CLINICAL INVESTIGATION PLAN (CIP)

Title of the clinical investigation/CIP:	**A prospective, randomized, multicenter study evaluating saypha® VOLUME Lidocaine* for the correction of nasolabial folds**
Short title:	**SAVINO** (**sa**ypha® **V**olume L**I**docaine in **N**asolabial F**O**lds)
Investigation ID:	CPH-101-201477
CIP version:	6.0
CIP version date:	**18.03.2021**
Sponsor:	CROMA-PHARMA GmbH Industriezeile 6, 2100 Leobendorf, Austria Phone: +43 2262 684 680; Fax: +43 2262 6846 8165 E-mail: office@croma.at; Web: www.croma.at
Coordinating investigator:	[redacted]
Investigation site(s):	At least 3 sites located in Austria (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:	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.

* Beside saypha® Volume Lidocaine the product is also registered in some countries under the name Princess® Volume Lidocaine

Investigators and administrative structure of the clinical investigation

Investigators: This is a multicenter clinical investigation, which will be conducted in the European Union. 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.

Medical Monitor

[redacted]

Other institutions: [redacted]

This is a contract research organization, also referred as Sponsor's representative in this CIP, which will be responsible for clinical project management, ethics and regulatory submissions, clinical investigation monitoring, investigational device vigilance and expedited safety reporting, data management, statistical analysis, and clinical investigation report writing.

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

Contact for reportable events

[redacted]

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.

Approval and signature pages

Clinical investigation plan agreed to by the Sponsor

Approval and signature pages

Clinical investigation plan agreed to by the Coordinating investigator

_____ _____

[redacted] Date

Approval and signature pages

Principal investigator agreement

I agree:

- To assume responsibility for the proper conduct of the clinical investigation at the site specified above, and to conduct the investigation in compliance with this clinical investigational 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, 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 favourable 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 investigational medical device as described in this CIP and any other information provided by the Sponsor including, but not limited to, the current Investigator's Brochure, or equivalent document.
- To ensure that all persons providing assistance during the clinical investigation are adequately informed about the investigational medical device and of their study-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 study product, 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: _____

Investigator's address: _____

_____

Investigator's signature: _____

Date: _____

Synopsis

Investigation title	A prospective, randomized, multicenter study evaluating saypha® VOLUME Lidocaine for the correction of nasolabial folds
Short title	**SAVINO** (**SA**ypha **V**olume L**I**docaine in **N**asolabial F**O**lds)
Investigation ID	CPH-101-201477
Investigation sites	At least 3 sites located in Austria
Phase of development	Investigation according to § 40 (2) MPG
Aesthetic Indication	Moderate to severe nasolabial folds
Planned duration	The duration of the clinical investigation will be a maximum of 24 months for each participating subject. The total expected duration of the clinical investigation is about 27 months with an expected recruitment period of about 3 months. Recruitment halts due to COVID-19 pandemic lead to the prolongation of the recruitment period and the extension of the total duration of the clinical investigation. In case it is observed by the investigators that at a given visit no aesthetic effect is any more visible in approximately 75 % of the subjects, the study can be terminated at an earlier time point, but not before week 52.
Objectives	• To evaluate the performance of saypha® VOLUME Lidocaine for the correction of nasolabial folds using injection into the deep dermis or supraperiostal • To evaluate the safety and long term safety of saypha® VOLUME Lidocaine when used for correction of nasolabial folds • To evaluate the duration of the aesthetic effect
Study design	A prospective, randomized, multicenter investigation. Following informed consent and screening, eligible subjects with moderate to severe nasolabial folds will be injected with saypha® VOLUME Lidocaine into the deep dermis or supraperiostal, and will return for follow-up assessments at Week 2, 4, 24, 36, 52 and optional at Week 65, 78 and 104 after the treatment. A Touch-up treatment may be done at Week 2, if deemed appropriate by the investigator. The performance of the investigational device will be evaluated by the investigator by assessing severity of nasolabial folds using the Nasolabial Folds Severity Rating Scale (NLF-SRS) at Week 4, 24, 36, 52 after the treatment and optional at Week 65, 78 and 104 and in comparison to Day 0. Telephone visits will be performed approximately 24 hours post-administration to monitor possible adverse events. In case any adverse events are reported during the telephone visits an unscheduled visit should be performed. A 'responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5 point-validated NLF-SRS at week 24 relative to Baseline (Day 0) score on both sides. Individual NLF-SRS grades per visit will be assessed separately for the right and left NLF. The assessment of the aesthetic effect by the investigator and the global aesthetic improvement (by the investigator and by subject), using the GAIS will be assessed at Week 4, 24, 36, 52 and optional at Week 65, 78, and 104 after the treatment. The subject will evaluate pain intensity associated with the treatment at Day 0 and at Week 2 (if Touch-up

	treatment occurred), and satisfaction with the treatment at Week 4, 24, 36, 52 and optional at Week 65, 78 and 104 after the treatment. Eligible patients will be randomized according the ratio 1:1 (manufacturing site C1: manufacturing site HQ). The safety will be evaluated based on occurrence of adverse events, which will be collected throughout the investigation. The concomitant medication will be documented throughout the study.
Number of subjects	Approximately 100+10 subjects will be included, to obtain the Week 24 performance data in at least 100 subjects. Approximately 10 drop outs are estimated
Eligibility criteria	Inclusion criteria: A subject must meet **ALL** of the following criteria to be eligible for the study: 1. Male or female 18 years of age or older 2. Presence of two fully visible, approximately symmetrical nasolabial folds, with each of the folds scored with 2 or 3 according to the 5-grade Nasolabial Folds Severity Rating Scale (NLF-SRS) as assessed by the investigator 3. Healthy skin in the facial area and free of diseases that could interfere in cutaneous aging evaluation 4. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation 5. Written signed and dated informed consent

	Exclusion criteria: A subject who meets **ANY** of the following criteria is **NOT** eligible for the study: 1. Pregnancy, lactation, planned pregnancy or unwillingness to use contraception at any time during the study (for women of child-bearing potential only) 2. History of mental disorders or emotional instability 3. History of allergic reaction or hypersensitivity to hyaluronic acid, lidocaine, or any amide-based anaesthetic 4. Presence of silicone implant or another non-absorbable substance (permanent fillers) in the nasolabial region 5. Any superficial or deep facial surgery or injection or implantation of any dermal fillers (including but not limited to hyaluronic acid, collagen, calcium hydroxylapatite, poly-l-lactic acid, polymethylmethacrylate, autologous fat injections), application of any absorbable and non-absorbable sutures (thread) for any purpose including wound care and facial lifting, any laser therapy (including but not limited to Neodym-YAG, KTP, IPL, Diode lasers as well as Erbium-YAG, CO_2 or other ablative lasers), dermoabrasion, or botulinum toxin application in the nasolabial region within previous 12 months prior to enrolment, or any chemical peeling procedures (including but not limited to glycolic acid, trichloroacetic acid or phenolic peels) within previous 3 months prior to enrolment, or planning to undergo such procedures in the treatment area during the study 6. Presence of infectious, inflammatory, or proliferative lesions in the nasolabial region 7. Cutaneous lesions in the treatment area 8. Known human immune deficiency virus-positive individuals 9. History of allergies against aesthetic filling products and recurrent (3 times a year) herpes simplex in the treated area 10. Tendency to hypertrophic scars and/or keloid formation 11. History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy
	12. Uncontrolled systemic diseases (such as diabetes mellitus) 13. Bariatric surgery within 12 months prior to enrollment or planned during the clinical investigation 14. Use of anticoagulant or thrombolytic medication from 10 days pre- to 3 days post injection 15. Any medical condition which, in the investigator's opinion, prohibits the inclusion in the study 16. Current or previous (within 30 days of enrolment) treatment with another investigational drug and/or medical device or participation in another clinical study 17. Previous enrolment in this clinical investigation 18. Subjects whose participation in clinical trials is prohibited by the Austrian Medical Devices Act (e.g., persons with a legal custodian appointed due to mental disability, prisoners, soldiers and other members of the armed forces, civil servants) 19. Any dental procedures one month before until one month after treatment with the investigational device
Investigational device and mode of administration	saypha® VOLUME Lidocaine is a sterile, biodegradable, viscoelastic, transparent, isotonic and homogenized injectable gel implant formulated in a physiologic buffer to a concentration of 23 mg/mL, with addition of 0.3% lidocaine hydrochloride.

	saypha® VOLUME Lidocaine is administered by injection into the deep dermis or supraperiostal. The volume applied depends on the size of the area which requires correction and will be selected by the investigator. It is recommended that a maximum volume of 4 ml per treatment is applied, but should not exceed 10 mL in total per treatment.
Treatment duration	A single application, with optional Touch-up treatment after two weeks, if the desired level of correction has not been achieved with the initial application
Primary performance endpoints	• The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24, within each manufacturing site, C1 and HQ, separately and for the whole analysis population
Secondary performance endpoints	The following secondary performance endpoints will be evaluated within each manufacturing site, C1 and HQ, separately and for the whole analysis population: • The average change versus baseline in the NLF-SRS grade at Week 4, Week 24, Week 36, Week 52 and, optional at Week 65, Week 78 and Week 104 as evaluated by the investigator • The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104
Exploratory performance endpoints	The primary and secondary performance endpoints will be evaluated within the subgroups defined by the injection technique and device, needle and cannula, respectively. The following endpoints will be assessed for the whole analysis population: • The proportion of subjects with the NLF-SRS grade reduced by ≥2 point versus baseline at Week 4, Week 24, Week 36 and Week 52 and optional at Week 65, Week 78 and Week 104. • The proportion of subjects with aesthetic improvement at Week 4, Week 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104, as evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS) • The proportion of subjects with aesthetic improvement at Week 4, Week 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104, as evaluated by the subject using the Global Aesthetic Improvement Scale (GAIS) • Subjects' satisfaction with aesthetic outcome of the treatment at Week 4, Week 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 using the Face-Q Satisfaction with outcome Scale as evaluated by the subject • The average pain intensity during and after the treatment, as evaluated by the subject using an 11-point Numeric Pain Rating Scale (NPRS) immediately after the last injection and 15 min. thereafter, respectively • The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 as evaluated by the independent reviewer of photographs.

	• Percentage of subjects having an aesthetic effect at Weeks 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 based on the investigator's life assessment.
Safety endpoints	• Occurrence and frequency of adverse events within each manufacturing site, C1 and HQ, separately and for the whole analysis population • Occurrence and frequency of adverse events within each subgroup defined by the injection device, needle and cannula, respectively.
Statistical methods	All analyses will be done in the Intent-to-treat population, defined as all subjects who received the investigational device and have at least one post-treatment assessment. NLF-SRS grades per visit will be calculated as the mean of grades assigned to the left and the right nasolabial fold, respectively. The absolute NLF-SRS change versus baseline will be computed by subtracting the value obtained on Day 0 and summarized by the visit using descriptive statistics. A 'responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5 point-validated NLF-SRS at week 24 relative to Baseline (Day 0) score on both sides. Individual NLF-SRS grades per visit will be assessed separately for the the right and left NLF. A Response rate of 90% at week 24 is estimated. Additionally, the two-sided 95% confidence intervals of the expected change from baseline will be given and proportions (with two-sided 95% confidence intervals) of subjects with NLF-SRS improvement (i.e, reduction in NLF-SRS grades) of ≥1 or ≥2, respectively, will be calculated. For it, the changes from baseline are assumed to be normal distributed and the count of responders follows a binomial distribution. Adverse events will be summarised by preferred term and system organ class, and also by intensity, relationship to the investigational medical device or procedure, and seriousness. A formal interim analysis of performance and safety data will be done upon completion of the Week 24 visit. Summaries will be provided for the whole analysis population, as well as within each manufacturing site, C1 and HQ, separately.

Schedule of procedures and events

Table 1. Schedule of procedures and events

Assessment	VISIT 1*	VISIT 2∞	VISIT 3	VISIT 4∞Ω	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9§	VISIT 10§	VISIT 11§
	Baseline **Day 0**	TC 24 h after treatment	**Week 2** (± 2 days)	TC 24 h after treatment	**Week 4** (± 4 days)	**Week 24** (± 7 days)	**Week 36** (± 7 days)	**Week 52** (± 7 days)	**Week 65** (± 7 days)	**Week 78** (± 7 days)	**Week 104** (± 7 days)
Informed consent	x**										
Demographic data[a]	x**										
Medical/ aesthetic history	x**										
Prior medication[b]	x**										
NLF-SRS grading of nasolabial folds[c]	x**				x	x	x	x	x§	x§	x§
Urine pregnancy test[d]	x**		x**		x	x	x	x	x§	x§	x§
Eligibility assessment	x**										
Treatment	x		x#								
Photography	x**		x**		x	x	x	x	x§	x§	x§
Pain assessment[e]	x		xΩ								
GAIS assessment[f]					x	x	x	x	x§	x§	x§
GAIS assessment by the subject					x	x	x	x	x§	x§	x§
Subject satisfaction[g]					x	x	x	x	x§	x§	x§

Assessment	VISIT 1*	VISIT 2∞	VISIT 3	VISIT 4∞Ω	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9§	VISIT 10§	VISIT 11§
	Baseline **Day 0**	TC 24 h after treatment	**Week 2** (± 2 days)	TC 24 h after treatment	**Week 4** (± 4 days)	**Week 24** (± 7 days)	**Week 36** (± 7 days)	**Week 52** (± 7 days)	**Week 65** (± 7 days)	**Week 78** (± 7 days)	**Week 104** (± 7 days)
Assessment of aesthetic effect by the investigator						x	x	x	x§	x§	x§
Adverse events[h]	x***	x∞	x	x∞ Ω	x	x	x	x	x§	x§	x§
Concomitant medication[h]	x***		x		x	x	x	x	x§	x§	x§

* Includes screening and treatment.
** Prior to application of the investigational device
*** From beginning of the treatment onwards
§ Optional the evaluation of the duration of the clinical investigation is planned for 104 Weeks at a maximum. In case it is observed by the investigators that no aesthetic effect is any more visible in approximately 75 % of the subjects, the study can be terminated at an earlier time point, but not before week 52..
# Touch-up treatment is optional (at investigator's discretion, if full correction was not achieved after initial treatment).
∞ Telephone communication approximately 24 hours post-administration in order to monitor adverse events. In case of AEs an unscheduled visit should take place.
Ω To be performed only if Touch-up treatment occurred
a Includes date of birth, sex, and race
b All medication taken by the subject within the previous 10 days
c Performed by the investigator using the Nasolabial Folds Severity Rating Scale (NLF-SRS); the severity of the left and the right fold will be separately graded
d In females of child-bearing potential only, including women who are postmenopausal for less than 12 months
e Evaluated by the subject immediately after injection and approximately 15 min. thereafter using an 11-point Numeric Pain Rating Scale
f Evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS)
g Evaluated by the subject using the FACE Q Satisfaction with Outcome
h To be collected throughout the investigation, from beginning of the treatment until the last visit, in order to identify potential adverse events post-administration an safety evaluation after 15 minutes needs to take place.

List of abbreviations

ADE	Adverse device effect
AE	Adverse event
BDDE	1,4-butanediol diglycidyl ether
C1	Manufacturing site C1 Beautyplant
CIP	Clinical investigation plan
CRF	Case report form
DCF	Data clarification form
DR	Deviation Report
EC	Ethics Committee
eCRF	Electronic Case report form
GAIS	Global Aesthetic Improvement Scale
GCP	Good clinical practice
HA	Hyaluronic acid
HQ	Manufacturing site Headquarter
IB	Investigator's brochure
ICF	Informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
mIU	Milli-international unit
NLF	Nasolabial fold
NLF-SRS	Nasolabial Folds Severity Rating Scale
NPRS	Numeric Pain Rating Scale
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TMF	Trial master file
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet
W/WW	Weight/WeightW

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1 Background

Skin aging is a natural and progressive process, driven by intrinsic and extrinsic factors. In addition to the skin, it also involves the skin support systems including the bone, cartilage, and subcutaneous compartments. Within the skin, aging results in reduced collagen production, fragmentation of elastin network, and decreased turnover of skin cells. The loss of extracellular matrix and its major component, hyaluronic acid (HA), which forms a viscoelastic surrounding for collagen and elastin fibres, results in reduced skin elasticity and turgor[1]. Due to reduced elasticity, the repeated muscle action produces prominent wrinkles and creases in the mimetic areas of facial skin, while concomitant involution of facial fat deposits and bone atrophy contribute to skin laxity and facial volume loss and redistribution, resulting in aged face[2].

Appearance of nasolabial folds is one of the typical clinical manifestations of facial aging, which also include flaccidity of the skin and subcutaneous tissue, wrinkle expression in the upper third of the face, tear through, drop of the angle of the mouth, loss of definition in the mandibular border, cervico-facial platysmal bands, and changes in skin pigmentation[3].

Perception of age and health is critical in the judgement of attractiveness. Young faces are generally perceived to be more attractive than old faces, and estimated age is negatively correlated with perceived attractiveness[4,5.] 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[6].

Dermal fillers are widely used for facial rejuvenation and correction of deep wrinkles, including nasolabial folds. These treatments provide desirable aesthetic outcomes with minimal invasiveness and without the downtime associated with surgery. HA dermal fillers are most popular because of their ease of administration, predictable effectiveness, good safety profile, and quick patient recovery. In order to improve the comfort of filler injections, a local anaesthetic (lidocaine hydrochloride) has been included in their formulation to reduce procedural pain and to bypass the need for additional anaesthesia[7].

2 Identification and description of the investigational device

Please refer to the saypha® VOLUME Lidocaine Investigator's brochure (IB)[8] for detailed information on the investigational device.

2.1 Device description

saypha® VOLUME Lidocaine is a sterile, biodegradable, viscoelastic, clear, transparent, isotonic and homogenized injectable gel implant. The implant consists of HA obtained from *Streptococcus equi* bacteria, which is highly cross-linked using 1,4-butanediol diglycidyl ether (BDDE) and formulated to a concentration of 23 mg/mL in a physiologic buffer (phosphate buffer pH 6.8-7.4, sodium chloride) with supplementation of 0.3% w/w lidocaine hydrochloride.

The device packaging contains one prefilled syringe with 1.0 mL of the injectable gel implant, two 27G ½″ disposable sterile needles and a product leaflet.

saypha® VOLUME Lidocaine is a class III medical device, which also contains an active pharmaceutical ingredient, a well-known local anaesthetic lidocaine hydrochloride, as an ancillary substance. It is an absorbable soft tissue filler for injection into the deep dermis or supraperiostal and remains in long term contact with human skin and connective tissues. HA is a natural component of human skin, hence saypha® VOLUME Lidocaine is naturally absorbed, with the lifetime of the device anticipated to last up to 9 months after treatment. The ancillary component, lidocaine hydrochloride, is rapidly released from

the device after injection, and due to short half-life of around 90 minutes is quickly eliminated from the body.

The device is manufactured in compliance with EN ISO 13485:2016. No materials of human or animal origin are used during manufacture or as raw materials.

Saypha® VOLUME Lidocaine is designed for single use and upon opening should not be re-sterilized or reused.

2.2 Manufacturer

saypha® VOLUME Lidocaine is manufactured by CROMA-PHARMA GmbH, Industriezeile 6, 2100 Leobendorf, Austria.

Enclosed needles are manufactured by [redacted]

Additionally, 25G x 2", 0.5 x 50 mm cannulas are provided to the investigational site to be used with the investigational deviceand manufactured by [redacted]

2.3 Intended Aesthetic purpose and mode of administration

saypha® VOLUME Lidocaine is a soft tissue filler, to be used in adults (18 years and older).

The device is intended to correct moderate to severe nasolabial folds. It is intended to be injected into the deep dermis or supraperiostal.

The amount injected depends on the size of the area to be corrected and the desired level of soft tissue augmentation. It is estimated that a maximum volume of 4 ml per treatment is needed[9,10], but should not exceed 10 mL in total per treatment or 20 mL per year.

A maximum of 4 mL is a commonly used amount to be injected for nasolabial fold treatment.

The injection technique, which is described in Section 6.2.2 Methods of use, is essential for success of the treatment. Therefore, saypha® VOLUME Lidocaine should be administered exclusively by physicians who have received specific training on its application and use in respective indications.

In the present clinical investigation, saypha® VOLUME Lidocaine will be used for correction of moderate to severe nasolabial folds.

2.4 Traceability

Each carton of saypha® VOLUME Lidocaine is identified and tracked by its code number and a unique kit number. Peel-off labels are attached on the carton box of the kit showing the code number and kit number. To ensure the traceability of each device the peel-off label should be placed in the medical file of the subject treated with the device.

3 Justification for the design of the clinical investigation

3.1 Non-clinical data and biocompatibility

HA is 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. HA has a considerable water-binding capacity, and by this mechanism it increases dermal volume and compressibility[11]. 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[12]. HA 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 BDDE. The cross-linked HA is degraded via the same mechanisms as native

chains, but at a much slower rate, extending the clinical effect of BDDE-cross-linked HA for up to one year[13].

Lidocaine hydrochloride, an ancillary component of the device, is a well-known local anaesthetic. 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[14]. Rapid release of lidocaine from HA gel, allowing for fast onset of action after injection, has been demonstrated *in vitro*[8].

In preclinical and biocompatibility studies, the sensitization, irritation, and toxicity potential (including genotoxicity) of saypha® VOLUME Lidocaine were investigated by adding device extracts to cell cultures, by intradermal administration in rabbits and guinea pigs and by intraperitoneal administration of device extracts/final product in rats and mice. The tolerability of saypha® VOLUME Lidocaine was tested by implanting the device into intradermal tissue of rabbits. All studies were performed in accordance with regulatory requirements and good laboratory practice. saypha® VOLUME Lidocaine was observed to be biocompatible and is expected to be well-tolerated. The device was classified as non-irritant and a non-sensitizer. No acute toxicity was evident in an acute systemic toxicity study in mice and in a repeated dose systemic toxicity study in rats. A gene mutation test showed saypha® VOLUME Lidocaine to be non-genotoxic[8].

3.2 Clinical data

Since the launch of the first BDDE-cross-linked HA dermal filler for aesthetic use in 1996, over 50 clinical studies have been conducted with this type of medical device, which included more than 9,000 subjects[13]. HA 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[12]. Over time, their use was extended to medical reconstructive purposes in the treatment of pathologic conditions like facial lipoatrophy, morphologic asymmetry of the face, and depressed scars. 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.

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. When used for infiltrative anaesthesia, lidocaine hydrochloride has fast onset of action and moderate duration of effect lasting 1.5-2 h[15]. Absorbed lidocaine is metabolized in the liver and eliminated via the kidneys with a half-life of around 90 minutes[16]. 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[15,16].

The performance and safety of HA 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[7,8].
saypha® VOLUME Lidocaine received the European Conformity (CE) mark in March 2016.
A prospective, open label, multicenter, post market study evaluating Princess® VOLUME Lidocaine for the correction of nasolabial folds has been conducted. The results regarding performance endpoints showed that Princess® VOLUME Lidocaine is effective in reducing nasolabial folds. At the primary endpoint (Week 24 assessment) 94.1% of the per-protocol subjects demonstrated ≥1 grade improvement in their nasolabial fold severity compared with the Baseline status. The finding regarding

safety endpoint indicated that Princess® VOLUME Lidocaine is safe and well tolerated. All reported AEs were mild. No serious AEs or deaths were reported in the investigation.

3.3 Justification for the clinical investigation

The current clinical investigation is designed to evaluate the performance of saypha® VOLUME Lidocaine for the correction of nasolabial folds using injection into the deep dermis or supraperiostal and to compare two different manufacturing sites.

In addition, this investigation should support the approval by obtaining clinical data on the performance and safety of saypha® VOLUME Lidocaine for the correction of nasolabial folds.

A prospective, non-comparative design was selected because it allows for the most efficient collection of clinical data on the investigational device, in a manner which is appropriate to address the purpose and objectives of the present investigation. In the absence of spontaneous improvement of nasolabial folds, it is reasonable to assume that the treatment effect can be adequately assessed by comparing the post-treatment observations versus baseline, eliminating the need for a control group. The randomization regarding manufacturing site, C1 and HQ, will be performed according the ratio 1:1 to present the resuts of the two manufacturing sites descriptively.

The primary performance endpoints are based on evaluation using a validated 5-point scale for assessment of severity of nasolabial folds, the Nasolabial Folds Severity Rating Scale (NLF-SRS), and is set at 24 weeks after administration of the device to address the minimum required durability of effect. Follow-up is extended a maximum up to 104 weeks, to get additional information on long-term effects and to evaluate the aesthetic outcome. 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 validated 11-point Numeric Pain Rating Scale (NRPS)[17].

4 Risks and benefits of the investigational device 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 moderate-to-severe nasolabial folds, thereby improving their psychological and social wellbeing. This is achieved by a minimally invasive procedure with a short downtime, which results in an immediate and long-lasting effect, persisting for 6-12 months.

4.2 Anticipated adverse device effects

The safety profile of BDDE-cross-linked HA dermal fillers, with or without lidocaine, is well established. In general, these devices are well tolerated and safe, with a low frequency of side effects[18]. Adverse effects that have been observed with devices similar to saypha® VOLUME Lidocaine are summarized in Table 2, on the following page.

“A prospective, open label, multicenter, post market study evaluating Princess® VOLUME Lidocaine for the correction of nasolabial folds” all 62 screened and enrolled subjects were treated with the investigational medical device at Baseline. The mean number of used devices was 2.7 (standard deviation [SD]: 0.8) and the mean injected volume was 1.15 mL (SD: 0.46) for the right nasolabial folds, and 1.16 mL (SD: 0.45) for the left nasolabial folds. At Week 2, eight subjects received touch-up treatment using a mean of 1.1 mL (SD: 0.4) investigational medical devices. The mean injected volume for touch-up treatment was 0.45 mL (SD: 0.3) for the right nasolabial folds, and 0.29 mL (SD: 0.3) for the left nasolabial folds. The results show that adverse device effects include injection site hematoma, hypoesthesia and pain, one subject showed nervous system disorder and one subject had syncope. However, all ADEs were mild and had resolved within a maximum of 13 days of their onset.

Table 2. Adverse effects of cross-linked hyaluronic acid dermal fillers (with or without lidocaine)

Common	Rare	Very rare
• Redness, erythema • Swelling, oedema • Pain, itching, burning, discomfort • Tenderness • Bleeding • Bruising, hematoma	• Hypersensitivity, angioedema • Infection, abscess • Herpes reactivation • Irritation, inflammation, granuloma • Malar oedema • Implant visibility, nodules, beading, lumpiness, implant-site mass • Firmness, induration • Discoloration, dispigmentation, puncture marks • Paresthesia, numbness • Implant migration • Scar sarcoidosis • Scleromyxedema • Teleangiectasia (generalized) • Vasculitis cutaneous • Vasospasm • Vasovagal reaction during injection	• Vascular compromise or arterial occlusion (typically presented as immediate skin blanching, followed by a Livedoid pattern, discoloration or necrosis) • Retinal artery occlusion, vision loss • Necrosis

Common AEs like swelling, redness, tenderness, pain and bruising are typically mild in severity and usually resolve within 1-2 days after injection; resolution of bruising may take a little bit longer. Discomfort and pain may be reduced or prevented by application of ice before the injection. Redness, swelling and bruising may be prevented or alleviated by application of ice-packs for 5-10 minutes after the injection.

Additional information on AEs, especially serious events like arterial occlusion and necrosis is provided in the IB.

In case impending tissue necrosis, which may occur with any dermal filler, a recent consensus statement on the treatment of HA filler-induced impending necrosis recommends immediate treatment with high doses of hyaluronidase (e.g., at least 200 units of Vitrase®, or equivalent), followed by warm compress, vigorous massage and topical nitroglycerin paste. If no improvement is seen within 60 minutes, additional quantities of hyaluronidase should be injected (3-4 cycles in total). An oral aspirin regimen (e.g., 650 mg per day) should help prevent further clot formation. Daily follow-up is advised.

In case of an adverse event the Expert Consensus Recommendations for treatment of Soft Tissue Filler Complications[19]should be followed in the discretion of the investigator. The current Expert Consensus Recommendations for treatment of Soft Tissue Filler Complication are filed in the Investigator´s File.

4.3 Possible interactions with concomitant medical treatments

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

Anticoagulant and antiplatelet drugs may increase the risk of bleeding or bruising, so the subject should be asked about use of such medications, and the prescribing physician should be consulted to appropriately assess the risk level.

Sodium hyaluronate is incompatible with quaternary ammonium compounds such as benzalkonium chloride solutions. 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 the subjects and exclusion of those who may have an increased risk of developing certain types of AEs (see Section 6.3.5), proper injection technique (described in Section 6.2.2), appropriate training of the investigators to ensure correct application of the device, and regular follow-up visits over the following 104 weeks (maximum), which will allow for timely recognition and management of potential AEs. After insertion of the needle / cannula, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular. Furthermore, the subjects will be instructed to immediately contact the investigator in case of occurrence of any AE between the scheduled visits.

4.5 Risk-to-benefit rationale

HA-based dermal fillers, such as saypha® VOLUME Lidocaine, are generally considered very safe and effective, and have been widely used for soft tissue augmentation worldwide. There is also no scientific evidence demonstrating adverse events of fillers or hyaluronidase in pregnant women. Observed adverse effects are mainly related to the injection procedure, are transient and mostly mild. While few serious adverse effects have been reported, these are very rare and not expected to occur when the device is correctly applied. This is supported by a remarkable safety track record of saypha® VOLUME, with few ADEs reported among almost 2 million units sold since 2009, combined with favorable safety data from one clinical trial.

The performance and safety of lidocaine-containing HA dermal fillers for correction of nasolabial folds have been well documented in medical literature, and saypha® VOLUME Lidocaine has been approved for use in this indication. Considering the potential benefits of correction, in particular the immediate and long-lasting improvement of distressing aesthetic defect, and the low risk of the treatment when used appropriately by an experienced user, the benefits clearly outweigh the potential risks.

Participation in any clinical trial is currently associated with increased risk and additional challenges due to the COVID-19 pandemic caused by SARS-CoV-2. First and top priority of CROMA-PHARMA GmbH and [redacted] is the safety of the subjects and all persons involved in the clinical investigation.

Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) as well as national health authorities in Europe have issued guidelines that aim to provide recommendations for conduct of clinical trials during the COVID-19 pandemic. Given the circumstances of the recurrently relapsing pandemic or dynamically evolving epidemic situation with regard to the spread of COVID-19, CROMA-PHARMA GmbH and [redacted] will pay special attention to protect subjects participating in the investigation and clinical site staff involved in clinical investigations against infection with SARS-CoV-2 as requested by the EMA guidelines. Both, CROMA-PHARMA GmbH and [redacted], will continue to observe the situation with care and will re-evaluate and amend the risk mitigation measures, if deemed appropriate.

CROMA-PHARMA GmbH has evaluated all currently available safety data on saypha® VOLUME Lidocaine. Based on the local mode of administration once or twice, the low systemic exposure, and the safety profile, it is concluded that the treatment with saypha® VOLUME Lidocaine is not believed to put trial subjects under an increased risk for viral infections including SARS-CoV-2. At present, there is no change in the risk-benefit ratio foreseen that mandates any changes to the current protocol instructions.

However, the risk of exposure to infected people cannot be excluded as the subjects may need to expose themselves to public areas (e.g. commute to the investigation site) and have additional human contact (e.g. with clinical site staff). Appropriate risk assessments and mitigation measures will be considered to protect the health and well-being of involved persons and to ensure the integrity of the data obtained during the clinical investigation.

If site visits are not possible, safety data will be collected remotely by the Clinical Research Associate via telephone or electronic communication to ensure subject safety.

Investigators are responsible for taking appropriate measures to ensure the safety of individual subjects in accordance with preventive measures enacted by local authorities.

4.6 COVID-19 pandemic contingency plan

Without compromising the safety of subjects and integrity of the investigation, it is expected that all efforts are made to secure attendance of subjects at the clinical investigation site for all visits, ensuring efficacy and safety assessments for the investigation. This includes but is not limited to complying with recommendations/regulations issued by local health authorities, the increase of protective safety and hygiene measures (e.g. mask obligation, hand disinfection, distance control) for both subjects and site personnel, and the regular monitoring of the health status of subjects. Those safety and hygiene measures will have no influence on the conduct of the investigation but are being implemented to minimize the risk of spread of COVID-19 infection.

To minimize exposure of subjects to public areas and transportation, CROMA-PHARMA GmbH is reimbursing the travel costs of subjects on their way to and from the investigation site when using a taxi.

It will be at the discretion of the investigator to decide whether subject on-site visits are considered necessary to ensure subject safety in periods when on-site visits are not interfering with the primary endpoint of the CIP (e.g. for visits 5, 7, 8-11).). If deemed necessary, the investigator may provide a letter to the subjects on the way to sites explaining why commuting is required in this case.

If on-site visits are not possible due to preventive measures issued by city or local authorities or site obligations, the affected site will postpone on-site visits and will perform phone calls and collect safety and performance data to ensure subject safety as far as possible.

In general, more intense telephone contacts between clinical site staff and enrolled subjects will be utilized to closely monitor the situation and status of subject participation. In the eCRF, it will be recorded whether a given assessment was done remotely or not done. Any telephone contact or unscheduled visit will be recorded. For any of these records, it will be reported if this was due to the COVID-19 pandemic.

If a subject is tested positive for COVID-19, the investigator may withdraw the subject from further participation. The continuation may be decided in cooperation between the investigator and the sponsor if the subject recovers prior to the next scheduled visit. A COVID-19 infection will be documented as AE.

5 Objectives and hypotheses of the clinical investigation

5.1 Objectives

The objectives of this clinical investigation are:

- To evaluate the performance of saypha® VOLUME Lidocaine for the correction of nasolabial folds using injection into the deep dermis or supraperiostal.
- To evaluate the safety of saypha® VOLUME Lidocaine when used for correction of nasolabial folds.
- To evaluate the duration of the aesthetic effect.

5.2 Hypotheses

This is a non-comparative study and does not entail formal hypothesis testing.

5.3 Claims and intended aesthetic performance of the investigation that are to be verified

The device is intended to correct moderate to severe nasolabial folds.

The intended aesthetic purpose of the device is to create volume and thereby improve moderate to severe nasolabial folds and to achieve aesthetic improvement. The product is designed to be injected into the deep dermis or supraperiostal.

The device is an absorbable implant intended to be used for adult human beings. It is totally resorbed. The device is intended for single use, it is sterile, non-active and without measuring function. No materials of animal origin are used during manufacturing or as raw materials. A drug substance (Lidocaine) is integrated into the device. The ancillary role of Lidocaine is to reduce the pain associated with injections into the skin.

The safety profile of lidocaine-containing HA dermal fillers is well established. Based on the equivalence of saypha® VOLUME Lidocaine with these products and available non-clinical safety data, it is anticipated that it will share the same safety profile, described in Section 4.2. All AEs and device deficiencies occurring during the investigation will be collected and reported.

6 Design of the clinical investigation

6.1 Design description

The present investigation is designed as a prospective, non-comparative, randomized, multicenter study. As justified in Section 3.3, this type of design is considered appropriate in view of the purpose and objectives of the study.

The investigation will consist of 11 visits (the three last visits are optional): the baseline (Day 0) visit, which will entail informed consent, screening assessments, the treatment, and early post-treatment assessments, telephone communication approximately 24 hours post-administration for monitoring of adverse events and follow-up visits at Week 2, 4, 24, 36, 52, 65 (optional), 78 (optional) and 104 (optional) after the treatment. Procedures to be performed at each visit are specified in Table 1. Schedule of procedures and events, which is located on page 11 and in section 6.

In case it is observed by the investigators that at a given visit no aesthetic effect is any more visible in approximately 75 % of the subjects, the study can be terminated at an earlier time point, but not before week 52.

6.1.1 Randomization

Subjects will be randomly assigned to manufacturing site (C1 and HQ) by means of a computer-generated randomization list with a 1:1 allocation. Eligible subjects are assigned random numbers in ascending order within each block beginning with the lowest number available. It is mandatory to stick to this procedure throughout the study.

6.1.2 Primary performance endpoints

The performance of the investigational device will be evaluated using the following primary endpoints (see section 7.4.1) (justification is provided in Section 3.3):

- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24, within each manufacturing site, C1 and HQ, separately and for the whole analysis population.

6.1.3 Secondary performance endpoints

The following secondary performance endpoints will be evaluated within each manufacturing site, C1 and HQ, separately and for the whole analysis population (see section 7.4.1):

- The average change versus baseline in the NLF-SRS grade at Week 4, Week 24, Week 36 and Week 52 and optional at Week 65, Week 78 and Week 104 as evaluated by the investigator.

- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4, Week 36 and Week 52 and optional at Week 65, Week 78 and Week 104.

6.1.4 Exploratory performance endpoints

The primary and secondary performance endpoints will be evaluated within the subgroups defined by the injection device, needle and cannula, respectively.

The following endpoints will be assessed for the whole analysis population:

- The proportion of subjects with the NLF-SRS grade reduced by ≥2 point versus baseline at Week 4, Week 24, Week 36 and Week 52 and optional at Week 65, Week 78 and Week 104.
- The proportion of subjects with aesthetic improvement at Week 4, Week 24, Week 36 and week 52 and optional at Week 65, Week 78 and Week 104 as evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS).
- The proportion of subjects with aesthetic improvement at Week 4, Week 24, Week 36 and week 52 and optional at Week 65, Week 78 and Week 104 as evaluated by the subject using the Global Aesthetic Improvement Scale (GAIS).
- Subjects' satisfaction with aesthetic outcome of the treatment at Week 4, Week 24, Week 36 and week 52 and optional at Week 65, Week 78 and Week 104 as evaluated by the subject.
- The average pain intensity during and after the treatment, as evaluated by the subject using an 11-point Numeric Pain Rating Scale (NPRS) immediately after the last injection and 15 min. thereafter, respectively.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4, Week 24, Week 36 and week 52 and optional at Week 65, Week 78 and Week 104 as evaluated by the independent reviewer of photographs.
- Percentage of subjects having an aesthetic effect at Weeks 24, Week 36, Week 52 and optional at Week 65, Week 78 and Week 104 based on the investigator's life assessment.

6.1.5 Safety endpoints

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

- Occurrence and frequency of adverse events within each manufacturing site, C1 and HQ, separately and for the whole analysis population.
- Occurrence and frequency of adverse events within each subgroup defined by the injection device, needle and cannula, respectively.

6.1.6 Schedule of procedures and events

6.1.6.1 *Baseline Visit (Visit 1)*

After written informed consent is obtained, the following assessments will be performed during Baseline Visit at Day 0:

- Demographic data collection
- Medical history (including information on prior facial aesthetic or surgical procedures)
- Prior medication
- Urine pregnancy test (in women of child-bearing potential)
- Photography
- Evaluation of inclusion and exclusion criteria
- NLF-SRS grading of nasolabial folds
- Treatment
- Pain assessment
- Adverse events
- Concomitant medication

6.1.6.2 *Telephone communication approximately 24 h after initial treatment (Visit 2)*

- Monitoring of post-administration adverse events
- In case of AEs an unscheduled visit may take place.

6.1.6.3 *Week 2 Visit (Visit 3)*

The following assessments will be performed 2 weeks (± 2 days) after Visit 1:

- Photography (only if Touch-up treatment performed)
- Touch-up treatment (optional, to the discretion of the injector)
- Pain assessment (only if Touch-up treatment performed)
- Urine pregnancy test (in women of child-bearing potential)
- Adverse events
- Concomitant medication

6.1.6.4 *Telephone communication 24 h after Touch-up treatment (Visit 4)*

- Monitoring of post-administration adverse events
- In case of AEs an unscheduled visit may take place.

6.1.6.5 *Week 4 (Visit 5), Week 24 (Visit 6), Week 36 (Visit 7), Week 52 (Visit 8), Week 65 (Visit 9, optional), Week 78 (Visit 10, optional) and Week 104 (Visit 11, optional) Visits*

The following assessments will be performed respectively 4 weeks (± 4 days), 24 weeks (± 7 days), 36 weeks (± 7 days) and 52 weeks (± 7 days) and 65 weeks (± 7 days), 78 weeks (± 7 days) and 104 weeks (± 7 days) after Visit 1 (last 3 visits are optional):

- Photography
- Urine pregnancy test (in women of child-bearing potential)
- NLF-SRS grading of nasolabial folds by the investigator
- GAIS assessment by the investigator
- GAIS assessment by the subject
- Subject satisfaction
- Assessment of aesthetic effect by the investigator
- Adverse events
- Concomitant medication

6.1.6.6 *Unscheduled Visits due to COVID-19 pandemic*

In case a planned on-site visit cannot take place due to COVID-19, the investigator may perform an unscheduled visit either as delayed on-site visit or as safety phone call.

- In case of unscheduled on-site visits, the investigator will perform all assesments forseen at the on-site visit that was cancelled due to COVID-19 pandemic.
- In case of unscheduled safety phone calls the investigator will record adverse events and concomitant medication. The investigator will additionally record the scores from the GAIS assessment by the subject and the subject satisfaction questionnaire via phone. The subject will confirm the correctness of the scores recorded via phone during the next on-site visits with his name, date and signature. The questionnaires will remain with the source data and will not be transferred into the TMF.

6.1.7 Replacement of subjects

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

6.2 Investigational device

6.2.1 Packaging, labelling and storage

Each device will be provided in a folding box containing one syringe prefilled with 1.0 mL of the injectable gel implant, two 27G ½″ disposable sterile needles and a product leaflet. Peel-off labels are attached on the carton box of the kit showing the code number and a unique kit number. To ensure the traceability of each device the peel-off label should be placed in the medical file of the subject treated with the device.

Additionally, 25G x 2”, 0.5 x 50 mm cannulas are provided to the investigational site to be used with the investigational device.

An additional label, indicating that the device is exclusively for use in a clinical investigation, will be placed on the outer commercial package of each investigational device, if required by national regulations.

The investigational device must be stored in the original box, at 2-25°C in a dry place, protected from light, heat and frost. The investigator must ensure that upon receipt of the investigational device and other study supplies, these are kept in an appropriate and secure location, with access limited to authorized individuals.

6.2.2 Methods of use

The investigational device will be administered to eligible subjects on study Day 0. A Touch-up treatment at week 2 is optional at investigator’s discretion, if full correction was not achieved after initial treatment.

Preparation for administration

The skin to be treated should be thoroughly cleaned and disinfected prior to injection of the device and appropriate aseptic technique should be employed throughout the procedure.

Prior to use the device, the luer-lock adapter should be held securely and the tip cap should be removed by twisting and pulling carefully, which should prevent formation of bubbles. The syringe should be held and the enclosed needle firmly attached. The needle or cannula should be secured tightly by twisting clockwise. The syringe is held correctly if the backstop opens at the back, toward the hand in which it is held. These steps are illustrated in the Instructions for Use.

Injection technique

The injection technique used is essential for success of the treatment. Therefore, all investigators must complete a specific training in the injection technique before using the medical device.

The investigational device should be injected into the deep dermis or supraperiostal. Superficial injections, near the interface of the epidermis and papillary dermis, can result in visible white, yellow, or blue nodules, which may be persistent. Deep injections into the subcutaneous fat may result in loss of the filler in the vast subcutaneous space, requiring larger volumes.

After insertion of the needle or cannula, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle or cannula is not intravascular.

The following injection techniques should be used:

Retrograde technique (Linear Threading technique): introduction of the entire needle/cannula along the wrinkle or skin depression and injecting while slowly withdrawing the needle/cannula.

Bolus technique:

The vertical supraperiosteal depot technique, where small depots of the filler (0.02-0.05 mL) are placed via serial vertical injections (2-3 mm apart) directly on the periosteum.

A minimum of 30 subjects should be treated either with the Retrograde technique or with the Bolus technique.

Lateral movements of the needle must be avoided since these may result in a fanlike dissection of the sub-epidermal plane, increasing the incidence of local AEs like bruising, swelling, redness, pain, or tenderness at the injection site.

The device should be injected slowly with the least amount of possible pressure for the same reason. If the needle or cannula is blocked, the pressure on the plunger rod should not be increased, but the injection stopped and the needle or cannula replaced.

If a larger volume of the filler is needed to achieve the correction, small volumes should be injected in two sessions, instead of high volumes in one session.

The injection must be stopped just before the needle or cannula is pulled out of the skin to prevent leakage of the device or placement too superficially in the skin.

The remainder of the investigational device from the same syringe after application to one fold can be used for the application to the other fold of the same subject at the same visit but not for any other subject or any other visit of the same subject.

In case of a vascular event, injection must be stopped immediately, and high dose hyaluronidase, massage and heat (gauze with hot water) should be applied. In addition, nitroglycerin paste may encourage vasodilatation. More details are provided in Section 4.2.

Completion of administration

After injection the investigator may apply a light massage for uniform distribution of the filler.

Application of ice packs for 5-10 min. post injection is optional and may reduce redness and swelling.

The subject should be requested to stay in the office for several minutes after the injection, to detect possible blanching caused by arterial occlusions.

Prior to discharge the subject should be advised to follow restrictions specified in Section 6.3.7.

6.2.3 Applied volume of the device

The amount of the device injected will depend on the defect to be corrected and will be selected by the investigator. The actual volume injected will be estimated by the investigator and recorded in the eCRF, together with information on injection technique, area of application, date, and exact start time and end time of injection.

The maximum recommended dosage is a volume of 4 mL per treatment, but should not exceed 10 mL in total per treatment or 20 mL per year.

6.2.4 Touch-up treatment

A Touch-up treatment may be performed at the Week 2 visit at the investigator's discretion, if correction is not deemed satisfactory after the first injection. It will be documented in the eCRF with the same level of details as the initial treatment. For the Touch-up treatment the same injection technique and the same device (needle or cannula) as used during initial treatment at visit 1 must be applied for a respective subject.

6.2.5 Precautions

- The device must not be used if the expiry date has lapsed, or if the packaging or contents are damaged.
- The device should only be used with the needle or cannula and syringe provided by the manufacturer.

- The needle or cannula must not be manipulated or bent, if the needle or cannula is blocked, pressure on the plunger rod should not be increased, instead injection should be stopped and the needle or cannula replaced.
- After use the syringe, needle or cannula and remaining contents should be disposed appropriately and the device should never be re-used.
- The device should not be injected into blood vessels, bones, tendons, ligaments, nerves, muscles or naevi.
- Injections into the periorbital area (crow's feet, eye circle, eye lids), glabellar region and nasal alae are not recommended.
- Overcorrection should be avoided.
- 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.

6.2.6 Rescue medication

In case of overcorrection or occurrence of nodules or vascular compromise, a commercially available hyaluronidase injection (e.g. [redacted] or similar) may be used at the discretion of the investigator.

In case of an adverse event the Expert Consensus Recommendations for treatment of Soft Tissue Filler Complications[19]should be followed in the discretion of the investigator. The current Expert Consensus Recommendations for treatment of Soft Tissue Filler Complication are filed in the Investigator´s File.

6.2.7 Investigational device accountability

The investigational device must not be used outside the context of this clinical investigation plan (CIP).

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

At the end of the clinical investigation, all remaining supplies, including empty boxes of investigational devices that have been used, must be returned to the Sponsor for accurate accounting of the investigational device. 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 after accountability was performed. Used needles shall be disposed immediately after the use as per routine procedure for medical waste disposal at the site.

Considering the number of subjects to be enrolled, the average volume of the device administered in the clinical investigation of saypha® VOLUME (0.9 mL per fold), and potential additional Touch-up treatment, it is anticipated that approximately 300 units of the investigational device will be used during this clinical investigation.

6.3 Subjects

6.3.1 Number of subjects and duration of the clinical investigation

Approximately 100 + 10 subjects with moderate to severe nasolabial folds will be enrolled and treated with the investigational device in order to obtain the Week 24 performance data in at least 100 subjects (approximately 50 of them in each manufacturing site). Approximately10 drop outs are estimated.

Each subject will participate in the study for maximum of 104 weeks. Considering the anticipated recruitment period of 3 months, the total expected duration of the clinical investigation will be

maximum of 27 months. Recruitment halts due to COVID-19 pandemic lead to the prolongation of the recruitment period and the extension of the total duration of the clinical investigation.

6.3.2 Recruitment strategy

The study subjects will be recruited by the investigator, among subjects who attend the investigation site seeking the corrective treatment for nasolabial folds. The investigator may also offer participation in the study to potential candidates identified in their subject database. In case of an unexpectedly low recruitment rate, the investigation may be advertised. In such case, the advertising strategy and materials will be submitted to the Ethics Committee (EC) for prior review and approval.

6.3.3 Subject identification

The study participants will be assigned a unique 5-digit number, with the first two digits identifying the site and the last three digits identifying the subject, e.g. 01-001. At each site the investigator will assign numbers to subjects in ascending order e.g. 001, 002, 003 etc. See also Section 6.3.10 for subject's confidentiality.

6.3.4 Inclusion criteria

A subject must meet all the following criteria to qualify for participation in this investigation

1. Male or female 18 years of age or older
2. Presence of two fully visible, approximately symmetrical nasolabial folds, with each of the folds scored 2-3 according to the 5-grade NLF-SRS as assessed by the investigator
3. Healthy skin in the facial area and free of diseases that could interfere in cutaneous aging evaluation
4. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation
5. Written signed and dated informed consent

6.3.5 Exclusion criteria

Subjects meeting any of the following criteria should not be enrolled:

1. Pregnancy, lactation, planned pregnancy or unwillingness to use contraception at any time during the study (for women of child-bearing potential only)
2. History of mental disorders or emotional instability
3. History of allergic reaction or hypersensitivity to hyaluronic acid, lidocaine, or any amide-based anaesthetic
4. Presence of silicone implant or another non-absorbable substance (permanent fillers) in the nasolabial region
5. Any superficial or deep facial surgery or injection or implantation of any dermal fillers (including but not limited to hyaluronic acid, collagen, calcium hydroxylapatite, poly-l-lactic acid, polymethylmethacrylate, autologous fat injections), application of any absorbable and non-absorbable sutures (thread) for any purpose including wound care and facial lifting, any laser therapy (including but not limited to Neodym-YAG, KTP, IPL, Diode lasers as well as Erbium-YAG, CO_2 or other ablative lasers), dermoabrasion, or botulinum toxin application in the nasolabial region within previous 12 months prior to enrolment, or any chemical peeling procedures (including but not limited to glycolic acid, trichloroacetic acid or phenolic peels) within previous 3 months prior to enrolment, or planning to undergo such procedures in the treatment area during the study
6. Presence of infectious, inflammatory, or proliferative lesions in the nasolabial region
7. Cutaneous lesions in the treatment area

8. Known human immune deficiency virus-positive individuals
9. History of allergies against aesthetic filling products and recurrent (3 times a year) herpes simplex in the treated area
10. Tendency to hypertrophic scars and/or keloid formation
11. History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy
12. Uncontrolled systemic diseases (such as diabetes mellitus)
13. Bariatric surgery within 12 months prior to enrollment or planned during the clinical investigation
14. Use of anticoagulant or thrombolytic medication from 10 days pre- to 3 days post injection
15. Any medical condition which, in the investigator's opinion, prohibits the inclusion in the study
16. Current or previous (within 30 days of enrolment) treatment with another investigational drug and/or medical device or participation in another clinical study
17. Previous enrolment in this clinical investigation
18. Subjects whose participation in clinical trials is prohibited by the Austrian Medical Devices Act (e.g., persons with a legal custodian appointed due to mental disability, prisoners, soldiers and other members of the armed forces, civil servants)
19. Any dental procedures one month before until one month after treatment with the investigational device

6.3.6 Withdrawal criteria and procedures

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
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 study, use of prohibited medication, or similar)
3. Investigator's decision, triggered by safety, behavioural or administrative reasons
4. Informed consent withdrawal

A subject is free to withdraw the consent and leave the investigation at any time with no obligation to specify the reason for withdrawal. Efforts should be made, however, to get in touch with subjects who did not attend the scheduled visit and clarify the reason for default.

Reasons, circumstances and findings related to early withdrawal should be fully described in 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 the Week 104 visit. In the event that the withdrawal is caused by an AE, the procedures stated in Section 14.6 must be followed.

6.3.7 Life-style and other restrictions

Contraception

The safety of saypha®VOLUME Lidocaine for use during pregnancy has not been established, so females of childbearing potential should use contraception or avoid unprotected sexual intercourse

throughout the clinical investigation. Any pregnancy occurring during the subject's participation in the investigation will be reported as an AE and followed-up as described in Section 14.6.

Other restrictions

The following restrictions apply to all subjects:

- Make-up should not be applied for 12 hours after injection;
- Prolonged exposure to sunlight or UV radiation must be avoided for 36 hours after injection; day care with UV protection should be used daily throughout the entire clinical investigation;
- To minimise 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 the injection;
- Subjects should abstain from frequent solarium visits;
- Subjects should abstain from alcohol on injection days.
- Use of saunas or Turkish baths is prohibited for one week after the injection.

6.3.8 Medical care upon termination of the clinical investigation

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

6.3.9 Screening/baseline failures

Data for screening/baseline failures (screened subjects who did not receive investigational device for whatever reason) will be collected in source documentation at the site and documented in the Screening log but will not be entered into the eCRF.

6.3.10 Subject identification, privacy and data confidentiality

Subjects' privacy and data confidentiality will be protected in line with the principles of good clinical practice, the European Data Protection Directive and other applicable international and national requirements. Subjects will provide authorisation 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 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) in their file. The investigator must maintain these documents in strict confidence. 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 8.3. 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, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

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. Schedule of procedures and events and in section 6.1.6.

It is the investigator's obligation to assure documentation of all relevant data in the subject's medical record, such as informed consent, subjects eligibility, medical history and concomitant diseases, date of enrolment into the clinical investigation, visit dates, results of examinations, application of medical device, and AEs.

6.4.1 Demographic data

The following demographic data will be collected: date of birth, gender and race.

6.4.2 Medical history

Medical history will be collected at Day 0, from subject interview and medical records (if available), covering relevant past medical history with particular reference to facial aesthetic or surgical procedures.

6.4.3 Pregnancy test

In females of childbearing potential, including women who are postmenopausal for less than 12 months, a urine pregnancy test will be performed using a dipstick test with sensitivity of ≤20 mLU of human chorionic gonadotropin per mL. The result will be recorded in the subject's medical record and the eCRF. This test must be done at each on-site visit except visits 2 and 4 which will be performed by telephone communication approximately 24h post-treatment.

6.4.4 Photography

Clinical photography of the subject's face will be taken by the investigator or their designee using the 3D LifeViz mini camera with dual beamer pointers (Quantificare).

A standardized procedure for study photography, which will be described in a separate Photo Manual, will be provided to the investigators. This Photo Manual will ensure consistency of the background, camera settings, lighting, and subject position between the visits and across the sites. Obtained photographs must be immediately uploaded to a secure storage system and a backup copy keep in the investigator physician's computer.

6.4.5 NLF-SRS grading of nasolabial folds

NLF-SRS is a validated, 5-point rating scale ranging from Grade 0 (none) to Grade 4 (extreme) as outlined in Table 3. The visual guide is provided in Figure 1. The severity of nasolabial folds will be evaluated by the investigator according to the NLF-SRS. The left and right nasolabial fold will be separately graded, and the assigned grades will be recorded in the subject's record and the eCRF.

Table 3. Nasolabial Folds Severity Rating Scale (*NLF-SRS*)

CROMA NLF-SRS grade	Description
0	None/minimal: No visible/minimal nasolabial folds
1	Mild: Shallow but visible nasolabial fold with a slight indentation
2	Moderate: Moderately deep nasolabial fold
3	Severe: Very deep nasolabial fold with prominent facial feature
4	Extreme: Extremely deep and long nasolabial fold with skin redundancy

Figure 1: Visual guide for Nasolabial folds severity rating scale (NLF-SRS)

6.4.6 Aesthetic improvement/GAIS assessment

The aesthetic improvement after correction of nasolabial folds will be evaluated at Week 4, 24, 36 and 52 and optional at week 65, 78 and 104 by the investigator and also by the subject using the Global Aesthetic Improvement Scale (GAIS)[20], presented in Table 4, and recorded in the eCRF.

Table 4. Global Aesthetic Improvement Scale (GAIS)

In case a scheduled on-site visit is not possible due to COVID-19 pandemic situation, the investigator will record the scores for GAIS assessment by the subject as reported by the subject via phone. The correctness of the latter recods will be confirmed by the subject during the next possible on-site visit with his signature. The countersigned subject questionnaire has to be kept with the source data and must not to be transferred into the TMF.

6.4.7 Assessment of aesthetic effect

The investigator will assess whether the aesthetic effect is still present in the subject. A live-assessment of the treated areas will be performed and the treated areas will be compared to the subject's photographs obtained at the Baseline Visit. The presence of the aesthetic effect will be recorded as either "Yes" or "No" in the subject's medical record and in the eCRF.
If a subject no longer has an aesthetic effect as of Week 52, this may prematurely lead to the termination of the clinical examination of the respective subject.
In this case new injections can be placed at previously injected locations.

6.4.8 Pain assessment

After initial administration and optional Touch-up treatment of the investigational device, the subject will be asked by the 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[17]. Pain intensity will be assessed twice, immediately after injection, and approximately 15 (±5) minutes thereafter, 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 in the Pain assessment form and the eCRF. To avoid over-reporting of pain, a non-leading question *„How do you feel?"* should be asked prior to pain assessment. Only spontaneously reported pain, or pain graded ≥4 will be recorded as an AE.

6.4.9 Subject's satisfaction assessment

Subject's satisfaction with the treatment in order to evaluate the performance of the device and consistency in alignment with subject expectation will be assessed using the FACE-Q questionnaire "Satisfaction with Outcome" scale. This is a validated instrument for evaluation of satisfaction with the outcome of a facial aesthetic procedure.[21] The subject will be asked to complete the questionnaire. The statement selected by the subject will be recorded in the Subject's satisfaction form and the eCRF.

In case a scheduled on-site visit is not possible due to COVID-19 pandemic situation, the investigator will record the scores for the FACE-Q questionnaire by the subject as reported by the subject via phone. The correctness of the latter records will be confirmed by the subject during the next possible on-site visit with name, date and signature. The countersigned subject questionnaire has to be kept in the source data and not to be transferred into the TMF.

6.4.10 Outcome evaluation by the independent reviewer of photographs

An independent photo reviewer will evaluate the treatment outcome using the NLF-SRS scale and based on the photographs. The independent photographic reviewer, who will assess treatment effect based on photographs of the subjects, will be dislocated from the investigation sites and will not discuss any findings with the investigators or independent clinical evaluators during the trial and until the final database lock. Moreover, an evaluation of nasolabial folds severity by an independent blinded photographic reviewer using the 5-point NLF-SRS scale and based on photographs will take place at the end of the study.

6.4.11 Safety monitoring

The safety of the investigational device will be monitored throughout the investigation, from Day 0/visit 1 until the final visit (visit 9). AEs will be collected at each visit. In addition, the subjects will be instructed to immediately contact the investigator by phone in case of occurrence of any untoward event between the visits. The procedure for collection, recording and reporting of AEs is described in Section 14.

In order to identify potential adverse events post-administration a safety evaluation after 15 minutes needs to take place.

In case a scheduled on-site visit cannot take place due to COVID-19 pandemic, the investigator should attempt to postpone the visit or make a safety-phone call to monitor the safety of the investigational device.

6.4.12 Prior and concomitant medication and non-drug therapies

Prior medication is defined as all medication taken within 10 days (whether continuing or not) prior to Day 0. Concomitant medication is defined as all medication taken from Day 0 (including medication taken immediately pre-injection and post-injection) until the Week 104 visit.

At each visit the subject must be asked about any new medication taken or changes in current medication, as well as, about any aesthetic procedure applied in the area treated with the investigational device.

All prior and concomitant medication and non-drug therapies will be recorded in the subject's medical record and the eCRF.

Prohibited medication and aesthetic treatments

- Immune therapy, i.e., treatment with biologics designed to boost the body's natural defences (from Day 0 until the end of the clinical investigation). COVID-19 vaccination is not prohibited.
- Anticoagulant, or thrombolytic drugs (from 10 days pre- until 3 days post-injection)
- Treatment with any investigational drug or other investigational medical device (throughout the clinical investigation).
- Facial surgery or implantation of dermal fillers other than the investigational device (from 12 months prior to Day 0 until the end of the clinical investigation)
- Absorbable and non-absorbable sutures (thread), laser therapy or dermabrasion (from 12 months prior to Day 0 until the end of the clinical investigation)
- Botulinum toxin treatment in the area treated with the investigational device (from 12 months prior to Day 0 until the end of the clinical investigation)
- Chemical peeling (from 3 months prior to Day 0 until the end of the clinical investigation)
- Skin needling or mesotherapy (from Day 0 until the end of the clinical investigation)
- Bariatric surgery (from 12 months prior to Visit 1 until the end of the clinical investigation)
- Dental/oral surgery or modification like bridge-work or implants (from four weeks before until four weeks after the IMD injection)

6.4.13 Factors that may compromise the outcome

There are no foreseeable factors that may significantly compromise the outcome. A substantial body weight change could possibly affect the results in individual subjects. Since this is an investigation, designed to mimic a real-life situation, this random and relatively rare event that can either improve or deteriorate the outcome will not be controlled. It is possible that women will prevail in the study population, but this reflects common clinical practice.

6.4.14 Early Termination Visit

At Early Termination Visit, or whenever the subject is withdrawn from the clinical investigation, all attempts should be made to perform the assessments described for Visit 6 (see section 6.1.6.5).

For safety reasons, the following assessments are recommended to be completed at a minimum:

- Record any new AE or changes of AEs
- Record changes in concomitant medication and procedures
- NLF assessment – investigator

6.4.15 Unscheduled Visit

An unscheduled visit may be performed at any time during the study if judged necessary by the investigator, such as for a severe reaction, clinically significant AE or suspected pregnancy. The investigator should treat these side effects appropriately.

In case the unscheduled visit results in early termination of the subject, the assessments for the Early Termination Visit should be performed (see section 6.4.14). Details of the event are to be recorded in the subject's records and in the eCRF.

In case a planned on-site visit cannot take place due to COVID-19, the investigator may perform an unscheduled visit either as delayed on-site visit and/or as safety phone call.

- In case of unscheduled on-site visits, the investigator will perform all assesments forseen at the on-site visit cancelled due to COVID-19 pandemic.
- In case of unscheduled safety phone calls the investigator will record adverse events and concomitant medication. The investigator will additionally record the scores from the GAIS assessment by the subject and the subject satisfaction questionnaire via phone. The subject will confirm the correctness of the scores recorded via phone during the next on-site visits with name, date and signature.

6.5 Monitoring plan

The conduct of this clinical investigation will be monitored by the Sponsor's representative, who will appoint a Monitor of the investigation. 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 and the eCRF with the investigator and their staff. The site must not enroll any study participant before this initiation visit.

During the investigation, further monitoring visits will be performed according to ISO 14155:2011, the applicable standard operating procedures, and local regulations. The eCRF will be reviewed against source data for adherence to the CIP, as well as for completeness, accuracy and consistency of data. Additionally, the Monitor will check the progress of enrolment, and will ensure that the investigational device is stored, dispensed and accounted for according to the respective specifications. Key study personnel must be available to assist the Monitor during these visits. The Monitor will inform the investigator or their authorized designee of any eCRF entry error, omission, or illegibility. The Monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or their authorized designees.

The investigator and their institution must permit the monitoring of the investigation, and provide the Monitor direct access to those portions of the subject's primary medical records, which directly concern this clinical investigation. In the course of risk-mitigation strategy adaption due to the pandemic situation the Monitoring plan was adapted and the option to perform remote monitoring was included in the monitoring strategy and submitted to the ethics committees and regulatory authority. Remote monitoring

will be implemented in case on-site monitoring is not possible to ensure patient safety. Remote monitoring will not include SDV and will be limited to eCRF checks until on-site visits can be resumed.

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

Up to approx. 100 + 10 subjects with moderate to severe nasolabial folds will be randomized with a 1:1 allocation to the manufacturing sites C1 and HQ, in order to obtain the 24-week performance and safety data from approximately 50 of them in each manufacturing site. This sample size is considered appropriate for the clinical investigation and sufficient to provide robust estimations on performance and safety parameters in the study population. A sample size of approximately 50 allows a meaningful range estimation, the confidence interval, for the true proportion of success (reduction in NLF-SRS grades of ≥1) at week 24. With a sample size of 50, a confidence level of (1- α) with α=0.05 and an estimated proportion of 0.9 a two-sided 95% confidence interval for the true proportion using the large sample normal approximation is given through [0.817; 0.983]. Thus, in compliance with the study design, the true proportion is expected in the range of the confidence interval with an error probability of 5%.

A 'responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5 point-validated NLF-SRS at week 24 relative to Baseline (Day 0) score on both sites. Individual NLF-SRS grades per visit will be assessed separately for the right and left NLF. A Response rate of 90% at week 24 is estimated.

7.2 Analysed data sets

The primary data set for analyses of performance of the investigational device and of aesthetic effects will contain all data collected in the Intent-to-treat population, which is defined as all subjects who received the investigational device and have at least one post-treatment assessment. Certain sensitivity analyses may be also done in the Per-protocol population, which is defined as all subjects who received the investigational device and have completed the Week 24 assessments without major CIP deviations.

All safety analyses will be based on the safety analysis set, defined as all subjects who received the investigational device.

7.3 Missing data

Missing data will not be estimated and/or imputed in any way.

7.4 Methods of analysis

In general, collected data will be listed and descriptive statistics will be performed, with all repeating measurements being tabulated by the visit. For continuous variables, descriptive statistics will include the number of observations, minimum, maximum, mean and standard deviation, or median and interquartile range, as appropriate based on data distribution. For discrete variables, summary statistics will include the total number of observations, frequency and percentages.

Demographic data, initial amount of the filler applied, and occurrence of the Touch-up treatment with the amount of the filler applied will be listed by subject and summarized using descriptive statistics within each manufacturing site, C1 and HQ, separately and for the whole analysis population. Other data collected will be listed per subject and summarized as described in the SAP.

7.4.1 Performance endpoints

As two facial folds of each subject will be considered, there are two measurements per subject for NLF-SRS. No great differences between the folds are expected, thus the mean of both measurements will be used for analyses. NLF-SRS grades per visit will be calculated as the mean of grades assigned to

the left and the right nasolabial fold, respectively. The absolute NLF-SRS change versus baseline will be computed by subtracting the value obtained on the corresponding visit from that obtained on Day 0 . Absolute NLF-SRS change from baseline will be summarized by the visit using descriptive statistics and additionally the 95% confidence intervals of the expected change from baseline will be given. In addition, the proportion (with two-sided 95% confidence intervals) of subjects with NLF-SRS improvement (i.e., reduction on both sides in NLF-SRS grades) of ≥1, or ≥2, respectively, will be calculated.

Individual GAIS grades, subjects' satisfaction with aesthetic outcome, and pain ratings will be summarized and tabulated by visit using descriptive statistics.

Summaries will be provided for the whole analysis population, as well as within each manufacturing site, C1 and HQ, separately.

7.4.2 Safety endpoints

AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) and listed by subject. Incidence of AEs will be summarised by preferred term (PT) and system organ class (SOC), and also by intensity, relationship to the investigational medical device or procedure, and seriousness. Summaries will be provided for the whole analysis population, as well as within each manufacturing site, C1 and HQ, separately and within each subgroup defined by the injection device, needle and cannula, respectively.

8 Data management

8.1 Case report forms

A CRF will be completed for each subject enrolled in the investigation who received the investigational device.

A web-based validated electronic CRF (eCRF) will be used to document the subjects' data during the course of the study. The eCRF is designed to accommodate the specific features of the study design. All data obtained after the subject has given informed consent must be recorded in the eCRF. The investigator will assure that all data are entered promptly, completely, and accurately according to the eCRF instructions, and conform to source documents. Data for all subjects screened for study have to be documented on a respective form (see Section 6.3.9) and entered in the eCRF.

Only investigators and authorized designees are allowed to make entries in the eCRF. This will be regulated by appropriate reading and writing access. Completed eCRFs per visit, must be electronically signed by the investigator or authorized designee. Any change or addition will be recorded by an audit trail system.

It is the investigators' obligation to assure documentation of all relevant data in the subject's file, such as medical history, concomitant diseases, date of study enrolment, visit dates, results of examinations, administrations of medication, and AEs.

8.2 Data management procedures

All data management activities will be conducted by the Sponsor's representative following their Standard Operating Procedures. The database will be built by the Sponsor's representative, and they will handle the data cleaning process, including logical check, medical checks, and query processes. Details on data handling will be described in the Data Management Plan. Computerized validation check programs on completeness, correctness, plausibility (such as range checks, cross-checks) will verify the data according to the Data Validation Plan. All identified discrepancies will be queried in the EDC and addressed to the investigator or designee. The investigator or their designee must carefully answer any query issued by Data Management.

The database will be soft locked when it is considered complete and accurate (i.e. all CRF pages entered, all data cleaning activities performed). The database will be hard locked after all the changes following the data review meeting have been performed and the database is considered complete and accurate. All changes will be tracked (audit trail). Sponsor approval prior to database hard lock is mandatory.

8.3 Data retention

The investigator shall retain all study records during the clinical investigation and for the period required by the applicable regulatory requirements, or for at least 15 years after the premature termination or completion of the clinical investigation, whichever is longer. However, the investigator should contact the Sponsor prior to destruction of any records or reports pertaining to the clinical investigation, in order to ensure they no longer need to be retained or in case of changes in between in the duration of the clinical documents archiving according to GCP. In addition, the Sponsor should be contacted if the investigator plans to leave the site, so that arrangements can be made for transfer of records.

The medical files of study participants must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

8.4 Report of the clinical investigation

Following completion of the clinical investigation, the results will be evaluated and the Clinical investigation report will be generated, including a summary of all available data, statistical measures, tabulated results, graphical results, and interpretations. A complete list of all adverse events will be enclosed. This report will be submitted to authorities as appropriate, within the timeframes defined per national regulation or by the EC.

A formal interim report will be established as described above for the final report after week 24 visits.

9 Amendments to the clinical investigation plan

Any change to the CIP concerning the purpose of the study, the study design or the subject's eligibility can only be made in form of a written amendment to the CIP. Such amendments have to be discussed and signed by the Sponsor, the Coordinating Investigator, and the other 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, or the rights, safety or welfare of subjects taking part in the investigation will also have to be reviewed and approved by the EC and regulatory authorities, if applicable, prior to implementation.

Amendments that might have an impact on study procedures to be performed and/or the well-being of the subjects require additional informed consent, which has to 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 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 favorable opinion of the EC if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the Sponsor and the EC as soon as possible in accordance with national regulations.

All CIP deviations will be listed and their impact on evaluability of respective subjects will be discussed in a data review meeting prior to the hard data base lock.

Given the pandemic situation due to COVID-19, an increase of CIP deviations is assumed. The conduct of the investigation may be affected by lockdowns, restrictions, illness or other reasons which may prevent the subject to visit the site and perform the assessments as defined in the CIP (e.g. missed visits, delayed visits, unscheduled visits, safety phone calls). COVID-19 pandemic related deviations from the CIP are defined separately from the other CIP deviations to allow a more accurate assessment and classification of PDs for this investigation. The monitor is responsible to verify the relatedness of CIP deviations to the COVID-19 pandemic and include it in the deviation report in case not documented in the eCRF.

11 Device accountability

Investigational device accountability is described in Section 6.2.7.

12 Statements of compliance

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

- International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects - Good clinical practice;
- Declaration of Helsinki, in its currently adopted version;
- Applicable sections of the national medical device law.

By acting in accordance with this CIP, the investigators and the study site personnel fulfil the requirements of the International Standard ISO 14155:2011.

The clinical investigation will not commence until a favourable opinion from the respective EC has been received. All additional requirements imposed by the 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

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. Before consenting, the subject must be left with ample time to consider and ask questions. 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. The subject must then sign and date the ICF prior to the conduct of any study procedures. The consent taker (investigator) must sign and date the ICF as well.

A copy of the Subject information Sheet and ICF will be given to the subjects for their records. The rights and welfare of the study participants will be protected by emphasizing to them that the quality of their

medical care will not be adversely affected if they decline to participate in this clinical investigation or in case of withdrawal of their consent during the clinical investigation.

If amendments to the final CIP affect the subject's participation in the clinical investigation (e.g. a change in any procedure), the Subject information Sheet and the ICF must be updated to incorporate this modification, 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 investigational medical device.

- For study subjects this definition includes events related to the procedures involved, as well pregnancy in females.
- For users or other persons this definition is restricted to events related to the investigational medical device.

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

- This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. In addition, this includes any event that is a result of a use error or intentional misuse.

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

- Death;
- Serious deterioration in the health of the subject that either resulted in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-subject hospitalization 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, or
  - Malignant tumour;
- Foetal distress, foetal death, a congenital abnormality or birth defect.

A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

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

Unanticipated Serious Adverse Device Effect (USADE) is defined as a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the investigator's Brochure.

Device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use errors, and inadequate labelling.

Device deficiency that might have led to an 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 at each visit by clinical examination 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 addition, the subjects will be instructed to immediately contact the investigator/study site in case of occurrence of any untoward event between visits.

14.3 AE/SAE documentation

For each AE the following must be reported:
- description of the event (event term)
- start date
- start time (for events occurring on the treatment day)
- outcome
- end date (if applicable)
- severity
- action taken (none, medical and/or surgical)
- the relationship to the investigational device, the relationship to the procedure
- seriousness criteria.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

Each AE should be reported separately. The investigator will record all AEs on the "AE" page of the eCRF. For SAEs, the Serious Adverse Event Form must also be completed. Complete description of all AEs should be also available in the source documents.

AEs occurring after provision of informed consent and prior to application of the investigational medical device will be recorded as part of the medical history. Any medical condition that is present at screening should also be considered as medical history and not recorded as an AE. However, if the condition deteriorates after administration of the investigational device, at any time during the course of the investigation, it should be recorded and reported as an AE.

If the severity 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. The duration of the recorded AE will cover the period of all intensity/seriousness levels. No separate AEs will be recorded for each intensity level.

Changes in the assessment of the relationship to the investigational medical device or procedure should also be clearly documented.

Any medication necessary for the treatment of an AE must be recorded on the "Concomitant Medication" page of the eCRF.

14.4 AE/SAE assessment

All AEs will be assessed in terms of:
- seriousness (yes, no)
- severity
- relationship to the investigational medical device or study procedures
- outcome.

14.4.1 Severity assessment

The severity of an AE/SAE 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

14.4.2 Causality assessment

The investigator is obligated to estimate the relationship between each AE/SAE and the investigational medicinal device or study procedure. Clinical judgement should be used and the relevant documents like IB consulted. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. The relationship should be determined using one of the following causality levels[22]:

Definite: The AE/SAE is associated with the investigational device or with procedures beyond reasonable doubt when it is a known side effect of the product category the device belongs to, or of similar devices and procedures; has a temporal relationship with investigational device use/application or procedures; involves a body-site or organ that the investigational device or procedures are applied to or have an effect on; 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 exposure), when clinically feasible, and reintroduction of its use (or increase of the level of exposure) impact on the event; 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; and/or harm to the subject is due to error in use.

Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Possible: The relationship with the use of the investigational device 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.

Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Not related: Relationship to the device or procedures can be excluded when the AE/SAE is not a known side effect of the product category the device belongs to or of similar devices and procedures; has no temporal relationship with the use of the investigational device or the procedures; 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 exposure, when clinically feasible, and reintroduction of its use (or increase of the level of exposure) do not impact on the event; involves a body-site or an organ not expected to be affected by the device or procedure; 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); and/or harm to the subject are not clearly due to use error.

14.4.3 Outcome assessment

The outcome of an AE will be assessed as follows:

Resolved*:* The subject has fully recovered from the event, or the condition has returned to the level observed at baseline.

Ongoing*:* The event is ongoing at the time of reporting and the subject has still not recovered.

Resolved with sequelae*:* As a result of the AE, the subject suffered persistent and significant disability/ incapacity (e.g. became blind, deaf or paralyzed).

Fatal*:* The subject died due to the event.

Unknown*:* If outcome is not known or not reported.

14.5 AE/SAE reporting requirements and contact details

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 Medical Monitor within 24 hours of awareness of the event via fax. Contact details are as follows:

[redacted]

This also applies to any significant AE, which in the investigator's opinion could affect the safety of the study subjects or the conduct of the study.

Information about an SAE will be collected and recorded on the SAE Report Form. 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 to the Medical Monitor until the SAE has resolved or, in the case of permanent impairment, until the SAE has stabilized.

[redacted] will inform the sponsor about all SAEs without undue delay after receipt of the respective report from the Investigator.

Reporting to ECs and regulatory authorities will follow pertinent national legislation.

At the end of the study, a reconciliation of all reported SAEs will take place and be enclosed as a list in the Clinical investigation report (see Section 8.4).

14.6 AE/SAE 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 until the last day of the clinical investigation at the site, whichever occurs first.

Any pregnancy must be notified to [redacted] within the same timelines as an SAE (within 24 hours after being made aware of the pregnancy) on a Pregnancy Notification Form. The pregnant subject should be withdrawn immediately from the clinical investigation upon confirmation. Any pregnancy must be followed-up until the pregnancy outcome. 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 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.

All SAEs judged to be related to the investigational medical 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.

14.7 Foreseeable AEs and anticipated ADEs

Foreseeable AEs and anticipated ADEs are listed in Section 4.2 Anticipated adverse device effects.

14.8 Device deficiency reporting requirements

All investigational medical device deficiencies will be recorded on a Device Deficiency Report Form.

Device deficiencies with SADE potential should be reported by the investigator to [redacted] within 24 hours after the site became aware of the device deficiency. Contact information is provided in Section 14.5.

[redacted] will forward the deficiency with SADE potential report to the Sponsor within 24 hours after receipt of the respective report from the investigator.

If a device deficiency is associated with an AE, the corresponding AE documentation procedures must be adhered to as well.

14.8.1 Handling of deficient medical devices

Any medical device alleged to be deficient must not be used by the investigator and must be returned to the Sponsor.

14.9 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 enrolment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrolment rate, achievement of the total enrolment, or non-compliance with the CIP or other clinical research requirements.

The investigator, 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 EC, as specified in applicable regulations.

17 Publication policy

The results of the clinical investigation may be published and/or presented at scientific meetings. The results, however, 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 at least 90 days 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 for at least 6 months after receipt of the manuscript or abstract.

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