endpoint (primary analysis, sensitivity analyses) missing data may be regarded as non-response.

In addition, there will be no imputation of missing values. All data will be analyzed as they appear in the data base.

7.6 Software used for statistical analysis

The SAS software version 9.4 or higher will be used for the statistical analysis and for the reporting of this study.

7.7 Deviations from the planned statistical analysis

Any deviations from the planned statistical analysis have to be discussed in the final study report and should be defined in the SAP. If the deviation has any impact on the effectiveness analysis, the deviation has to be specified in an amendment to the CIP.

7.8 Amendments

If an amendment impacts the integrity of the clinical investigation, the data collected before and after the amendment must be analyzed statistically to assess the effect of the amendment on effectiveness or safety analysis. This analysis must be included in the clinical investigation report.

7.9 Randomization

The randomization list will be prepared by a biostatistician using SAS, Procedure PLAN. The randomization list is a document that consists of randomization numbers, which uniquely assign each subject to one of the two devices at a 2:1 ratio (test device: comparator device). Randomization will be performed using randomly permuted blocks.

8 Data handling and data management

8.1 Source documents and other records maintained by the investigator

It is the treating investigators' obligation to assure documentation of all relevant data in the subject's source record, such as the informed consent process and date of enrollment into the clinical investigation, medical / aesthetic history, prior and concomitant treatments, visit dates, clinical observations including AEs (including reporting and follow-up of AEs), results of all assessments, information related to medical device application, and the date of subject's exit from the investigation, including the reason.

Any form completed by the subject (including the eDiary) is also considered as a source document and must be kept in the subject's source record. The location of the source documents shall be documented.

In addition, the investigator must maintain all other essential documents pertaining to the clinical investigation as defined by GCP and applicable regulatory requirements.

8.2 Case report forms

A CRF will be completed for each subject who signed an ICF. Data on each subject screened / randomized in the investigation will be recorded pseudonymously in the web-based validated electronic CRF (eCRF), which is designed to accommodate the specific features of the clinical investigation design

and complies with regulatory requirements on electronic data transfer. The system is compliant with 21 CFR Part 11 regulation.

Only the treating investigator and their authorized designees are allowed to make entries in the eCRF. This will be regulated by appropriate read and write access. Completed eCRFs will be electronically signed by the treating investigator or their authorized designee.

All site personnel, sponsor and CRO personnel seeking access must go through a thorough training process before they are granted access. Furthermore, all study personnel will be instructed how to fill in the CRFs. The CRF Completion Guide will provide additional information additional instructions for CRF documentation.

Data required according to this protocol are to be recorded on the eCRFs as soon as possible. The Principal Investigator must assure that all data are entered completely, and accurately according to the CRF Completion Guide, and is ultimately responsible for conformance of CRF entries with source data.

Completed eCRFs will be electronically signed by the Principal Investigator or their authorized designee (only treating investigators).

Any subsequent change, deletion or addition will be recorded by an audit trail system, which will require re-signing of the CRF.

Data recorded from screening failures

The minimum data to be recorded for screening failures in the subject´s source records and in the CRF will be given in the CRF Completion Guide.

8.3 Data management procedures

All data management activities will be conducted by the sponsor's representative following their standard operating procedures. They will build the database and handle the data cleaning process, including logical checks, medical checks, and query process. Subject data necessary for analysis and reporting will be transmitted into a validated database. Details on data handling and data cleaning will be described in the Data Management Plan (DMP).

Procedures for verification, validation and securing of electronic clinical data management systems (CDMS)

The study specific eCRF and ePRO are implemented on a validated CDMS. The validation requirement for the study specific eCRF and ePRO is served by the following components:

- The data entry screen testing and edit check testing serve as evidence of a database that performs for its intended use of capturing and cleaning of clinical data (user acceptance testing).
- The validation of electronic clinical data management systems will be done according to the regulatory requirements and respective SOPs.
- Any validation is performed on a self-contained development and test environment of the CDMS, eCRF and other applications. These environments are identical to the productive version. The test data are not mixed with data of other environments.

Procedures for Data Cleaning

Computerized validated check programs on completeness, correctness, plausibility (such as range checks, cross-checks, edit checks) will verify the data according to the listing of all planned programmed data integrity checks, the Data Cleaning Plan (DCP). All identified discrepancies will be queried and addressed to the respective site staff. The investigator or their authorized designee must carefully answer any query issued by Data Management.

Coding of concomitant diseases, adverse events and concomitant treatments will be coded using the MedDRA system and the WHO Drug Global. Device deficiencies will be coded using International Medical Device Regulators Forum (IMDRF) Annex A.

Upon completion of data collection and all data cleaning activities, i.e., when the database is considered complete and accurate, it is considered soft locked and reviewed by the sponsor together with the clinical investigation team during the DRM.

The database will be hard locked after sponsor's approval. All changes will be tracked by audit trail. Once hard locked the final clean datasets will be exported for final statistical analysis.

Interim analysis

An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit at Week 48 after last injection of the initial treatment phase (Visit 9 (SV1)). For the interim analysis the database will be cleaned and a data base lock prior to export for data analysis will be done.

8.4 Data retention

The investigator shall retain all clinical investigation records (including all individual subject-related documents (e.g., subject´s questionnaires, eDiary and ICF), device-related records, investigation-related correspondence, and all other documents contained in the Investigator's Site File) during the clinical investigation and for the period required by the applicable regulatory requirements, or the time period specified in the contract between the sponsor and the investigator, whichever is longer.

In any case, the investigator must contact the sponsor in writing prior to destruction of any records pertaining to the clinical investigation, to get confirmation that these no longer need to be retained. In addition, the sponsor should be informed in writing if the investigator plans to leave the site or chooses to store the records at a different physical address than the site address, to ensure traceability of the records and appropriate arrangements for the transfer of custody.

The source records of subjects taking part in the investigation must be retained in accordance with local legislation and the maximum period permitted by the hospital, institution or private practice.

8.5 Report of the clinical investigation (CIR)

Following completion of the clinical investigation, the results will be evaluated, and the Clinical Investigation Report (CIR) will be generated. Based on the interim analysis results an interim Clinical Investigation Report (iCIR) will be generated. Both, the iCIR and CIR will include a summary of all available data, statistical measures, tabulated results, graphical results (if any), and interpretations. A complete list of all adverse events will be enclosed. The reports will be submitted to relevant authorities as appropriate, within the timeframes defined per national regulation and/or to the IRB/EC as applicable.

9 Amendments to the clinical investigation plan (CIP)

Any change of this CIP can only be made in form of a written amendment. Such amendment must be discussed, agreed upon and signed by the sponsor, the Coordinating Investigator and the Principal Investigators before implementation.

Any amendment which may affect the validity of the data or information resulting from original CIP, the risk-benefit ratio for the subject, the scientific soundness of the investigation, change of the principal investigator or the rights, safety or welfare of subjects taking part in the investigation will also have to be reviewed and approved by the IRB/EC and regulatory authorities, if applicable, prior to implementation.

Amendments with impact on procedures to be performed, risk-benefit ratio for the subject and/or the well-being of the subjects require additional informed consent, which must be given in writing by all subjects enrolled in the clinical investigation who are affected by the amendment.

10 Deviations from the clinical investigation plan

A CIP deviation is a failure to follow, intentionally or unintentionally, the requirements of the CIP. As required by national regulation or guidelines, requests for deviations and reports of deviations will be provided to the IRB/EC if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

Under emergency circumstances, deviations from the CIP may proceed without prior approval by the sponsor and favourable opinion of the IRB/EC if the rights, safety and well-being of human subjects need to be protected. Such deviations will - however - be documented and reported to the sponsor and the IRB/EC as soon as possible in accordance with national regulations. **No waivers to the CIP will be granted by the sponsor.**

The investigator must maintain accurate, complete and current records of any deviation from the CIP, including the date and reason for each deviation.

The investigator shall notify the sponsor and the reviewing IRB (as applicable) of any deviation from the CIP made to protect the life or physical well-being of a subject in emergency as soon as possible, but in no event later than five working days after the emergency occurred.

All CIP deviations will be listed and their impact on evaluability of respective subjects will be discussed during the interim DRM and during DRM prior to the hard data base lock.

11 Device accountability

The device accountability is described in section 6.2.6.

12 Statements of compliance

This clinical investigation will be conducted in compliance with this CIP and the following standards and regulatory requirements:

- International Standard ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good Clinical Practice (GCP)
- Declaration of Helsinki, in its currently adopted version
- Applicable national medical device laws / regulations.

By acting in accordance with this CIP, the investigators and the investigation site personnel fulfil the requirements of ISO 14155:2020.

The clinical investigation will not commence until a favorable opinion from the respective EC has been received. All additional requirements imposed by the IRB/EC will be followed. A prior regulatory approval will also be sought, if required by national regulations.

Insurance coverage for damages emerging from the clinical investigation will be provided according to applicable legal requirements.

13 Informed consent process

The informed consent form (ICF) must be notified to, or approved by, the IRB/EC and regulatory authorities, if required by local regulations.

Written informed consent must be obtained from each subject prior to initiation of any of the investigation-specific procedures.

The investigator or their authorized designee must give each subject complete and adequate verbal and written information about the investigation. The investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical investigation. It must be emphasized that participation is voluntary and that the subject has the right to withdraw from the clinical investigation at any time without any justification and without prejudice. They also must be informed that the quality of their medical care will not be adversely affected if they decline to participate in the investigation or in case of subsequent consent withdrawal. Before consenting, the subject must be left with ample time to consider and ask questions.

The subject must then sign and date the Informed Consent Form (ICF) prior to the conduct of any investigation-related procedures. The consent taker (the investigator or, according to local laws, their designee) must sign and date the ICF as well.

The investigator will document the entire informed consent process in the subject´s source record (e.g., date (and time as applicable) of informed consent / signature, who has informed the subject, and that s/he has informed the subject, that the subject had ample time to consider, that the subject and the investigator have signed the ICF). In addition, the date (and time as applicable) of informed consent / signature will be recorded in the eCRF.

A signed and dated copy of the ICF will be given to the subject for their records. The other copy of the signed and dated ICF will remain in the Investigator´s Site File.

If subject's participation in the investigation or decision to participate in the investigation is or may be affected by an amendment to the CIP (e.g., a change in any procedure) or any other important new information, which may relate to the subject's willingness to continue participation in the clinical investigation, the ICF must be amended accordingly, and the subject must sign the amended ICF indicating that they re-consent to participate in the clinical investigation.

14 Adverse events, adverse device effects and device deficiencies

14.1 Definitions

Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the device and whether anticipated or unanticipated. This definition includes events related to the test device, the comparator device and events related to the procedures involved.

- For subjects taking part in the clinical investigation this definition includes events related to the device and procedures involved, as well as pregnancy in females.

  Note 1: The event of pregnancy meets the SAE criterion if it results in a spontaneous abortion or a congenital anomaly or it is suspected that the device or study procedure interacted with the contraceptive method and has led to pregnancy. Pregnancy is not considered an (S)AE *per se.*

  Note 2: Injection site reactions the subject is specifically asked about in the subject diary (see section 6.4.19) will ***not*** be collected as AEs during the first four 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). Any injection site reactions that continue for more than 28 days post-administration will be assessed and documented as AEs by the treating investigator as described in the sections below.

  Note 3: Injection site reactions the subject is ***not*** specifically asked about in the subject diary (i.e., 'Other' symptoms at the injection site not listed in section 6.4.19) and that are ***not*** synonymous to one of the pre-defined injection site reactions will be assessed and documented as AEs by the treating investigator as described in the sections below.

- For users or other persons this definition is restricted to events related to the use of both devices (test device or comparator device).

Adverse Device *Effect* (ADE) is an AE related to the use of the device.

This includes This definition includes

- AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device
- any event resulting from use error or from intentional misuse of the investigational medical device.
- the comparator device

Serious Adverse Event (SAE) is an AE that led to any of the following conditions:

- Death;
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

- A life-threatening illness or injury, or
- A permanent impairment of a body structure or a body function including chronic diseases, or
- In-subject or prolonged hospitalization, or
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

- Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

Planned hospitalization for pre-existing condition or a procedure required by the CIP without a serious deterioration in health is not considered a SAE.

Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

Serious health threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals (according to ISO 14155).

Adverse Events of Special Interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such events may require further investigation in order to characterize and understand them. Depending on the nature of the event, rapid communication by the sponsor to other parties may also be needed (see section 14.5).

For this clinical investigation, AEs of special interest are defined as embolic events, with possible, probable, or causal relationship to an intravascular injection of the device, as:

- Changes in vision (i.e. loss of vision, blurriness, double vision, pain in or around your eye, blindness, blind spots, problems moving the eyes)
- Skin changing color around the eyelids or around the site of injection
- Other embolic phenomenons, e.g., stroke, skin necrosis, or impending necrosis

Unanticipated (Serious) Adverse Device Effect:

- **Unanticipated Serious Adverse Device Effect (USADE)** is defined as a SADE which by its nature, incidence, severity (intensity) or outcome has not been identified in the current risk assessment and the current version of the Investigator´s brochure (IB) (adapted according to ISO 14155)
- ***For USA only*: Unanticipated adverse device effect (UADE)** is defined as any ***serious*** adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity (intensity), or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (according to investigational device exemption (IDE) regulations / 21 CFR 812.3(s)).

Device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the test device or the comparator device.

Device deficiency that might have led to a SAE if a) suitable action had not been taken, or b) intervention had not been made, or c) if circumstances had been less fortunate, is classified as a special type of deficiency and is handled under the SAE reporting system.

14.2 Method of detecting AEs

AEs will be detected by observation and by asking the subject about the occurrence of AEs. Care should be taken not to introduce bias when eliciting AE information from the subject. Open-ended and non-leading verbal questioning is the preferred method and appropriate questions include:

- *"How are you feeling?"*
- *"Have you had any medical problems since your last visit/contact?"*
- *"Have you taken any new medication since your last visit/contact?"*

In order to identify potential AEs post-administration of device safety evaluation 15 minutes after the device administration needs to take place (see section 6.4.20).

All SOI(s) documented by the subject in the eDiary (see section 6.4.19) must be verified by the investigator either by specific questioning of the subject and/or physical examination or visual inspection. SOI(s) *considered clinically significant* should be documented as AE(SI)(s). SOIs that turn out to be not clinically significant (see section 20.5.1 for examples) due to any reason are not considered as AE(SI) and need not to be documented as AE(SI) in the eCRF. However, the investigator should add a statement in the subject's source records why the SOI was not considered clinically significant, i.e., as AE(SI).

All AESIs (serious and non-serious, see section 14.1 for definition) and any other embolic event (regardless of seriousness and / or relationship to device or procedure) resulting from SOI assessment have to be reported by the investigator to the sponsor's representative within 24 hours of awareness of the event (see section 14.5).

In addition, the subjects will be instructed to immediately contact the investigator/investigation site in case of occurrence of any untoward event between visits and an unscheduled visit will be performed (see section 6.5.17). Throughout the entire investigation the investigator should also verify results of all assessments with respect to possible AEs.

14.3 AE/SAE documentation

For each AE the following must be reported:

- Description of the event (event term)
- Seriousness
- Start date
- Intensity
- Action taken with subject (none, medical and/or surgical / non-pharmaceutical procedure)
- Action taken with device (none [no action taken], device withdrawn [no touch-up treatment(s) / repeat-treatment due to AE], device interrupted [touch-up treatment(s) / repeat-treatment later than required by study design due to AE or injection interrupted due to AE during treatment session])
- Outcome
- End date (if applicable)
- The relationship to the device and procedure, respectively

The information will be documented in subject´s source record and in the eCRF.

Each AE and any new information concerning these events has to be documented, even if the investigator feels that it is not connected with the device or procedure.

The AE will be described in precise, standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information (including affected body site(s)). In such cases, the diagnosis will be documented as the AE and not the individual

signs/symptoms. In case of any injection site reaction the exact location (e.g., upper or lower lips) should be clearly noted.

Each AE should be reported separately. The investigator will record all AEs in subject´s (medical) record and on the ”Adverse Events” page of the eCRF. For SAEs, the “Serious Adverse Event Reporting Form” must also be completed. Complete description of all AEs should be also available in source documents of the subject.

Adverse events will be documented beginning after provision of informed consent until the last visit of the subject. The follow-up period will be prolonged outside the investigation, if a related AE is ongoing and not stabilized after 24 weeks after last injection of the repeat-treatment phase (see section 14.6 for details).

AEs initially observed during or after baseline treatment are defined as treatment-emergent AEs (TEAEs). AEs occurring after informed consent but before baseline treatment will be defined as non-TEAEs. Any medical condition that is present prior to day of screening should be considered as medical history (i.e., concomitant disease) and not recorded as an AE. If such condition, however, deteriorates after the device administration, at any time during the investigation, it should be reported as an AE.

If the intensity or seriousness of an AE changes over time, the most severe intensity or seriousness of the AE will be recorded and included in the analysis. No separate AEs will be recorded for each intensity or seriousness level.

Changes in causality assessment should also be clearly documented. AEs related to the device as well as to investigation procedure must be documented. Any medication and non-pharmacological procedure necessary for the therapy of an AE must be recorded on the respective page of the eCRF.

Adverse events in users or other persons

- For any AE in users or other persons the Adverse Event (AE) Documentation Form for Users / Other Persons must be completed according to the Instructions for Completion.
- If the AE fulfills one of the criteria for seriousness the SAE Report Form must be completed, additionally and reporting responsibilities have to be fulfilled (see section 14.5).
- If the AE is related to a device deficiency, the corresponding Device Deficiency Form has to be completed, too (see section 14.9).

14.4 AE assessment

All AEs will be assessed in terms of seriousness, intensity, relationship to the device or clinical investigation procedures, and outcome.

14.4.1 *Seriousness*

The seriousness of an AE is assessed by comparing AE features against the SAE definition provided in section 14.1.

14.4.2 *Intensity*

The intensity of an AE will be graded as follows:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and/or requires medical intervention.

14.4.3 *Causality*

The investigator is obligated to estimate the relationship between each AE/SAE and the test device, the comparator device or clinical investigation procedure. Clinical judgement should be used and relevant documents like Instructions for Use or Investigator´s brochure consulted.

The presence of confounding factors, such as concomitant treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the final analysis all AEs assessed with the relationship “possible”, “probable” or “causal relationship” will be classified as “related”.

The relationship should be determined using one of the following causality levels:[45]

Causal relationship: The AE/SAE is associated with the test device, comparator device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures
- the event has a temporal relationship with the device use/application or procedures
- the event involves a body-site or organ that
  - the devices or procedures are applied to
  - the devices or procedures have an effect on
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible)
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out
- harm to the subject is due to error in use and/or
- the event depends on a false result given by the investigational device used for diagnosis, when applicable

Note: In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

Probable: The relationship with the use of the test or comparator device, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Possible: The relationship with the use of the test or comparator device, or the relationship with procedures, is weak but cannot be ruled out completely.

Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment).

Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Not related: Relationship to the test device, comparator device or procedures can be excluded when:

- the event has no temporal relationship with the use of the device, or the procedures related to application of the device
- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event
- the event involves a body-site or an organ that cannot be affected by the device or procedure

- the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors)
- the event does not depend on a false result given by the device used for diagnosis, when applicable

Note: In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

14.4.4 *Outcome assessment*

The outcome of an AE will be assessed as follows:

Recovered / Resolved:	The subject has fully recovered from the event.
Not recovered / resolved (Ongoing):	The subject has not recovered from this event.
Recovering / Resolving:	The subject is recovering from the event.
Recovered / Resolved with sequelae:	The subject is experiencing the aftereffects of a condition or injury (sequelae).
Fatal (Death):	The subject died due to this event.
Unknown:	The outcome of this event is unknown

14.5 AE/SAE and pregnancy reporting requirements

14.5.1 *General AE/SAE reporting requirements*

Note: For any AE (including a SAE) all appropriate sections of the eCRF must be completed.

Any SAE must be reported by the investigator to **the sponsor's representative immediately but not later than 24 hours** of awareness **of the event via Email**. Contact details will be provided in a separate manual.

This also applies to serious and non-serious AESIs (see section 14.1 for definition), any other embolic event (regardless of seriousness and / or relationship to device or procedure), and any significant AE, which in the investigator's opinion could affect the safety of the subjects taking part in the investigation or the conduct of the investigation.

In general, information about an SAE will be collected and recorded on the SAE Reporting Form. The SAE Reporting Form will be provided by the sponsor´s representative to the investigational sites and will contain additional process information for how to report.

The investigator will be requested to supply as much detailed information as possible regarding the SAE that is available at the time of the initial contact. The investigator should also complete missing or requested information and submit follow-up reports until the SAE has resolved or, in the case of permanent impairment, until the SAE has stabilized.

The sponsor's representative will inform the sponsor about any SAEs immediately after becoming aware of the respective SAE report from the investigator.

Should an SAE occur after the final visit, which is considered at least possibly related to the device or procedure, such events should always be reported to CROMA-PHARMA GmbH or its representative, even after the end of the clinical investigation.

At the end of the clinical investigation, a reconciliation of all reported SAEs will take place and be enclosed as a list in the Clinical Investigation Report.

For further information on reporting and notification requirements per country for Investigators see sections below.

Detailed reporting by the sponsor or sponsor's representative to IRBs/ECs, all Investigators and regulatory authorities will follow pertinent national legislation described in detail in Safety Management Plan (SMP).

Signals from adverse events or device deficiencies that might indicate a serious (public) health threat (see section 14.1) can be detected by either the sponsor or principal investigator but will be evaluated by the sponsor / sponsor´s representative. If required, occurrence of a serious (public) health threat will be reported according to regulatory requirements.

14.5.2 *Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE) reporting*

The investigator must report any SAE/SADE to **the sponsor´s representative immediately but not later than 24 hours** of awareness of the **event via Email**.

The sponsor will report the results of UADE evaluation to all investigators, to the reviewing IRBs and to the respective competent authority (FDA) within ten working days after receipt of the first notice of the effect.

14.5.3 *Reporting of visual disturbances*

For reports received by the sponsor´s representative containing any event relating to incidences of visual disturbances, the following information must be urgently requested.

The request will be made in the form of a query to the site (by using the 'Device Safety Query for Additional Information' form):

- Depth of injection (i.e., subcutaneous or supraperiosteal)
- The injection volume
- The symptoms that were observed
- The time to event onset, and resolution
- Any interventions that were implemented
- The symptoms that were observed
- The time to event onset, and resolution
- Any interventions that were implemented

If a response to the aforementioned queries is not received **within 24 hours**, a follow-up reminder will be sent, and the queries escalated to the Medical Monitor and Project Manager at the sponsor´s representative.

14.5.4 *AESIs and other embolic events reporting*

All AESI (serious and non-serious) and any other embolic event (regardless of seriousness and / or relationship to device or procedure) have to be reported by the investigator to **the sponsor's representative within 24 hours** of awareness **of the event via Email using the SAE Reporting Form.**

The sponsor's representative will report all AESIs and any other embolic event (regardless of seriousness and / or relationship to device or procedure) to the respective competent authority (FDA) in an expedited manner (see sections 14.5.1 to 14.5.3).

14.5.5 *Pregnancy*

Any pregnancy must be notified to the contact given above within the same timelines as an SAE (within 24 hours after being made aware of the pregnancy). The Pregnancy and Lactation Exposure Form will be provided by the sponsor´s representative to the investigational sites and will contain additional process information for how to report. If pregnancy is associated with an SAE (e.g., if the mother is hospitalized for hemorrhage), a separate SAE Reporting Form must be filed in addition to Pregnancy and Lactation Exposure Form. The pregnant subject must be withdrawn immediately from further treatment, if applicable. The pregnant subject may remain in the study for safety assessments during the scheduled study visits.

14.6 AE/SAE and pregnancy follow-up

The investigator will take all appropriate and necessary measures required for resolution of the AE.

All AEs must be followed-up by the investigator until recovery, or until the investigator determines that the subject's condition is stable, or subject's last day of the clinical investigation at the site, whichever occurs first. All subjects excluded from repeat-treatment should continue to be followed until the resolution of all ongoing, related AEs.

All SAEs/AESIs judged to be related to the device (SADEs) must be followed by the investigator until the subject has recovered, recovered with sequelae, died, or until the investigator determines that the subject's condition is stable, whichever occurs first.

In addition, those subjects who have a related AE ongoing (i.e., not recovered / not resolved) and not stabilized (i.e., recovering / resolving) after 24 weeks after last injection of the repeat-treatment phase will be followed for a longer follow-up outside the investigation. The follow-up for these subjects would continue until resolution (i.e., recovered / resolved) or stabilization of the condition (i.e., recovered / resolved with sequelae).

AEs to be followed outside the investigation will be reported to the sponsor´s vigilance department using the Post-Study-AE-Follow-Up Form. Contact details and additional process information for how to report will be given on the respective form.

Any pregnancy must be followed-up until the pregnancy outcome at least once in each trimester and pregnancy outcome (including pregnancy duration and health status of a newborn or cause of premature termination, as applicable) will be reported to the sponsor´s representative using a Pregnancy Query Form for the status of pregnancy. If it is still on-going at the end of the clinical investigation, follow-up will be continued outside of the context of clinical investigation.

14.7 Foreseeable AEs and anticipated ADEs

Foreseeable AEs and anticipated ADEs are listed in section 4.2. Reporting requirements are given in section 14.5.

14.8 Risk assessment process for potentially unacceptable risks

Any person identifying an event or information that could have an impact on subjects', users' or other persons' safety, has an obligation to inform the principal investigator and the sponsor of their concerns.

All potentially unacceptable risks arising during the course of the clinical investigation will be managed by the sponsor / sponsor´s representative following pertinent national legislations.

14.9 Device deficiency

14.9.1 *Device deficiency documentation*

At least the following items need to be documented with in the subject´s source records and the eCRF for each device deficiency:

- Date of device deficiency or detection date of device deficiency
- Description of the device deficiency
- Nature of device deficiency (i.e., malfunction, use error, and inadequate labelling)
- If an individual is affected by the device deficiency (subject, user, or other persons)
- Relationship to an (S)AE, if any
- If the device deficiency could have led to a SADE (including the circumstances)
- Relationship between study intervention and device deficiency
- Action taken with the deficient device

This includes device deficiencies related to the test device or the comparator device.

14.9.2 *Device deficiency reporting requirements*

All device deficiencies must be recorded on a Device Deficiency Reporting Form. The Device Deficiency Reporting Form will be provided by the sponsor´s representative to the investigational sites and will contain additional process information for how to report.

Device deficiencies should be reported by the treating investigator to the sponsor's representative within 24 hours after the site became aware of the deficiency using the same contact as for SAEs (see section 14.5).

If a device deficiency is associated with an AE, the corresponding AE documentation (see section 14.4) and reporting procedures (see section 14.5) must be adhered to as well.

The sponsor's representative will forward the Device Deficiency Reporting Form to the sponsor within 24 hours after receipt of the respective report from the investigator.

14.10 Data monitoring committee

Not applicable.

15 Vulnerable populations

Vulnerable populations will not be included in this clinical investigation.

16 Suspension or premature termination of the clinical investigation

The sponsor reserves the right to terminate the clinical investigation for any reason (e.g., safety, new data on the risk/benefit, ethical or administrative reasons). Written notice, outlining the reasons for the termination, will be submitted to the investigators in advance of such termination. The sponsor will provide instructions if assessments beyond the regular per protocol procedures should be necessary.

The sponsor may suspend enrollment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the CIP or other clinical research requirements.

The investigator, IRB/EC, or regulatory authority (if applicable) may also suspend or prematurely terminate the clinical investigation at the investigational sites for which they are responsible.

If the clinical investigation is prematurely terminated, the sponsor or the sponsor's representative will promptly inform the relevant authority (if applicable) of the termination and its reason(s); the investigator or the sponsor (or representative) will promptly inform the IRB/EC, as specified in applicable regulations.

16.1 Clinical investigation stopping rules in case of vascular occlusion

In the event of any vascular occlusion secondary to dermal filler injection, or other adverse events secondary to such vascular occlusion, and which are avoided or prevented only by urgent treatment, the enrollment and treatment will be suspended, and a root cause investigation has to be conducted to determine the cause of the event. Such investigation will involve the investigator who treated the affected subject and the sponsor or designee.

Such cases, which may include e.g., impending necrosis, subjects with early signs of a stroke, or subjects with vision loss, all of whom undergo urgent treatment and have resolution of their necrosis, stroke, or vision loss symptoms, will result in actions as defined above, during which further enrolment and treatment will be on hold.

- If the treating investigator didn't properly follow the treatment procedure, he/she will be re-trained before being allowed to recruit further subjects.
- In case this event was unanticipated (see section 4.2 for foreseeable AEs and anticipated ADEs) and the investigator did follow the treatment procedure correctly, the entire clinical investigation has to be immediately suspended and no subjects should be enrolled until the event can be properly

characterized and an appropriate treatment strategy to avoid this unanticipated event can be devised.

17 Publication policy, financing and other agreements

This CIP, other investigation-related documentation, data, and all other information generated will be held in strict confidence. No information concerning the clinical investigation, or the data will be released to any unauthorized third party without prior written approval by the sponsor.

All data, results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations.

17.1 Registration and Publication in Publicly Accessible Database

In accordance with the applicable regulations, a description of the clinical investigation will be registered in a publicly accessible database before recruitment of the first subject. If required by the national regulations, the content will be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

Irrespective of the outcome, positive, inconclusive and negative results of the clinical investigation will be entered in a publicly accessible database where the clinical investigation was registered within the timeframes required by the respective regulations. It shall be accompanied by a summary written in a manner that is understandable to laypersons as applicable.

The clinical investigation will be posted on the “clinicaltrials.gov” site.

17.2 Scientific Publication

The results of the clinical investigation may be published and/or presented at scientific meetings.

However, results should not be published without prior written consent by the sponsor and such consent will not be unreasonably withheld. All manuscripts and abstracts, which refer to data originating from the clinical investigation, must be submitted to the sponsor for comments within a time period specified in the contract between the sponsor and the investigator prior to submission for publication.

If the proposed publication contains any invention related to the clinical investigation, the sponsor is entitled to file respective patent applications and – on this ground – to delay the submission for publication or presentation of medical results.

17.3 Financing

The financial aspects of the investigation will be documented in a separate agreement between the sponsor and the investigator/institution. All expenses arising in connection with the investigation, the remuneration of the investigators for performance of the investigation and the indemnification of the subjects for their participation will be reimbursed in accordance with the respective contracts.

17.4 Agreements

There will be an agreement between the sponsor and the Principal Investigator(s)/investigation site(s) and any other relevant parties (e.g., investigators, CRO(s)), which defines the responsibilities of each party in this clinical investigation. All agreements will be in writing and signed and dated by all parties involved.

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19 Protocol Amendments

19.1 Protocol Amendment 1

The following overview outlines the changes implemented with Amendment 1 to the CIP. (Note: new text in **bold letters**, text which was deleted is ~~crossed out~~).

Change	CIP Sections affected	Rationale
Eligibility Criteria		
IC#1 (*Baseline treatment*): Male or female subjects aged ~~21 – 65~~ **22 - *75*** years (inclusive) of age ***at Screening***	Synopsis Section 6.3.3	The lower age limit was adapted to only enroll adult patients. The upper age limit was increased to show effectiveness and safety also in older subjects as the use of dermal fillers is getting more common in in the age group over 65 years of age.
InC#2 (*Baseline treatment)* and InC#1 (*Repeat-treatment*): Subjects with bilateral, approximately symmetric moderate to severe midface volume deficit (severity scores of 2 or 3 on the 5-point Midface Volume Deficit Severity Scale), as assessed by the ~~treating investigator in conjunction with the independent~~ blinded evaluator at the site ~~(note: final decision is taken by the independent blinded evaluator).~~	Synopsis Section 6.1.3 Section 6.3.3 Section 6.3.5 Section 6.4.13	**Per FDA comment:** Originally, it was planned that both, the treating investigator and the blinded evaluator at the site would do the assessment independently of each other. However, in order to avoid a possible unblinding of the treating investigator in case a disagreement between both, it was decided that the treating investigator will not assess MVDSS.
InC#3 and InC#4 (*Baseline treatment*): 2. Females of childbearing potential must have a negative urine pregnancy test and must agree to use a ***[***highly***]*** effective method of birth control throughout the entire study. ~~4.~~ Male~~s~~ 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). ***[Highly]*** Effective methods of birth control include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion), vasectomized partner (provided that is the sole sexual partner of the subject and that the vasectomized partner has received medical assessment of the surgical success) ~~For~~	Synopsis Section 6.3.3 Section 6.3.8	InC#3 and InC#4 were combined into one single exclusion criterion covering birth control in males and females. This allows correct documentation in the eCRF for both genders. In the case of two separate inclusion criteria, one would be not be applicable for participating women and men, respectively. Abstinence is allowed as "effective method" of birth control for duration of study involvement also for US subjects. It was already allowed for Austrian subjects per European regulations where abstinence is considered as a highly effective method.

Change	CIP Sections affected	Rationale
~~**Austria only:** *and*~~ ~~S~~sexual abstinence (if in line with the preferred and usual lifestyle of the subject and defined as refraining from heterosexual intercourse during the entire period of the trial). Note: Sexual abstinence is defined as highly effective for Austria only.		
InC#5 and ExC#12-14, #22 and #24 (*Baseline treatment*): **InC:** 5. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of ***the entire investigation*** ~~***study***~~, […] **ExC:** 12. […] or is planning to undergo such procedures during the ~~trial~~ ***entire investigation*** 13. […] and during the ~~trial~~ ***entire investigation*** 14. […] and during the ~~trial~~ ***entire investigation*** 22. […] ***and the entire investigation*** 24. […] during the ~~study~~ ***entire investigation***	Synopsis Section 6.3.3	Specification in wording to point out that the treating investigator has to ensure prior to enrollment that the subject does not plan to undergo any of the procedures during the entire period of the investigation (i.e., Visit 1 up to 24 weeks after last injection of repeat-treatment). Corresponding exclusion criteria were added to re-check the eligibility of the subject for repeat-treatment (see below).
ExC #3 (*Baseline treatment)*: ***History of*** hypersensitivity to hyaluronic acid preparations, lidocaine or any amide-based anesthetic	Synopsis Section 6.3.3	Specification of wording to clarify the exclusion criterion.
ExC#10 (*Baseline treatment)*: 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	Synopsis Section 6.3.3	Semi-permanent / long-lasting fillers (like [redacted], an injectable PLLA) are completely excluded. PLLA and PMMA products are semi-permanent / long-lasting fillers and would make the injection of HA fillers more difficult due to the fibrosis.
ExC#16 (*Baseline treatment)*: Planned dental/oral surgery or modification (bridgework, implants) within four weeks prior to each injection and to a minimum of four weeks post injection **(baseline treatment and touch-up treatment** ~~treatment, touch-up and re-treatment)~~	Synopsis Section 6.3.3	Wording updated. This is an ExC for the initial treatment phase. The ExC is to be checked again separately in the repeat-treatment phase, because the subject cannot plan dental treatments one year in advance.

Change	CIP Sections affected	Rationale
Eligibility Criteria - Touch-up treatments (TUP 1 and TUP2)		
ExC#1 *(Touch-up treatments)*: Occurrence of a ***related*** Serious Adverse Event or Adverse Event of Special Interest (i.e., changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke) during or after the ~~baseline~~ ***previous*** injection***s***	Synopsis Section 6.3.4	Adaption required due to additional touch-up treatment of the repeat-treatment phase. Only related SAEs will be considered.
ExC#2 *(Touch-up treatments)*: Subjects who experienced visual changes ***considered abnormal clinically significant*** or other serious medical conditions during or after the ~~baseline~~ ***previous*** injection***s***	Synopsis Section 6.3.4	Adaption required due to additional touch-up treatment of the repeat-treatment phase. Definition of "visual changes" in line with section 6.4.8 was added.
Eligibility Criteria – Repeat treatment		
NEW InC #2 (*Repeat-treatment*): ***Subject has completed initial treatment phase up to Visit 9 (SV1)***	Synopsis Section 6.3.5	To ensure that - no withdrawals of the initial treatment phase are enrolled in repeat-treatment phase - no new subjects are enrolled in repeat-treatment phase
ExC #1 (*Repeat-treatment*): Occurrence of a ***related*** Serious Adverse Event or Adverse Event of Special Interest (i.e., changes in vision [loss of vision, blurriness, double vision, pain in or around the eye, blindness, blind spots, problems moving the eyes], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke) during or after the baseline injection and/or touch-up injection***s***	Synopsis Section 6.3.5	Adaption required due to additional touch-up treatment of the repeat-treatment phase. Only related SAEs will be considered.
ExC #2 and 3 (*Repeat-treatment*):	Synopsis Section 6.3.5	Adaption required due to additional touch-up treatment of the repeat-treatment phase. In addition, definition of "visual changes" in line with section 6.4.8 was added to ExC#3.

Change	CIP Sections affected	Rationale
2. Occurrence of ~~an ongoing~~ related Adverse Event ***that occurred during the initial treatment phase, and is ongoing at the time of the repeat-treatment*** ~~after the initial treatment~~ (i.e., relationship is classified as "possible", "probable" or "causal relationship"; outcome is "not recovered / resolved", "recovering / resolving", "recovered / resolved with sequelae" or "unknown") 3. Subjects who experienced visual changes ***considered abnormal clinically significant*** or other serious medical conditions during or after the baseline ~~/~~***or*** touch-up injection***s, respectively***		
NEW ExCs added for *Repeat-treatment*: ExC#11-15 and ExC#20-22 (Repeat-treatment phase)	Synopsis Section 6.3.5	These criteria are already verified at start of initial treatment phase. To additionally ensure subject´s safety and validity of effectiveness results these criteria are verified at start of repeat-treatment as far as applicable.
ExC #24 (*Repeat-treatment)*: 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 ***RT1*** ~~1 (Screening)~~	Synopsis Section 6.3.5	Correction of timepoint.
Withdrawal criteria		
Withdrawal criterion in case of abnormal clinically significant visual changes was specified: Abnormal clinically significant changes in visual examination after treatment MUST lead to withdrawal from <u>further treatment</u> in case an eye specialist confirms that the result is related to a vascular injection of the dermal filler. However, the subjects may remain in the investigation at least for safety assessments during the scheduled study visits.	Synopsis Section 6.1.1 Section 6.3.6 Section 6.4.8	Withdrawal criterion in case of significant visual changes was specified to ensure subjects stop the treatment but stay in the investigation at least for further safety follow-up.
Withdrawal criterion in case of neurological symptoms after treatment was added: Experience of neurological symptoms indicative of a vaso-occlusional event after treatment MUST lead to withdrawal from <u>further treatment</u>	Synopsis Section 6.1.1 Section 6.3.6 Section 6.4.9	Withdrawal criterion in case any neurological symptoms indicative of a vaso-occlusional event appear after treatment was added to ensure subjects stop the treatment but stay in the

Change	CIP Sections affected	Rationale
in case a neurologist confirms that the result is related to a vascular injection of the dermal filler. However, the subjects may remain in the investigation at least for safety assessments during the scheduled study visits.		investigation at least for further safety follow-up.
Schedule of procedures and assessments		
A follow-up period of 24 weeks post repeat-treatment was added.	Synopsis Schedule of procedures and assessments (Table 3) Section 6.1.1 Section 6.5.8	**Per FDA comment:** This follow-up period of 24 weeks post repeat-treatment will allow for reasonable time to assess potential late adverse events with the product for both scenarios – repetitive use of the test device or switch from the comparator device to the test device.
In repeat-treatment phase an optional touch-up treatment (TUP2) was added.	Synopsis Schedule of procedures and assessments (Table 3) Section 6.1.1 Section 6.1.4 Section 6.5.12	**Per FDA comment:** Subjects may prefer the option of a touch-up treatment in the event of repeat-treatment asymmetry or need for minor correction. Therefore, a touch-up treatment option as with initial treatment is offered to the subjects.
An additional screening phase prior to the repeat-treatment phase was added. Starting from Visit 9 (SV1) subjects will be screened for eligibility every 4 weeks (Visits SV2 to SV4) over a total period of up to 12 weeks. As soon as the subject is eligible in MVDSS score, a full eligibility assessment for repeat-treatment will be done and repeat-treatment at Visit RT1 will be performed.	Synopsis Schedule of procedures and assessments (Table 2, Table 3) Section 6.1.1 Section 6.1.4 Section 6.3.1 Section 6.5.9 Section 7.1	The additional screening phase was added to ensure a sufficient number of subjects qualifying for repeat treatment. With this screening phase approximately 300 subjects are estimated to qualify for repeat-treatment. This number of subjects is sufficient to investigate the safety of the product after repeat-treatment.
Endpoints and Objectives		
Objectives and endpoints: Timepoints for evaluation of effectiveness endpoints were chosen to be relative to the last injection received, i.e., after last injection of initial treatment phase or after last injection of repeat-treatment phase.	Schedule of procedures and assessments (Table 1, Table 2, Table 3) Section 5.2 Section 5.3 Section 6.5 Section 7	**Per FDA comment:** Originally, the primary endpoint would be measured 24 weeks after the baseline treatment. If a subject receives a touch-up treatment, the time from the last treatment to the primary endpoint would be different than those that don't receive a touch-up treatment. Therefore, the time point for the primary endpoint was changed to be relative to the last injection received, so if a touch-up treatment is given, then the primary

Change	CIP Sections affected	Rationale
		endpoint should be 24 weeks from the touch-up treatment. This also applies to all other endpoints and accordingly to the objectives.
Objectives and endpoints: The secondary effectiveness objectives and endpoints were refined. The endpoints were divided into separate sections according to the treatment phase: • The effectiveness of the investigational device during initial treatment phase will evaluated using secondary effectiveness endpoints (see section 5.3.3.1) • The investigational device during repeat-treatment phase (saypha® VOLUME Lidocaine) will be evaluated using the other effectiveness endpoints (see section 5.3.3.2)	Synopsis Section 5.2 Section 5.3 Section 7.3.7	In order to present the setting more clearly, the endpoints for initial and repeat-treatment phase were separated. In addition, it was clearly pointed out, that the other effectiveness endpoints in the repeat-treatment phase will be analyzed descriptively.
Safety objectives and endpoints: The safety of the investigational device will be evaluated by treatment group including cross-over group (in repeat-treatment) and by treatment phase. This is also reflected in the planned statistical analysis.	Synopsis Section 5.2 Section 5.3 Section 7.3.8	**Per FDA comment:** The safety objectives and endpoints were adapted to specifically evaluate for switch from the comparator device to the test device (cross-over between the treatment phases and the devices).
An **interim analysis** (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit at Week 48 after last injection of the initial treatment phase (Visit 9 (SV1)). Based on the interim analysis results an **interim Clinical Investigation Report** (iCIR) will be generated.	Synopsis Section 6.1.3 Section 7.3.1 Section 8.3 Section 8.5	To evaluate safety and effectiveness after 48 weeks after last injection of the initial treatment
Assessments and Procedures		
Midface Volume Deficit Severity Scale (MVDSS): Severity of midface volume deficit will be evaluated using the 5-point MVDSS scale by the blinded evaluator only. Treating investigator will not perform MVDSS.	Synopsis Section 6.4.13 Section 6.5	In order to avoid a possible unblinding of the treating investigator in case a disagreement between both, it was decided that the treating investigator will not assess MVDSS.

Change	CIP Sections affected	Rationale
Global Aesthetic Improvement Scale (GAIS): 1. GAIS was replaced by a ***modified GAIS***: The modified GAIS is a 5-point scale with a balanced distribution of categories as follows: “much worse” – “worse” – “no change” – “improved”- “much improved”. 2. The modified GAIS will be ***not*** evaluated for the repeat-treatment phase. 3. There will be no comparison of the appearance in the mirror (subject) or live (blinded evaluator) at the current visit vs. photographs. Instead, both will review the photographs taken at the current and the Baseline visit	Synopsis Schedule of procedures and assessments (Table 1) Glossary Section 5.2 Section 5.3 Section 6.1.1 Section 6.4.11 Section 6.4.16 Section 6.5	**Per FDA comment:** Initial version of the GAIS did not appear to be balanced, as there are 3 “improved” categories, one “no change” category, and one “worse” category. Now, there are 2 “improved” categories, one “no change” category, and 2 “worse” categories. The repeat-treatment part is mainly focusing on safety. The comparison of two photos is more suitable to get a valid statement than the comparison between mirror /live against a photo.
4. In addition to clinical photography (3D photos), another baseline photo (2D) should be taken on-site at Visit 1, e.g., by using a smart phone or a digital camera.		This 2D photo will be used as baseline photo to evaluate the aesthetic improvement (GAIS) in case of restrictions during the COVID-19 pandemic. In case a personal meeting between the subject and the site representative is not possible in a protocol conformal manner at a follow-up visit of the initial treatment phase, the subject will be asked to take a current (2D) photo of his/her face and to evaluate the aesthetic improvement by comparing the appearance on the current photo against this baseline photo. Details are outlined in an addendum to the CIP
Nasolabial Folds Severity Rating Scale (NLF-SRS) was added to assess the effect of midface treatment with saypha® VOLUME Lidocaine on the nasolabial folds based on the blinded evaluator´s live assessment. Correspondingly, additional objective and endpoint were added.	Synopsis Schedule of procedures and assessments (Table 1, Table 3) Glossary Section 5.2 Section 5.3 Section 6.1.1 Section 6.4.15 Section 6.5 Section 20.2	Midface treatment has the potential to influence nasolabial folds and many Physicians prefer to indirectly influence nasolabial folds via a midface treatment over direct treatment of the nasolabial folds. Therefore, an exploratory objective and endpoint were added, respectively.

Change	CIP Sections affected	Rationale
Subject's pain assessment: Numeric Pain Rating Scale (NPRS) will be performed for the right and the left midface area, separately.	Synopsis Schedule of procedures and assessments (Table 1, Table 3) Section 5.3.1	It was decided to record the pain separately for the right and left side of the face in order to be able to draw differentiated conclusions from the results.
Visual Exams: Visual exams will be done for all subjects at Visit 3 and Visit RT2, irrespectively, if the subject receives a touch-up treatment or not.	Schedule of procedures and assessments (Table 1, Table 3) Section 6.5	Correction of discrepancy between Schedule auf procedures and assessment section and visit descriptions (Section 6.5)
Basic neurological examination added: A basic neurological examination was added as additional risk mitigation strategy and safety assessment. This assessment will be performed by treating investigator in subjects that show signs of ophthalmic complications due to filler injection.	Synopsis Schedule of procedures and assessments (Table 1, Table 3) Section 4.4 Section 6.1.1 New section 6.4.9 Section 6.5 Section 18	**Per FDA comment:** A high proportion of subjects with ophthalmic complications also develop CNS complications. This basic neurological examination (F.A.S.T [27, 28]) was added to ensure patient safety.
Subject Diary: Subjects will record injection site reactions 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).	Synopsis Schedule of procedures and assessments (Table 1, Table 3) Section 5.3.4 Section 6.1.1 Section 6.4.19 Section 7.3.8 Section 14.1	The observation time for injection site reactions recorded in the diary after each treatment was aligned for touch-up treatment. Originally, an overall 4-weeks diary period after baseline / repeat-treatment was planned. Now, after **each** treatment, there is a 4-weeks follow up time via diary.
Handling and administration of medical devices		
Risk mitigation strategy: The sponsor has chosen only board-certified specialists (dermatologists or plastic surgeons) as principal investigators for this investigation who in addition to board certification have years in experience with dermal fillers, both in clinical investigations as well as in daily routine activities.	Section 4.4	**Per FDA comment:** The sponsor has chosen experienced physicians for the study to mitigate the risks of dermal filler use for the indication of midface augmentation, and to ensure the safety of study subjects. This information was now explicitly added to the CIP.
Definition and description of the **anatomic area** considered to be the midface were added.	Section 6.2.2	**Per FDA comment:** Definition and description of the anatomic area considered to be the midface, along with

Change	CIP Sections affected	Rationale
		a visual depiction (see Figure 3) of the areas of midface treatment were added. This was added for patient safety and to ensure investigators are provided with clear and standardized administration instructions for the subject device and comparator.
Administration of test device was specified: Instructions given for the administration of [redacted] apply now for saypha® VOLUME Lidocaine, too.	Section 6.2.2 (Table 16)	To provide same level of instruction given to treating investigators to ensure patient safety and comparable results between the 2 devices.
Applied volume of the devices per side and documentation was specified	Synopsis Section 6.2.3 Section 6.4.10	**Per FDA comment:** FDA raised a safety concern in the event of exaggerated asymmetric injection. Therefore, a maximum volume of device per side of the midface was defined to ensure an appropriate volume is injected per treatment area for the safety of study participants. As the CIP allows subjects with slight asymmetries to be enrolled (per InC#2), the expected outcome of an optimal aesthetic result will potentially require moderate differences in treatment volumes by side. This was considered when the maximum volume of 6.0 mL for one side (and 4.0 mL for the second one) was introduced.
Kit numbers of kits used will be documented in the eCRF.	Section 6.4.10	To have complete documentation of injection-related data available.
No stratification between needle and cannula (1:1) will be performed. Instead, it will be ensured via monitoring of data management overview to get a minimum of 100 subjects randomized to the test device treated with either needle or cannula.	Synopsis Section 6.1.2 Section 6.2.2 Section 6.3.1 Section 6.4.10	In general, in this study the use of needle or cannula is based on the treating investigator´s medical decision. Originally it was planned to stratify in a 1:1 ratio (needle versus cannula). The approach was changed to have a setting which is more similar to real-life situation but ensures a minimum of 100 subjects treated with test device via needle or cannula, each, to collect adequate safety data.
If an **optimal aesthetic correction** has not been achieved after the baseline treatment, as **evaluated by the treating investigator**, a touch-up treatment at Week 2 (Visit 3) (and any following injection during the repeat-treatment	Synopsis Section 6.1.1 Section 6.2.2	It should be in the discretion of the investigator, which approach is used for each injection to have a setting which is more similar to real-life situation.

Change	CIP Sections affected	Rationale
phase) may be performed using the same device, as initially applied at Visit 2. Using the same injection equipment (needle/cannula) and injection technique as initially applied at Visit 2 is no longer required per CIP.		
All investigation sites will be required to have an **emergency plan** on site in line with the respective guidelines to be able to promptly react in case of a suspected vascular occlusion or allergic reaction	Section 4.4 Section 6.2.5	**Per FDA comment:** The investigation sites will be required to have a plan in place for emergencies with a minimum medication readily available in place to promptly react in case of a suspected vascular occlusion or allergic reaction
19. *CROMA-PHARMA GmbH: Investigator's brochure, PRINCESS® VOLUME LIDOCAINE / SAYPHA® VOLUME LIDOCAINE.* 2021. **Version C_CT_IB_006_~~01~~*03***	Section 1.2 Section 2.1 Section 3.1.1 Section 3.2.1 Section 4.1 Section 4.2.1 Section 4.3 Section 4.5 Section 5.4 Section 6.2.1 Section 6.2.2 Section 6.2.4 Section 6.2.6 Section 18	**Per FDA comment:** Investigator's brochure of saypha® VOLUME Lidocaine was updated due to new biocompatibility information requested by the FDA (now Version C_CT_IB_006_03, dated 2021). In the course of this update some updates on clinical data and post-market surveillance were added and, accordingly, have become part of the CIP.
Number of study sites, subjects and duration of the clinical investigation		
Approximately ~~15 / 16~~ **17** investigation sites located in the USA and the EU (correction of discrepancies in v1.0 of the CIP)	Cover page Synopsis Section 6.3.1 Section 7.3.9	**Per FDA comment:** Approximately 17 located in the USA (appr. 16 sites) and the EU (1 site in Austria) are planned to enroll subjects. (Note: an updated list of the sites, including names, addresses and positions of the corresponding Principal investigators, is kept separately from the CIP)
Enrollment levels for subjects with **Fitzpatrick skin types** (FST) I to III and IV to VI, respectively, were implemented.	Section 6.3.1 Section 6.4.2 Section 6.6	**Per FDA comment:** Enrollment levels for subjects with FST IV-VI were implemented to ensure the safety and effectiveness of dermal fillers in subjects of diverse background is evaluable for the test device.

Change	CIP Sections affected	Rationale
Duration of the investigation and participation per subject in the investigation per subject were adapted: Each subject will take part in the investigation for up to ~~62~~ ***92*** weeks. The total anticipated duration of the investigation, from the first-subject-first visit to the last-subject-last-visit, is around ~~90~~ ***114*** weeks, based on expected recruitment period of about ~~30~~ ***22*** weeks.	Synopsis Section 6.3.1	Updates were required due to prolongation of the repeat-treatment phase and screening phase for repeat-treatment.
Adverse events, adverse device effects and device deficiencies		
The follow-up period of AEs will be prolonged outside the investigation, if a related AE is ongoing and not stabilized after 24 weeks following repeat-treatment.	Section 6.4.20 Section 14.3 Section 14.6	**Per FDA comment:** The follow-up of the repeat-treatment phase is only 24 weeks (compared to 48 weeks of the initial treatment phase). To ensure subject´s safety for the same period of time as after baseline treatment, subjects who have a related AE ongoing and not stabilized after 24 weeks following repeat-treatment will be followed outside the investigation.
Safety Reporting in the EU will be according to Regulation (EU) 2017/745 – Medical Device Regulation (MDR) from beginning of the study.	Section 14.5.1	The safety reporting would have been according to the DIRECTIVES 90/385/EEC AND 93/42/EEC until 26th May 2021. This timepoint elapsed in the meantime. Safety reporting will be according to the EU MDR, only.
Corrections and other updates		
Task added at Visit 2: ***Re-assess and evaluate eligibility criteria*** (see section 6.3.3)"	Section 6.5.2	This was missing by error, aligned with schedule of procedures (Table 1).
Method of blinding of the blinded evaluator was specified: The blinded evaluator at the site is not blinded for treatment allocation during the repeat-treatment phase. However, he/she will be blinded for the treatment a subject received during the initial treatment phase until final database lock.	Schedule of procedures and assessments (Table 2, Table 3) Glossary Section 6.1.3	Included for clarification.
(e.g., investigators, CRO(s) ~~and core laboratories~~),	Section 17.4	Correction: There are no laboratories used in the study
• Discomfort ~~and discomfort~~ with palpation	Section 6.4.19	Correction
Coding of ***concomitant*** ~~accompanying~~ diseases	Section 8.3	Correction: Alignment of wording throughout the CIP.

Change	CIP Sections affected	Rationale
Abbreviations added to the List of Abbreviations	List of abbreviations	Some abbreviations were missing in version 1.0 of the CIP; some abbreviations are new.
32. FDA: Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. March 2020; ~~September 21, 2020~~ **Updated on August 30, 2021.**	Section 4.4 Section 18	Updated to current version.
Grammatical changes and corrections of typos		
Clarification of study restrictions: Beard longer **than** three-day beard […]	Section 6.3.8 Section 6.6	Correction: Grammar
Grammatical changes and corrections of typos are not displayed in detail in this summary of changes. Refer to the tracked change version of the CIP.	Not applicable	Not applicable

The integration of the changes into the document resulted in CIP version 2.0.

19.2 Protocol Amendment 2

The following overview outlines the changes implemented with Amendment 2 to the CIP. (Note: new text in **bold letters**, text which was deleted is ~~crossed out~~).

Change	CIP Sections affected	Rationale
Eligibility Criteria and prohibited treatments		
ExC#15 (*Baseline treatment*): Development of bleeding disorder and/or use of anticoagulant, antiplatelet, ~~or~~ thrombolytic medication, ***anti-inflammatory drugs (oral/injectable corticosteroids or non-steroidal anti-inflammatory drugs, e.g.,*** [redacted] ***or*** [redacted] ***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 ~~three~~ ***seven*** days post injection (baseline treatment and touch-up treatment)	Synopsis Section 6.3.3.2	**Per FDA comment:** Use of anticoagulant, antiplatelet or thrombolytic medication is prohibited for 7 days after each treatment (instead of only 3 days). In addition, use of anti-inflammatory drugs or other substances known to increase coagulation time is prohibited from ten days prior to seven days after each injection.
ExC#16 (*Repeat-treatment*): Development of bleeding disorder and/or use of anticoagulant, antiplatelet, ~~or~~ thrombolytic medication, ***anti-inflammatory drugs (oral/injectable corticosteroids or non-steroidal anti-inflammatory drugs, e.g.,*** [redacted] ***or*** [redacted] ***) 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 ~~three~~ ***seven*** days post injection (repeat-treatment ***and touch-up treatment***)	Synopsis Section 6.3.5.2	
Prohibited treatments: • Anticoagulant, antiplatelet, or thrombolytic drugs ~~(e.g., acetylsalicylic acid)~~, ***or anti-inflammatory drugs (oral/injectable corticosteroids or non-steroidal anti-inflammatory drugs, e.g.,*** [redacted] ***or*** [redacted] ***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- until ~~three~~ ***seven*** days after **each** injection of the device	Section 6.3.9	

Change	CIP Sections affected	Rationale
Schedule of procedures and assessments		
Addition of on-site follow-up visits at 2 weeks after the respective touch-up treatment: **Visit 3b:** 2 weeks after TUP1 **Visit RT2b:** 2 weeks after TUP2	Synopsis Schedule of procedures and assessments (Table 1, Table 3) Section 6.1.1 New section 6.5.6 New section 6.5.14 (Note: Numbering of subsequent sections were changed accordingly)	**Per FDA comment:** Each subject needs to be seen in person 2 weeks after each treatment to allow for a sound differentiation between injection site reactions and adverse events.
Visit RT3 will be performed during the repeat treatment phase at Week 4 (± ~~7~~ ***5*** d) after last injection		Visit window aligned to initial treatment phase with Visit 4 also performed at Week 4 (± 5 d) after last injection.
Subject diary: Documentation of 'Other' injection site reactions		
Injection site reactions the subject is ***not*** specifically asked about in the subject diary (i.e., 'Other' symptoms at the injection site not listed in section 6.4.19) and that are ***not*** synonymous to one of the pre-defined injection site reactions will be assessed and documented as AEs by the treating investigator.	Section 6.4.19 Section 14.1	Clarification for handling of free text field entries ('Other') in the subject diary
Interim Analysis		
The interim analysis (IA) will be performed after all subjects have completed the follow-up visit at Week 48 after last injection of the initial treatment phase (Visit 9 (SV1)).	Synopsis Section 7.3.1	**Clarification:** The IA will be 48 weeks after last injection of the initial treatment – not at Week 24 as given by mistake in the synopsis and section 7.3.1 of the former CIP version.
Analysis of subgroups		
Additional information provided which and how subgroup analyses will be addressed.	Synopsis Section 7.3.10	**Per FDA comment:** Subgroup analyses will be performed on both safety and effectiveness data by additional demographic factors age groups, race and ethnicity. Details will be given in the SAP.
Number of subjects		
Enrolment target of approximately 20 to 30 subjects per site and the maximum expected number of subjects per site was added.	Section 6.3.1	**Per FDA comment:** The enrolment target of approximately 20 to 30 subjects per site and the maximum expected number of subjects per site was added to explain the planned distribution of patients across all sites.

Change	CIP Sections affected	Rationale
The clinical investigation is planned to be conducted at approximately 17 study sites with enrolment target of approximately 20 to 30 subjects per site. The maximum expected number of subjects to be enrolled per each site will be 45.		
Corrections and other updates		
IDE no. was added: G210347	Synopsis	Not applicable
Subject number will be assigned automatically by the eCRF system when entering data and not assigned by the site staff: ~~Assign subject number /~~ Randomization o Assign the subject number ***by entering subject data into eCRF*** (see CRF Completion Guidelines)	Schedule of procedures and assessments (Table 1) Section 6.5.1	Correction of process.
Information added: Serious and non-serious AESIs must be reported by the investigator to **the sponsor's representative immediately but not later than 24 hours** of awareness. This was only stated in section 6.4.19.	Section 14.5.1	Not applicable
Sponsor´s representative will notify EC about reportable safety events.	Section 14.5.3	Correction of process.
Heading of section 7.4 "Subject data listings" was missing and added. Numbering of subsequent sections were changed accordingly.	Table of contents Section 7.4	Correction
There will be a Data Review Meeting (DRM) before the interim analysis and the final analysis, respectively. These meetings will be not Blind Data Review Meetings, as no blinded staff will participate.	Section 7.2	Clarification
Grammatical changes and corrections of typos		
Grammatical changes and corrections of typos are not displayed in detail in this summary of changes. Refer to the tracked change version of the CIP.	Not applicable	Not applicable

The integration of the changes into the document resulted in CIP version 3.0.

19.3 Protocol Amendment 3

The following overview outlines the changes implemented with Amendment 3 to the CIP. (Note: new text in **bold letters**, text which was deleted is ~~crossed out~~).

Change	CIP Sections affected	Rationale
Endpoints and Objectives		
An additional <u>secondary</u> endpoint was added: • Mean change in midface volume deficit measured on the 5-point MVDSS and 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.	Synopsis Section 5.3.3.1 Section 7.3.7	The mean change in MVDSS rated by the blinded evaluating investigator will be used in addition to the responder rate to further evaluate the effectiveness of investigational device. This is a standard endpoint for the type of device investigated. The statistical section was changed accordingly.
An additional <u>other</u> endpoint was added: • Mean change in midface volume deficit measured on the 5-point MVDSS and based on the blinded evaluator´s live assessment at Week 4, 12, and 24 after last injection of repeat-treatment phase compared to the score at Visit RT1	Synopsis Section 5.3.3.2 Section 7.3.7	
Corresponding objective was changed: • To further assess effectiveness of saypha® VOLUME Lidocaine 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**)	Synopsis Section 5.2.2.2	The corresponding objective was changed accordingly.
Correction of the paragraph describing general topics applicable for the objectives: • For the initial treatment phase: ○ […] evaluation in general will be assessed for Visits 4 to 9 (SV1): Week 4, 8, 16, 24, ~~32~~, 36, and 48 after last injection of initial treatment phase	Synopsis Section 5.2.2.1	Correction: There is no visit at Week 32 after last injection of initial treatment phase.
Assessments and Procedures: Modified Global Aesthetic Improvement Scale (modified GAIS)		
1. Current photographs will be taken at each on-site visit after last injection of the initial treatment phase.	Synopsis Section 6.1.1 Section 6.4.16	Clarification: Current photographs (taken at each on-site visit after last injection of the initial treatment phase) will be reviewed to evaluate global aesthetic

Change	CIP Sections affected	Rationale
Global aesthetic improvement will be evaluated by reviewing these current photographs relative to the photographs taken at the Baseline visit (using the modified GAIS).		improvement relative to baseline photographs (taken at the Baseline visit).
2. Both – the blinded evaluator at the site and the subject – will assess the global aesthetic improvement (using the modified GAIS) at each on-site visit after last injection of the initial ~~and repeat~~ treatment phase, ~~respectively.~~	Synopsis Section 6.1.1	Correction: Global aesthetic improvement will only be evaluated during the initial treatment phase (*not* during the repeat-treatment phase).
3. Modified GAIS is a scale to assess the *global* aesthetic improvement. Wording was specified where required to avoid errors, including the objectives and endpoints covering the global aesthetic improvement: Objectives: **Global aesthetic** ~~*Aesthetic*~~ *improvement* • To evaluate **global** aesthetic improvement based on ***subject's*** assessments (initial treatment phase only) • To evaluate **global** aesthetic improvement based on the ***blinded evaluator's*** assessments (initial treatment phase only) Endpoints: **Global aesthetic** ~~*Aesthetic*~~ *improvement based on modified GAIS* • The percentage of subjects with a~~n~~ **global aesthetic** improvement over baseline (at Baseline visit) (subjects who have been rated as "much improved" or "improved"), based on ***subject´s*** assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment phase using the 5-point *modified* GAIS. • The percentage of subjects with a~~n~~ **global aesthetic** improvement over baseline (at Baseline visit) (subjects who have been rated as "much improved" or "improved"), based on the ***blinded evaluator`s*** assessment at Week 4, 8, 16, 24, 36, and 48, after last injection of initial treatment	Synopsis Schedule of procedures and assessments (Table 1) Section 5.2.2.2 Section 5.3.3.1 Section 6.1.4 Section 6.4.11 Section 6.4.16 Section 7.3.7	Clarification to avoid errors.

Change	CIP Sections affected	Rationale
phase using the 5-point *modified* GAIS.		
Corrections and other updates		
Schedule of procedures and assessments for the repeat-treatment phase: Note #18 was deleted.	Schedule of procedures and assessments (Table 3)	Due to changes in previous CIP version this note was no longer required.
Grammatical changes and corrections of typos		
Grammatical changes and corrections of typos are not displayed in detail in this summary of changes. Refer to the tracked change version of the CIP.	Not applicable	Not applicable

The integration of the changes into the document resulted in CIP version 4.0.

19.4 Protocol Amendment 4

The following overview outlines the changes implemented with Amendment 4 to the CIP. (Note: new text in **bold letters**, text which was deleted is ~~crossed out~~).

Change	CIP Sections affected	Rationale
Photography and data protection		
All photographs are submitted to the photo provider in a non-masked manner and will be masked at the photo provider prior to being forwarded to the Sponsor at the latest. Details will be given in a separate manual.	Schedule of procedures and assessments (Table 1) Section 6.3.12 Section 6.4.11	Clarification of processes at the photo provider
Emergency unblinding		
The blinded evaluator at the site will not have emergency access to the eCRF. Anyway, unblinding will be possible by checking the source data / subject´s medical records.	Section 6.1.3	Clarification of processes for emergency unblinding
Assessments and Procedures: Numeric Pain Rating Scale (NPRS) - Pain assessment		
The following instruction was deleted: ~~To avoid over reporting of pain, a non-leading question „*How do you feel?*“ should be asked prior to pain assessment.~~ ~~Spontaneously reported pain, or pain graded ≥4 on the Pain Assessment Form will be recorded as an AE.~~	Section 6.4.15 Section 14.2	Correction: Paragraphs in sections 6.4.15 and 14.2 were deleted as “pain after injection” is recorded as injection site reaction in the subject diary (see section 6.4.19 and by using the NPRS (section 6.4.15). Therefore. it does ***not*** need to be documented as AE in addition.
Signature page		
Sponsor’s medical representative changed: [redacted] was replaced by [redacted]	Approval and signature pages	Administrative change at the Sponsor
Corrections and other updates		
There will be a Data Review Meeting (DRM) before the interim analysis and the final analysis, respectively. Therefore, CIP deviations will be discussed during both meetings.	Section 10	Clarification
Grammatical changes and corrections of typos		
Grammatical changes and corrections of typos are not displayed in detail in this summary of changes. Refer to the tracked change version of the CIP.	Not applicable	Not applicable

The integration of the changes into the document resulted in CIP version 5.0.

19.5 Protocol Amendment 5

The following overview outlines the changes implemented with Amendment 5 to the CIP. (Note: new text in **bold letters**, text which was deleted is ~~crossed out~~).

Change	CIP Sections affected	Rationale
Eligibility Criteria		
ExC#24 (*Baseline treatment)* Subjects who experienced ~~fat~~ **weight** loss for a minimum of 10% ~~of body weight~~ 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 **ExC#23 (*Repeat-treatment*):** Subjects who experienced ~~fat loss~~ **weight change** for a minimum of 10% ~~of body weight~~ since study start or subjects who have the intention to change eating habits that result in a weight gain or loss >10% during the entire investigation	Synopsis Section 6.3.3 Section 6.3.5.2	Clarification reasons: Not only *fat* loss, but every type of body *weight* loss prior to study start, or *weight* changes since study start was excluded. In addition, it was clarified that body weight *changes* >10% (i.e., weight gain *and* loss) compared to prior baseline treatment may have an impact on assessment of the effectiveness parameters.
Assessments and Procedures:		
Any body weight changes of clinical relevance (*significant* weight loss or weight gain) compared to the Screening (Visit 1) measurement may represent an AE. The investigator should evaluate and document a possible diagnosis for the weight change as AE.	Section 6.4.3	Clarification reasons: Significant changes in weight may have an impact on the results of the investigation, especially if the treatment area (midface) is affected. Therefore, the weight of the subjects is checked on a regular basis. However, a significant change in weight may also indicate an underlying disease, and if confirmed, that must be documented as an AE.
Any ~~change~~ **worsening** of 2 lines or more in **Snellen acuity test** in best corrected visual acuity (i.e., with glasses/contact lenses) will be regarded as clinically significant, and the treating investigator must refer the subject to an eye specialist to evaluate if the result is related to a vascular injection of the dermal filler.	Section 6.4.8	Clarification reasons: Should the Snellen visual acuity after injection worsen by 2 lines of more compared to prior injection this might indicate an AE. Therefore, only worsening in Snellen visual acuity will be considered abnormal clinically significant.
Respective Baselines to assess clinically significant changes in visual examination results were clarified as follows:	Section 6.4.8	Clarification reasons: To clarify the respective baselines.

Change	CIP Sections affected	Rationale
• Results at each visit will be compared to the results prior to first injection of each treatment phase, i.e., Visit 2 for initial treatment phase and Visit RT1 for repeat-treatment phase. • At treatment visits, visual examinations will be performed before the injection and 30 min after the injection. The result post-injection (30 min after) will be compared to the results prior injection.		
Definition for AESI was clarified: **For this clinical investigation,** AEs of special interest are defined as **embolic events, with possible, probable, or causal relationship to an intravascular injection of the device, as** • Changes in vision (i.e. loss of vision, blurriness, double vision, pain in or around your eye, blindness, blind spots, problems moving the eyes) • Skin changing color around the eyelids or around the site of injection • Other embolic phenomenons, e.g., stroke, **skin necrosis** Consequently, ExC#1 (Touch-up treatments and Repeat-treatment) were updated: 1. Occurrence of a related Serious Adverse Event or Adverse Event of Special Interest (i.e., **embolic events, with possible, probable, or causal relationship to an intravascular injection of the device, as** changes in vision […], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke, **skin necrosis**) during or after the previous injections	Section 6.3.4.2 Section 6.3.5.2 Section 14.1	Clarification reasons.

Change	CIP Sections affected	Rationale
In general, symptoms of interest asked for in the eDiary may indicate embolic events to be assessed and documented as AE(SI) if clinically significant. Also, other (non-embolic) diagnoses resulting from investigator´s assessment of the symptoms of interest are to be assessed and documented as AE if clinically significant. Examples how to assess SOIs and how to establish diagnoses are given in new section 20.5.	Schedule of procedures and assessments (Table 1 / Table 3) Section 6.4.19 Section 6.5 (incl. applicable sub-sections) Section 14.2 Section 20.5	Clarification reasons: A clarification was included that a symptom of interest may be an AE(SI) and how these might be detected. Included to help investigators to identify clinically significant symptoms/diseases/worsenings and document these as AEs/AESIs.
Reporting of AESIs and other embolic events was clarified: All AESI (serious and non-serious**) and any other embolic event (regardless of seriousness and / or relationship to device or procedure)** have to be reported by the investigator to the sponsor's representative within 24 hours of awareness of the event via Email **using the SAE Reporting Form**. ~~In case, any of the abovementioned criteria apply (i.e., seriousness, anticipation criteria), t~~ The sponsor's representative will report the event all AESIs and any other embolic event **(regardless of seriousness and / or relationship to device or procedure) to the respective competent authority (FDA) in an expedited manner**.	Section 14.5.1 Section 14.5.4	**Per FDA comment**: The clinical investigation plan was updated to specify the reporting of AESI and other AEs indicating other embolic events (regardless of relatedness or seriousness) to the Agency.
Clarification: ~~Other~~ Symptom of interest (SOI). This includes also wording of one of the safety endpoints: Occurrence and frequency of adverse events during the entire study period including repeat-treatment phase (long-term safety). ~~Other~~ Symptoms of interest will be recorded in subject diary during the first 4 weeks (28 days) after each treatment (i.e., either 4 weeks after baseline and repeat-treatment, respectively, and 6 weeks in case of touch-up treatment) and documented as AE by investigator.	Synopsis Schedule of procedures and assessments (Table 1 / Table 3) List of abbreviations Section 5.3.4 Section 6.4.19 Section 6.5 (incl. applicable sub-sections)	Clarification reasons. These are symptoms of interest to identify potential AEs / AESIs.

Change	CIP Sections affected	Rationale
Number of subjects		
The maximum expected number of subjects to be enrolled per each site will be 45 ***but may be higher if agreed with the Sponsor.***	Section 6.3.1	To compensate for lower enrolling sites, it is allowed to increase enrollment after sponsor approval ensuring no statistical impact.
Participation in repeat-treatment phase (including the screening phase for repeat-treatment phase) is optional for the subject, i.e., subjects must be willing to undergo optional repeat-treatment. Optional participation was already stated in the CIP (e.g., synopsis "Treatment occasions", and Glossary). For clarification reasons, this was added to other key sections of the CIP and some paragraphs of the synopsis. InC#2 (Repeat-treatment) was updated: 2. Subject has completed initial treatment phase up to Visit 9 (SV1) ***and is willing to attend the study visits of the screening phase for repeat-treatment and repeat-treatment phase*** However, subjects still must qualify for repeat-treatment (phase) as per eligibility criteria given in Section 6.3.5.	Synopsis Schedule of procedures and assessments: (Table 1 to Table 3) Section 6.1 incl. Figure 1 Section 6.2.2 Section 6.5.9 Section 6.5.10	Clarification reasons: Participation in repeat-treatment phase is optional (including the screening phase for repeat-treatment). Subject´s participation in repeat-treatment phase depends on - willingness to participate as defined in InC#2 and - qualification for repeat-treatment as defined by other eligibility criteria.
Changes related to saypha® VOLUME Lidocaine		
IB for saypha® VOLUME Lidocaine was updated, and relevant safety information was reflected in the CIP. IB-0003 v6.0; dated 2024 was added as reference #46 to Section 18. References throughout the document were updated (~~[23]~~ to ***[46]***). Note, that these changes are not listed in the next column.	Sections listed, where relevant safety information was changed: Section 3.2.1 Section 3.3 Section 4.2.1	IB for saypha® VOLUME Lidocaine was updated with relevant safety data. These changes do not have an impact on the overall risk-benefit assessment of the underlying clinical investigation.

Change	CIP Sections affected	Rationale
Investigational sites and countries		
Investigation sites located in the USA (appr. 16 sites) and the EU (1 site in Austria) were planned to enroll subjects. The only investigational site in Austria (EU) was never initiated, and all subjects were recruited by the investigation sites located in the USA. EU-specific definitions and instructions regarding safety and safety reporting requirements were deleted. Methods of birth control are no longer defined as '*[highly] effective'* to cover both, EU, and US requirements, but only as '*effective*'. Correspondingly, InC#3 for baseline treatment was updated: **InC#3 (*Baseline treatment)*** 3. Females of childbearing potential must have a negative urine pregnancy test and must agree to use ***an*** ~~[highly]~~ effective method of birth control throughout the entire study […] This update includes foot note "E" in section 6.3.3.1.	Title Page Investigators and administrative structures Synopsis List of abbreviations Glossary Section 6.3.2 Section 6.3.8 Section 6.3.3.1 Section 14.1 Section 14.5.3 deleted	The only investigation site in Austria (EU) was never initiated due to faster overall recruitment in the USA.
Statistical considerations		
Process of PD rating ('minor', 'major excluding from PPS', 'major not excluding from PPS') with respect to analysis of the primary effectiveness endpoint was specified. Accordingly, the definition of the PPS was adapted: The PPS is defined as a subset of the subjects in the FAS ~~who had no major protocol deviations~~ ***without major protocol deviation(s) affecting the primary effectiveness endpoint and assessed as 'major excluding from PPS'.***	Synopsis Section 7.2	Clarification reasons: Excluding subjects with major PDs not affecting the primary endpoint would unnecessarily restrict the PPS, without any added information for the primary effectiveness assessment at Week 24.

Change	CIP Sections affected	Rationale
Clarification for use of PPS: All effectiveness analyses ***for the initial treatment phase*** will be conducted ~~for~~ ***using*** the PPS and the FAS. ***The effectiveness analysis for the repeat treatment phase will be conducted using the FAS only.*** Safety analyses will be based on the SAF. The evaluation of the primary and secondary effectiveness endpoint(s) will be performed both in the Per-Protocol Set (PPS) and in the Full Analysis Set (FAS) ***for the initial treatment phase, and only for the FAS for the repeat phase.***	Section 7.2 Section 7.3	Clarification reasons: Section 7.3 (and sub-sections concerned) already restricted use of PPS for analysis of the primary and secondary effectiveness endpoints (i.e., endpoints analyzed during the initial treatment phase up to Visit 9). With this amendment to the CIP, this was clarified. Note: Endpoints for used to analyze effectiveness in the repeat-treatment phase are 'Other endpoints' and were therefore never covered by these statements.
Adaption of sample size justification to match planned analysis of the primary effectiveness endpoint defined in section 7.3.7: The primary outcome measures for effectiveness will be evaluated by means of a one-sided two-group ***Farrington-Manning test for non-inferiority*** ~~large-sample normal approximation test of proportions~~ with the following hypotheses: […] Based on these assumptions, 437 subjects (saypha® VOLUME Lidocaine: n=291, [redacted]: n=146) will be necessary in order to achieve a power ***exceeding 83%*** ~~of 80%~~ with a one-sided α of 2.5%. […]	Synopsis Section 7.1	Farrington-Manning test for non-inferiority, as defined in section 7.3.7 for the analysis of the primary effectiveness endpoint, did not match the method used for sample size calculation (i.e., one-sided two-group large-sample normal approximation test of proportions). Therefore, sample size justification (but not the sample size itself) was adapted. This modification resulted in a slightly higher power of the planned primary analysis for non-inferiority (83% instead of 80%).
At this, pA is the response rate for saypha® VOLUME Lidocaine and pB is the response rate for [redacted] ***, and d0 equals to -0.1***. Thus, a negative value for this difference means that the response rate of saypha® VOLUME Lidocaine is lower than the response rate for [redacted] ~~The non-inferiority margin is -10%.~~ In addition to this, the response rates for both treatment groups ***along with their Clopper-Pearson exact 95% CIs*** will be tabulated.	Synopsis Section 7.3.7	For clarity, the information on non-inferiority margin was added here as well. Clopper-Pearson exact confidence intervals were added for a more informative presentation of the estimated results. The point estimates can only be correctly interpreted if their confidence intervals are also presented.
Sensitivity analyses of the primary effectiveness endpoint were adapted: *Sensitivity analyses* of the primary effectiveness endpoint will be performed on the FAS addressing the different reasons for non-adherence and covering	Synopsis Section 7.3.7	The first method for sensitivity analysis was deleted because single imputations are usually biased, and because it was too conservative. A multiple imputation with MNAR assumption was added instead.

the following aspects to underline the robustness of the results: ~~o Handling missing values concerning primary endpoint differently between the treatment groups: subjects who dropped out before Week 24 after last injection of the initial treatment phase will be regarded as non-responders in the treatment group with test device while classified as responder in the comparator group (if no data are reported indicating non-response);~~ o Complete case analysis: In this analysis only those subjects will be included for whom the primary endpoint could be calculated; o Subjects with non-allowed concomitant medication / treatments before Week 24 after last injection of the initial treatment phase may be regarded as non-responder. o ***Multiple imputation under MNAR assumption for imputing missing MVDS scores at Week 24 assessed live by the blinded evaluator.***		
Concerning the follow-up for initial treatment, the ***last*** measurements / assessments ~~at Visit 2~~ before first treatment are defined as baseline.	Synopsis Section 7.3.7	Clarification reasons: The definition for baseline was updated because some assessments are done at Screening, not at Visit 2.
Signature page		
Sponsor's medical representative changed: [redacted]-was replaced by [redacted] [redacted], DVM (Global Director Clinical Development) is Sponsor´s only non-medical representative to sign the CIP.	Approval and signature pages	Administrative change at the Sponsor

Change	CIP Sections affected	Rationale
Corrections, clarifications and other updates		
References to Section 16.1 describing activities following a related vaso-occlusional event clarified.	Synopsis Section 6.1.1 Section 6.4.8 Section 6.4.9	Clarification reasons.
No peel-off labels are attached on the carton box of the saypha® VOLUME Lidocaine kits.	Section 6.2.1	Correction.
Completer, withdrawals / dropouts and screening failures were defined per phase of the investigation.	Section 6.3.11	Clarification reasons.
Unless otherwise specified, all measurements will be summarized descriptively at each visit by treatment group ~~and injection equipment (i.e., needle or cannula)~~.	Synopsis Section 7.3	Correction: Specification of subgroup analyses are given in section 7.3.10.
Non-pharmaceutical procedures will be coded using MedDRA	Section 7.3.6	Correction.
Coding of device deficiencies was specified.	List of abbreviations Section 8.3	Specification.
Clarification that visual examinations need to be performed at Visit 3 also for no touch-up (TUP) subjects, not only for subjects receiving TUP.	Schedule of procedures and assessments (Table 1 and Table 3)	Clarification reasons.
Definition of TEAE was corrected.	Section 14.3	Correction.
Grammatical changes and corrections of typos		
Grammatical changes and corrections of typos are not displayed in detail in this summary of changes. Refer to the tracked change version of the CIP.	Not applicable	Not applicable

The integration of the changes into the document resulted in CIP version 6.0.

19.6 Protocol Amendment 6

The following overview outlines the changes implemented with Amendment 6 to the CIP. (Note: new text in **bold letters**, text which was deleted is ~~crossed out~~).

Change	CIP Sections affected	Rationale
Corrections, clarifications and other updates:		
Definition for AESI was clarified: For this clinical investigation, AEs of special interest are defined as embolic events, […] • Other embolic phenomenons, e.g., stroke, skin necrosis, **or impending necrosis** Consequently, ExC#1 (Touch-up treatments and Repeat-treatment) were updated: 1. Occurrence of a related Serious Adverse Event or Adverse Event of Special Interest (i.e., embolic events, with possible, probable, or causal relationship to an intravascular injection of the device, as changes in vision […], skin changing color around the eyelids or around the site of injection, other embolic phenomenon, e.g., stroke, skin necrosis **or impending necrosis**) during or after the previous injections	Section 6.3.4.2 Section 6.3.5.2 Section 14.1	**Per FDA request**: Definition of AESI was revised to include impending necrosis as another example of an embolic phenomenon that would meet the definition of an AESI.
Stopping rules were clarified: In the event ~~that vascular embolic event leading to skin necrosis, vision loss, and stroke occurs, the enrollment and treatment at the investigational site will be suspended and a root cause investigation has to be conducted to determine the cause of the event.~~ **of any vascular occlusion secondary to dermal filler injection, or other adverse events secondary to such vascular occlusion, and which are avoided or prevented only by urgent treatment, the enrollment and treatment will be suspended, and a root cause investigation has to be conducted to determine the cause of the event. Such investigation will involve the investigator who treated the affected subject and the sponsor or designee.**	Section 16.1	**Per FDA request**: Stopping rules were revised to include a rule for stopping the study in case of any vascular occlusion secondary to dermal filler injection.

Change	CIP Sections affected	Rationale
Such cases, which may include e.g., impending necrosis, subjects with early signs of a stroke, or subjects with vision loss, all of whom undergo urgent treatment and have resolution of their necrosis, stroke, or vision loss symptoms, will result in actions as defined above, during which further enrolment and treatment will be on hold.		
Signature page:		
Sponsor's non-medical representative changed: [redacted] ~~DVM~~ [redacted] [redacted] ~~Global Director~~ **Consultant** Clinical Development.	Approval and signature pages	Administrative change at the Sponsor

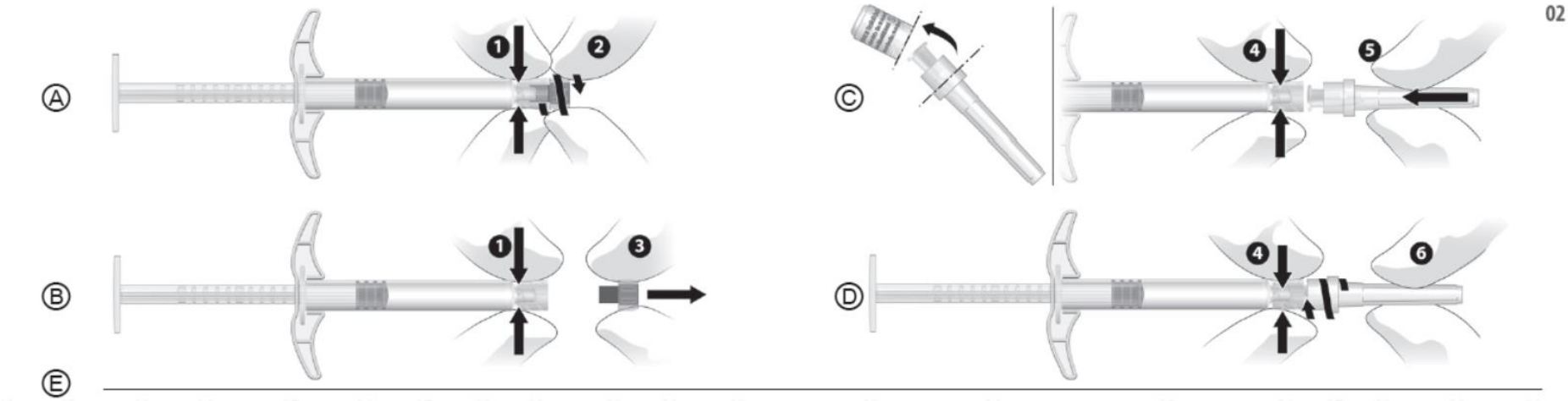
The integration of the changes into the document resulted in CIP version 7.0.

20 Annex

20.1 Croma Midface Volume Deficit Severity Scale (MVDSS)

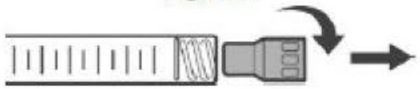
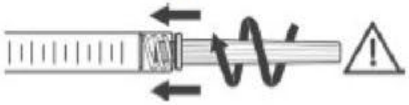
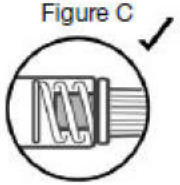
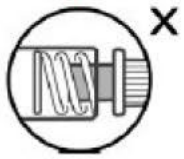
20.2 Croma Nasolabial Folds Severity Rating Scale (NLF-SRS)

20.3 saypha® VOLUME Lidocaine: Visual instructions how to attach needle / cannula to syringe



Hold the Luer-Lock adapter as shown in ❶. To remove the tip cap, twist ❷ and pull carefully ❸. Following the instruction above will prevent the formation of air bubbles. Hold the syringe as shown in ❹. Open the enclosed needle case and insert the needle firmly ❺ (do not use any other needle). Tightly secure the needle by twisting it clockwise ❻

20.4 [redacted] Visual instructions how to attach needle / cannula to syringe

STEP 1: Remove tip cap	STEP 2: Insert needle	STEP 3: Tighten the needle	STEP 4: Remove the needle cap
Figure A  Hold syringe and pull tip cap off the syringe, as shown in ***Figure A***.	Hold the syringe body and firmly insert the hub of the needle (provided in the [redacted] package) into the LUER-LOK® end of the syringe.	Figure B  Tighten the needle by turning it firmly in a clockwise direction (see ***Figure B***) until it is seated in the proper position, as shown in ***Figure C***. Figure C  Figure D  NOTE: If the position of the needle cap is as shown in ***Figure D***, it is not attached correctly. Continue to tighten until the needle is seated in the proper position.	Figure E  Hold the syringe body in one hand and the needle cap in the other. Without twisting, pull in opposite directions to remove the needle cap, as shown in ***Figure E***.

20.5 Assessment of Symptoms of Interest (SOIs)

20.5.1 *Not Clinically Significant SOIs (examples)*

Not clinically significant SOIs are those SOIs that cannot be verified e.g., through targeted subject questioning and/or examinations (also see section 14.2).

The below list is included as a guide and is not intended to be all inclusive:

- The subject is dissatisfied with treatment effect and reports SOI 'Face droop' because the lifting/volume effect did not turn out as desired,
- An anxious subject observes him/herself closely and reports an apparent feeling of 'Weakness or numbness in the arms or legs' but this cannot be verified in neurologic examination and subject confirms retrospectively that his/her mobility and sensitivity were not really restricted.
- The subject is unsure and selects an SOI by misinterpretation (e.g., 'difficulty speaking/speech impairment' although neither dysarthria nor aphasia occurred but he/she did not dare to speak normally to 'protect' the cheeks
- The SOI 'skin changing colour around eyes' corresponds to a local reaction that is already recorded in the diary as injection site reaction (e.g., 'bruising'),
- The SOI 'blurriness' is caused by a pre-existing underlying disease or treatment (e.g., due to dry eyes in a contact lens wearer).
- Technical failure(s). The subject ticked a SOI by mistake.

20.5.2 *Diagnoses resulting from SOI Assessment (examples)*

Verified diagnoses will be documented and assessed as AE(SI) (see section 14.3 and section 14.4 for details).

The below list is included as a guide and is not intended to be all inclusive:

- Symptoms of headache and fever might be symptoms of e.g., a 'common cold', 'influenza' or 'Covid-19' and shall be reported as the respective diagnosis.
- Symptoms of headache, difficulty speaking/speech impairment and face droop might be symptoms of e.g., 'stroke' and shall be reported as the respective diagnosis, if such.