CLINICAL INVESTIGATION PLAN (CIP)

Title of the clinical investigation/CIP:	**A prospective, open-label, multicentre, randomized study to evaluate the effectiveness, safety and long term safety of Saypha® FILLER Lidocaine for lip augmentation**
Short title:	**SayLip**
Investigation ID:	CPH-101-201479
CIP version:	2.0
CIP version date:	**27 JUN 2019**
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
Investigation site(s):	Up to three 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:	[redacted] An updated list of institutions that are involved in project management, monitoring, data management and statistics is kept separately from the CIP
CONFIDENTIAL	This clinical investigation plan is the property of Croma-Pharma GmbH and must be kept strictly confidential. Any unauthorized disclosure, copy or use of this document, or information contained herein, is prohibited.

Approval and signature pages

Sponsor approval

CIP identifier: **CPH-101-201479**

_____ _____

[redacted]

Date

_____ _____

[redacted]

Coordinating investigator agreement

CIP identifier: **CPH-101-201479**

I agree:

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

Investigator's name: [redacted]

Investigation site: [redacted]

Address: [redacted]

Investigator's signature: _____

Date: _____

Principal investigator agreement

CIP identifier: **CPH-101-201479**

I agree:

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

Investigation site: _____

Address: _____

_____

_____

Investigator's signature: _____

Date: _____

Investigators and administrative structure of the clinical investigation

Investigators: This is a multicentre clinical investigation, which will be conducted in Austria. An updated list of investigation sites and corresponding principal investigators will be kept separately from the CIP.

Sponsor: **Croma-Pharma GmbH**

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

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

Other institutions: [redacted]

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

Contact project management: [redacted]

Contact for reportable events is provided in section 14

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

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

Synopsis

Investigation title	**A prospective, open-label, multicentre, randomized study to evaluate the effectiveness, safety and long term safety of Saypha® FILLER Lidocaine for lip augmentation**
Short title	SayLip
Investigation ID	CPH-101-201479
Phase of development	Interventional
Indication	Moderate to severe deficiency of lip volume
PLANNED CLINICAL INVESTIGATION PERIOD	
Planned duration	The duration of the clinical investigation will be a maximum period of 18 months after the initial treatment for each participating subject. The estimated enrolment period is two to three months, hence the overall study duration is planned to be about 21 months.
CLINICAL INVESTIGATION OBJECTIVES AND PURPOSE	
Objectives	**Main objectives:** • To evaluate the effectiveness, safety and long-term safety of Saypha® FILLER Lidocaine for lip augmentation; • To assess the duration of the aesthetic effect of Saypha® FILLER Lidocaine for lip augmentation. **Additional objectives**: • To compare the effectiveness of Saypha® FILLER Lidocaine ('IMD-HQ' and 'IMD-C1') produced in the two different manufacturing sites ('HQ' and 'C1'). • To compare the IMD injection techniques: 'retrograde technique' and 'bolus technique' • To compare the injection equipment used: '27G ½" needle' versus cannula ('25G x 50mm cannula' or '22G x 70mm cannula')
CLINICAL INVESTIGATION DESIGN	
Study design	This is a prospective, open-label, multicentre, randomized study. Eligible subjects will undergo bilateral lip augmentation treatments with Saypha® FILLER Lidocaine in order to correct moderate to severe deficiency of lip volume (defined as grade 1 to grade 3 within Lip Fullness Scale; LFS). The treatment will be administered at the Baseline visit (Day 0). There will be an optional touch up treatment at Week 3 after initial treatment in order to achieve optimal cosmetic corrections. 24 hours after each treatment a telephone visit will be performed for safety evaluation (Visit 1a and Visit 2a in case of touch-up treatment). Baseline severity of lips volume deficiency will be determined at Screening/Baseline visit by the investigator using a validated Lip Fullness Scale (LFS) before the initial treatment (Visit 1/Day 0), at 6 weeks, and 6, 12 and optional 18 months post treatment. Independent blinded photographic reviews of lip fullness will be performed for the same time points by using the LFS. A 'responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5 point-validated LFS at a given visit relative to Baseline

	score. Individual LFS grades per visit will be calculated separately for the upper and the lower lip. Photos for the independent review will be taken before the initial treatment, at 6 weeks and 6, 12 and optional 18 months post initial treatment. Assessment of aesthetic improvement using the Global Aesthetic Improvement Scale (GAIS) and assessment of subject satisfaction using the Face-Q™ "Satisfaction with outcome" scale and the "Satisfaction with Lips" scale will be performed at 6 weeks and 6, 12 and optional 18 months after initial treatment. Assessment of the aesthetic effect of Saypha® FILLER Lidocaine will be performed by the investigator at 6 weeks and 6, 12 and optional 18 months after initial treatment. Subject's perception of pain will be evaluated immediately after injections were administered and 15 minutes after each treatment. The safety will be evaluated based on occurrence of adverse events, which will be collected at each visit throughout the clinical investigation.
SUBJECT SELECTION	
Number of investigation sites	Up to 3 sites located in Austria (AT)
Number of subjects	Approximately 110 subjects
Inclusion criteria	A subject must meet **ALL** of the following criteria to be **ELIGIBLE** for the study: 1. Adult female or male subjects 18 years of age at Screening/Baseline visit (Visit 1) 2. Presence of approximately symmetrical "very thin" lips (minimal red lip shows) to "moderately thick" lips (moderate red lip shows) as assessed with the LFS (severity grade of 1 to 3 on both lips) as determined by the investigator at Visit 1 3. For females of childbearing potential only: negative urine pregnancy test at Visit 1, and must agree to use an highly effective method of contraception for the duration of the clinical investigation 4. Healthy skin in the treatment area and free of diseases that could interfere in evaluation of treatment 5. Willingness to abstain from any cosmetic or surgical procedures in the treatment area for the duration of the clinical investigation 6. Willingness to take part in this clinical investigation documented by a personally signed/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. Prior surgery, scars or tattoo to the upper or lower lip or lip line; surgery and tattooing are prohibited until end of clinical investigation 5. Tooth gap, overbite, beard longer three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the

	investigator 6. Presence of any abnormal lip structure, such as a scar or lump or severe lip asymmetry, as judged by the investigator 7. Previous tissue augmenting therapy in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) with HA or collagen filler, or laser treatment, chemical peeling, dermabrasion or mesotherapy within 12 months before Visit 1 and until end of clinical investigation 8. Previous permanent implant or treatment with non-HA or non-collagen filler in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) and until end of the investigation 9. Previous toxin treatment in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) within 9 months before Visit 1 and until end of clinical investigation 10. Presence of cutaneous lesions, inflammatory and/or infectious processes (e.g. acne, herpes, etc.) or proliferative lesions in the treatment area 11. Known human immune deficiency virus-positive individuals 12. History of allergies against aesthetic filling products and recurrent (3 times a year) herpes simplex in the treated area 13. Tendency to hypertrophic scars, keloid formation and/or pigmentation disorders 14. History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy 15. Uncontrolled systemic diseases (such as diabetes mellitus) 16. Use of anticoagulant, antiplatelet or thrombolytic medication (e.g. acetylsalicylic acid) from 10 days pre- to three days post IMD injections 17. Planned dental/oral surgery or modification (bridge-work, implants) within two weeks prior to initial IMD injection and to a minimum of four weeks post IMD injections 18. Any medical condition which, in the investigator's opinion, prohibits the inclusion in the study 19. Current or previous (within 30 days of enrolment) treatment with another investigational drug and/or medical device or participation in another clinical study 20. Previous enrolment in this clinical investigation 21. Any dependent relationship of the subject with the investigator, investigation site or Sponsor (e.g. employees or relatives) 22. 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)

INVESTIGATIONAL DEVICE(S), DOSE AND MODE OF ADMINISTRATION	
Investigational device and mode of administration	Saypha® FILLER 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 3 mg/mL (0.3%) lidocaine hydrochloride. Saypha® FILLER Lidocaine is administered by injection into the lips. The volume applied depends on the size of the area which requires correction and will be selected by the investigator. A maximum volume of 2 mL for both lips in total (i.e., for upper plus lower lip) including touch up might be needed per treatment but the treatment should not exceed 10 mL in total per treatment or 20 mL per year. The manufacturing process of Saypha® FILLER Lidocaine established at Croma's manufacturing site 'Croma 1' ('C1') was recently implemented in addition in a new manufacturing facility (manufacturing site 'headquarter' ('HQ')). No changes were done to the finished product design or manufacturing technology or method of sterilization. The ingredients, the formulation, the packaging and the finished product specifications were not changed. The implementation of the second manufacturing site is not considered to impact the safety and effectiveness of the product. This study will compare the IMD produced at the new manufacturing site 'HQ' with the IMD produced at 'C1' site. Therefore, each subject will randomly be assigned to one of the two IMDs ('IMD-HQ' or 'IMD-C1') at a 1:1 ratio.
Treatment duration	Maximum 18 months
SUBJECT SELECTION	
Primary performance endpoints	The proportion of subjects ('responders') with the lip volume improved by ≥1 point versus baseline value at 6 weeks after initial treatment based on the investigator live assessment using the validated Lip Fullness Scale (LFS). 'Responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5 point-validated LFS at a given visit relative to Baseline score. Individual LFS grades per visit will be calculated separately for the upper and the lower lip.
Safety endpoints	Occurrence and frequency of adverse events

Secondary performance endpoints	• The percentage of responders, based on the investigator live assessment at 6, 12 and optional 18 months after the initial treatment using the validated LFS. • The percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS. • The percentage of subjects with an improvement relative to baseline photographs, (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on the investigator assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment using the 5-point GAIS. • The percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment, using the 5-point GAIS. • The extent of subject´s satisfaction with overall outcome of the treatment, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome". • The extent of subject's satisfaction with augmentation of lips, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Lips". • Subject's perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable. • Percentage of subjects demonstrating an aesthetic effect at Week 6, Month 6, 12 and optional Month 18 based on the investigator's life assessment. • Injection volume (initial and touch-up) required for an optimal augmentation of the lips with Saypha® FILLER Lidocaine.
STATISTICAL ANALYSIS	
Sample Size Calculation	The sample size calculation was made for the primary performance endpoint taking the overall population and the subgroups by IMD manufacturing site into account. With a sample size of 100, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.059 in the overall population and 0.083 in the two manufacturing site subgroups from the observed proportion for an expected proportion of 0.900 (i.e., a responder rate of 90%). In order to cover subjects' drop-out or lost to follow-up the sample size will be increased by 10 %, following 110 subjects will be enrolled (with 55 subjects per manufacturing site). Thus, a sufficiently precise estimation of the percentage of responders based on the investigator´s live assessment at Week 6 using the LFS can be derived.
Analysis Sets	*Safety Analysis Set (SAF)* The Safety Analysis Set (SAF) consists of all subjects who received at least one administration of the investigational medical device (IMD). *Full Analysis Set (FAS)* The Full Analysis Set (FAS) comprises all subjects who received at least one administration of the IMD and who had at least one post-treatment evaluation

	of the LFS. *Per-Protocol Set (PPS):* The Per-Protocol Set (PPS) includes all subjects of the FAS who have no major protocol deviations.
General Statistical Considerations	All effectiveness analyses will be done in the FAS and PPS. All safety analyses will be based on the SAF. Addionally an interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit at Month 6 (Visit 4). For the interim analysis the Statistical Analysis Plan (SAP) will be finalized prior to the IA database lock. The IA database will be cleaned and a data base lock prior to export for data analysis will be done.
Planned Statistical Analysis	All statistical analyses will be done using descriptive statistics. All summary tables and subject data listings will be prepared by visit if applicable. Summary statistics (mean, standard deviation, minimum, first quartile, median, third quartile, and maximum) will be provided for continuous variables, and the number and percentage of each category will be provided for categorical data. If applicable and unless otherwise specified statistical tests will be non-parametric and 2-sided at 0.05 level of significance. Two-sided 95% confidence intervals for the percentages of responders and mean LFS improvement at various time points will be given and proportions for the LFS improvements of ≥1 point will be calculated. Individual LFS grades per visit will be calculated as the mean of grades assigned to the upper lip and lower lip, respectively. All statistical analyses including will be outlined in detail in the statistical analysis plan (SAP) including all aspects of the interim analysis (IA), tables, figures and subject data listings. Any changes in the original statistical methodology will be documented in the statistical analysis plan as well. All data collected will be presented in subject data listings.
Subgroup Analyses	Besides the 'overall population' (including all subjects enrolled in the investigation), the following subgroups will be analyzed descriptively for the primary and main secondary performance endpoints: • IMD from manufacturing sites: 'HQ' and 'C1' • Injection technique: 'retrograde technique' and 'bolus technique' • Injection equipment: '27G ½″ needle' versus cannula ('25G x 50mm cannula' or '22G x 70mm cannula')

Schedule of procedures and events

Table 1. *Schedule of procedures and events*

Assessment	Screening/ Baseline	Telephone Visit	Touch up	Telephone Visit		Month 6	Month 12	Optional[††] Month 18
	Day 0*	24h after IMD admin.)	Week 3 ± 2 days	24h after IMD admin.)	Week 6 ± 5 days	Week 26 ± 7 days	Week 52 ± 7 days	Week 76 ± 7 days
	Visit 1	**Visit 1a**	**Visit 2**	**Visit 2a**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Informed consent	x**							
Eligibility assessment	x**							
Urine pregnancy test[b]	x**				x	x	x	x
Demographic data[a]	x**							
Medical history	x**							
Photography	x**				x	x	x	x
Initial treatment	x							
Touch-up treatment			(x)[†]					
LFS - independent photographic reviewer	x				x	x	x	x
LFS - investigator[c]	x**				x	x	x	x
GAIS - investigator					x	x	x	x
GAIS - subject					x	x	x	x
FACE-Q^{TM} “Satisfaction with outcome” - subject					x	x	x	x
FACE-Q^{TM} “Satisfaction with lips” - subject					x	x	x	x
Assessment of aesthetic effect - investigator					x	x	x	x
Pain assessment[e] using the NPRS - subject	x		(x)[†]					
Prior and concomitant medication	x**	x	x	x	x	x	x	x
Adverse event[d]	x***	x[§]	x***	x[§]	x	x	x	x
Device deficiencies	x		(x)[†]					

* Includes screening and (initial) treatment

** Prior to application of the investigational device

*** In order to identify potential AEs post-administration of IMD, AEs should be assessed 15 minutes after each administration (initial and touch-up treatment).

† Touch-up treatment is optional (at investigator's discretion, if full correction was not achieved after initial treatment).

†† The duration of the clinical investigation is planned for 18 months at a maximum and depends on the assessment of the aesthetic effect. In case it is observed by the investigator that no aesthetic effect is any more visible the study can be terminated at Month 12 (Visit 5) for the respective subject.

§ Safety follow-up via telephone: Any adverse events since injection? In case of an AE an unscheduled on-site visit should be performed.

a Includes year of birth, sex, race, and smoking status

b In females of child-bearing potential only, including women who are postmenopausal for less than 12 months

c Evaluated by the investigator using LFS. The upper and lower lip will be graded separately

d To be collected throughout the investigation, beginning immediately after start of initial treatment until the last visit.

e NPRS: Immediately and 15 minutes after initial and touch-up IMD treatment.

Abbreviations: LFS: Lip Fullness Scale; GAIS: Global Aesthetic Improvement Scale, NPRS: Numerical Pain Rating Scale

List of abbreviations

ADE	Adverse device effect
AE	Adverse event
BDDE	1,4-butanediol diglycidyl ether
C1	Manufacturing site 'Croma 1'
CE	*Conformité Européene* (European conformity)
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRO	Contract Research Organization
DDVS	Database Design Validation Specification
DMP	Data Management Plan
DRM	Data Review Meeting
EC	Ethics committee
eCRF	electronic Case Report Form
EU	European Union
ExC	Exclusion criterion
FAS	Full Analysis Set
GAIS	Global Aesthetic Improvement Scale
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HA	Hyaluronic acid
HQ	Manufacturing site 'Headquater'
IA	Interim analysis
IB	Investigator's brochure
ICF	Informed Consent Form
IFU	Instructions for use
IMD	Investigational medical device
ISO	International Organization for Standardization
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LFS	Lip Fullness Scale
MDD	Medical Device Directive
MedDRA	Medical dictionary for regulatory activities
mIU	Milli-international unit
mL	Milliliter
NLF	Nasolabial fold
NLF-SRS	Nasolabial folds severity rating scale

NPRS	Numeric Pain Rating Scale
PPS	Per-Protocol Set
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System organ class
TMF	Trial master file
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet
WHO	World Health Organization
WOCBP	Women of childbearing potential
w/w	Weight/weight

Glossary

Saypha® FILLER Lidocaine and Princess® FILLER Lidocaine are the same product marketed under different brand names in different countries. There is no difference in production, packaging and labelling. For the sake of simplicity the brand name of Saypha® FILLER Lidocaine will be used within the underlying CIP (contrary to the Investigator´s Brochure).

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1 Background

Age is the most significant factor contributing to the overall change in the appearance of an individual's face, including the lips, over time. Young faces tend to be convex with full lips, while aged face tends to be concave with flat lips.[1] During aging, photo damage, hereditary factors, gravity, loss and displacement of fat, bone resorption and smoking contribute to loss of lip volume. Furthermore, genetically thin lips and cosmetic asymmetries of the lips are also issues for many persons.[2,3] Perception of age and health is critical in the judgement of attractiveness. Forming an impression in other humans about facial attractiveness is fast, automatic and mandatory, and impacts impressions of other social traits of a person with real-world consequences.[4]

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.[5] Dermal fillers are widely used for facial rejuvenation and correction of deep wrinkles (e.g., nasolabial folds) and to increase lip volume. These treatments provide desirable aesthetic outcomes with minimal invasiveness and without the downtime associated with surgery.

Hyaluronic acid

Hyaluronic acid 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. Hyaluronic acid has a considerable water-binding capacity, and by this mechanism it increases dermal volume and compressibility.[6] 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.[7] Hyaluronic acid is degraded by enzymatic depolymerization via hyaluronidases and oxidation by free radicals. Native chains have a short half-life of 24-48 h, which may be significantly extended by cross-linking of the chains. The most commonly used cross-linking agent is 1,4-butanediol diglycidyl ether (BDDE). The cross-linked hyaluronic acid is degraded via the same mechanisms as native chains, but at a much slower rate, extending the clinical effect of BDDE-cross-linked hyaluronic acid for up to one year.[8]

Hyaluronic acid dermal filler for aesthetic use

Soft tissue fillers are nowadays widely used for smoothing skin wrinkles and folds, and volumizing facial contours. Various fillers are available on the market, but hyaluronic acid (HA) gels are most popular because of their versatility, ease of administration, predictable effectiveness, safety track record established during decades of use, and quick subject recovery after administration.[1,3]

Since the launch of the first BDDE-cross-linked hyaluronic acid dermal filler for aesthetic use in Europe in 1996, over 50 clinical studies have been conducted with this type of medical device, which included more than 9,000 subjects.[8] Hyaluronic acid gels are currently considered as the gold standard for dermal fillers and are widely used in aesthetic dermatology for facial rejuvenation and re-contouring, with a remarkable track record of performance and safety.[7] 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.

Lidocaine hydrochloride

In order to improve the comfort of filler injections, novel formulations containing a local anaesthetic, lidocaine hydrochloride, have been developed to reduce procedural pain and to bypass the need for additional anaesthesia.[9]

Lidocaine hydrochloride is a well-known local anaesthetic, which has been in clinical use for over 60 years. It is currently one of the most widely used local anaesthetics. Lidocaine exerts its anaesthetic effects by blocking fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons, which prevents depolarization and inhibits the generation and propagation of nerve impulses.[10] Rapid

release of lidocaine from hyaluronic acid gel, allowing for fast onset of action after injection, has been demonstrated *in vitro.* [11]

When used for infiltrative anaesthesia, lidocaine hydrochloride has fast onset of action (< 2min) and moderate duration of effect lasting 1.5-2 h.[12] Absorbed lidocaine is metabolized in the liver and eliminated via the kidneys with a half-life of around 90 minutes.[13] 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.[12, 13]

In soft tissue fillers the addition of lidocaine hydrochloride reduces pain and distress and provides a more comfortable injection experience.[14] The performance and safety of hyaluronic acid dermal fillers supplemented with lidocaine hydrochloride have been studied in several randomized clinical trials, which were mostly designed as split face trials, where the same dermal filler was administered with and without ancillary lidocaine. A detailed analysis of nine randomized clinical trials with the equivalent devices [redacted] has confirmed a statistically significant reduction in pain with formulations which contained lidocaine. The pain reduction was consistent across the studies, and present irrespective of the dermal filler tested. The frequency and severity of adverse events (AEs) was not different for dermal fillers with or without lidocaine, indicating no incremental safety risk.[15, 11]

2 Identification and description of the investigational device

Please refer to the Saypha® FILLER Lidocaine Investigator's brochure (IB[11]) for detailed information on the investigational device. Saypha® FILLER Lidocaine and Princess® FILLER Lidocaine are the same product marketed under different brand names in different countries. There is no difference in production, packaging and labelling. For the sake of simplicity the brand name of Saypha® FILLER Lidocaine will be used within the underlying CIP (contrary to the IB).

In this study Saypha® FILLER Lidocaine from two different manufacturing sites will be used and analyzed (IMD-HQ and IMD-C1, see section 2.2 for details). As the device from both manufacturing sites do not differ they are described in the following sections in one consolidated description.

2.1 Device description

Saypha® FILLER Lidocaine is conceived for medical purposes and aims to address reconstructive purposes in the treatment, for instance, of facial lipoatrophy, debilitating scars or morphological asymmetry and increase lip volume. The device received the CE mark in 2016 allowing device sales in European Union (EU). The chemical, physical and biological properties of Saypha® FILLER Lidocaine were extensively characterized during development (see sections 4 and 5 of the IB[11] for details). Compliance with general requirements defined in EN ISO 14630[A] was demonstrated.

Saypha® FILLER Lidocaine was classified as an implantable medical device in permanent contact with tissues or bones according to EN ISO 10993-1[B]. Hence, cytotoxicity, acute, repeated dose and subchronic systemic toxicity, local effects after implantation, sensitization, irritation, pyrogenicity and genotoxicity of Saypha® Filler Lidocaine were evaluated *in vitro* and *in vivo* in biocompatibility studies. All of the studies were conducted under GLP[C] principles and results are described in section 5.1 of the IB.

Table 2 shows the components and main characteristics of Saypha® Filler Lidocaine and Table 3 tabulates the single components of Saypha® Filler Lidocaine.

[A] EN ISO 14630: Non-active surgical implants — General requirements
[B] EN ISO 10993-1: Biological evaluation of medical devices — Part 1: Evaluation and testing
[C] GLP: Good Laboratory Practice

Table 2. *Main Characteristics of Saypha® Filler Lidocaine*

Components of Saypha® Filler Lidocaine • 23 mg/mLin a physiologic buffer (phosphate buffer pH 6.7–7.3 q.s., sodium chloride) • 3 mg/g [0.3%] lidocaine hydrochloride
Description of Saypha® FILLER Lidocaine • is a class III medical device incorporating the ancillary medicinal substance lidocaine hydrochloride as an integral part • is a sterile, biodegradable, viscoelastic, clear, isotonic and homogenized injectable gel implant (pre-filled in 1 mL glass syringes) • is designed for single use and must not be re-sterilized • has an anticipated lifetime up to nine months after treatment
In this investigation, Saypha® FILLER Lidocaine is administered by injection into the lips. The volume to be injected per lip depends on the size of the area which requires correction and will be selected by the investigator. A maximum volume of 2 mL for both lips in total (i.e., for upper plus lower lip) might be needed per treatment (i.e., initial treatment and touch-up treatment, respectively)[23] but should not exceed the maximum recommended volume of 10 mL per treatment session and 20 mL per year (also refer to section 6.2).

Table 3. *Main Characteristics of single components of Saypha® FILLER Lidocaine*

Component	Concentration	Description
Hyaluronic acid (HA)	23 mg/g	• HA, a natural polysaccharide, is obtained from *Streptococcus equi* bacteria is cross-linked using BDDE[D]. • BDDE covalently binds native HA molecules to each other with repeating bridges, creating a polymer 'network', transforming the viscous liquid into a gel. • Compared with native HA, the highly crosslinked HA gel is considerably more resistant against enzymatic and free radical breakdown, so that its tissue residence time is dramatically increased. • Native HA is added in order to adjust the rheological properties and injectability of the fillers. • HA is a natural component of human skin, hence the IMD is naturally absorbed.
Lidocaine hydrochloride	3 mg/g [0.3% w/w]	• Lidocaine hydrochloride (a medicinal product) is a well-known local anesthetic; it is added to Saypha® FILLER Lidocaine as an ancillary substance for reduction of procedural pain. and to improve the comfort of filler injections thus bypassing the need for additional anaesthesia; • Lidocaine hydrochloride is rapidly released from the implant and quickly eliminated from the body, with a half-life of around 90 minutes.[13]

[D] BDDE: 1,4-butanediol diglycidyl ether

2.2 Manufacturing

Saypha® FILLER Lidocaine is manufactured in compliance with several Regulatory Requirements including GMP[E] (see section 4.1.3 and section 10 of the IB[11]). The device is manufactured under clean room conditions in compliance with EN ISO 14644-1[F]. No materials of human or animal origin are used during manufacture or as raw materials; moreover, the use of non-animal origin substances theoretically reduces any potential for hypersensitivity.

The manufacturing process of Saypha® FILLER Lidocaine established at the current Croma's facility ('C1') was additionally implemented in a new manufacturing site ('HQ' = Headquater). Different process parameters were adapted and optimized during the transfer. While most production equipment was newly implemented to reflect the latest state of the art technology and to allow an upscaling of the manufacturing processes, the principle of the manufacturing process and sterilization were maintained. No changes were done to the finished product design or manufacturing technology or method of sterilization. The ingredients, the formulation, the packaging and the finished product specifications were not changed. Of note, the material used at the new manufacturing site 'HQ' is not CE-certified.

In this study, IMD from both manufacturing sites ('C1' and 'HQ') will be used and subjects will be randomly assigned in a 1:1 ration to IMD-C1 or IMD-HQ, respectively.

2.3 Manufacturer

2.3.1 *Saypha® FILLER Lidocaine*

- Design, manufacturing, primary packaging, secondary packaging, labelling inspection, final inspection, moist heat sterilization and release of the device are undertaken at the facilities 'C1' (Beautyplant, Industriezeile 6, 2100 Leobendorf, Austria) and 'HQ' (Croma-Pharma GmbH, Cromazeile 2, 2100 Leobendorf) in accordance with EN ISO 13485[G] and Good Manufacturing Practice (GMP).
- The device contains the medicinal substance lidocaine hydrochloride as an ancillary substance.

2.3.2 *Needles and cannulas for application*

- The device is delivered with two sterile single use needles (27G ½'') per syringe; the needles are Ethylene oxide sterilised and are medical devices according to their field of application, under class IIa (MDD 93/42/EEC, Annex IX, rule 6). The CE-Manufacturer is [redacted]
- Additionally, cannulas are provided with the investigational device. The cannulas are 25G x 50mm and 22G x 70mm.

2.4 Intended use and mode of administration

Saypha® FILLER Lidocaine is a soft tissue filler, approved for use in adults (EU: 18 years and older) for the correction of moderate to severe facial wrinkles and folds and to increase lip volume, and for medical reconstructive purposes in the treatment of, e.g., facial lipoatrophy, debilitating scars, or morphological asymmetry of the face.[16]

The device is designed to be injected into the submucosa of the lips. The amount injected depends on the size of the area to be corrected and the desired level of soft tissue augmentation. A maximum volume of 2 mL for both lips in total (i.e., for upper plus lower lip) might be needed per treatment[23], but should not exceed 10 mL per treatment session and 20 mL per year.

[E] GMP: Guideline for Good Manufacturing Practice for Pharmaceutical products
[F] EN ISO 14644-1: Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness
[G] EN ISO 13485: Medical devices — Quality management systems — Requirements for regulatory purposes

In the present clinical investigation, Saypha® FILLER Lidocaine will be used for correction of volume deficiency of the lips.

2.5 Traceability

Each kit of Saypha® FILLER Lidocaine is identified and tracked by its batch number (lot number). A set of two labels showing the batch number is situated at the bottom of each box. One of these labels should be attached to the subject's medical record. The investigational medical device is labelled according to applicable guidelines and national legal requirements.

3 Justification for the design of the clinical investigation

3.1 Non-clinical data and biocompatibility

Nonclinical biocompatibility studies have been conducted with Saypha® FILLER Lidocaine *in vitro* and *in vivo*.

Toxicity potential (including genotoxicity, see IB[11] sections 5.1.1, 5.1.2 and 5.1.6 to 5.19) of Saypha® FILLER 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. No acute toxicity was evident in an acute systemic toxicity study in mice, in repeated dose systemic toxicity and subchronic systemic toxicity studies in rats. A panel of three genotoxicity studies showed Saypha® FILLER Lidocaine to be non-genotoxic. The device was shown to be non-pyrogenic.

The tolerability of Saypha® FILLER Lidocaine was tested by implanting the device into intradermal tissue of rabbits (see IB section 5.13). Skin sensitization was perforemd in guinea pigs (see IB section 5.1.4) The potential to produce irritation following intracutaneous injection of Saypha® FILLER Lidocaine was evalutated in albino New Zealand White rabbits (see IB section 5.1.5). According to these nonclinical safety studies, Saypha® FILLER Lidocaine was observed to be biocompatible and is expected to be well-tolerated. The device was classified as non-irritant and a non-sensitizer. For details refer to the IB (section 5).

3.2 Clinical data

Saypha® Filler Lidocaine is an implantable class III medical device. Clinical data is available for Saypha® FILLER Lidocaine from one investigation (FINO trial; see below). However, clinical data is available for Saypha® FILLER, which is virtually the same dermal filler but without lidocaine.

A post-market clinical follow-up study (FLASH 1; CPH-410-201259) with Saypha® FILLER (without lidocaine) showed that the treatment was safe, well tolerated and efficacious in the treatment of facial lipoatrophy, morphological asymmetry and debilitating scars (53 subjects overall). It confirmed the effectiveness of the investigational device over a six-month period. The treatment outcome was declared highly successful by subjects, investigators and independent reviewer. There were no SAEs observed, and only few adverse device effects (ADEs) were recorded during the investigation (see section 4.2.1 for details on safety); all ADEs were limited to the injection site, apart from two events of headache, and have already been described in the literature as common adverse effects of crosslinked hyaluronic acid dermal fillers (see section 4.2). For details on this investigation refer to section 6.2.1 of the IB.[11]

Saypha® FILLER Lidocaine obtained the CE mark in 2016. Since its first market entry in 2016 up to the end of June 2018, 205,714 units of Saypha® FILLER Lidocaine have been released. The complaint ratio of 0.0112% confirms the favourable benefit/risk ratio of the device.[11]

FINO (CPH-401-201324) was a prospective, open-label, multicentre, post-market study evaluating the performance and safety of Saypha® FILLER Lidocaine for the correction of nasolabial folds (NLF). The study including 60 subjects showed that the IMD was effective in reducing NFLs. At the primary endpoint (Week 24 assessment) 96.7% of the intention-to-treat subjects demonstrated ≥1 grade improvement in their nasolabial folds severity based on the nasolabial folds severity rating scale (NLF-

SRS) compared with the baseline status. Saypha® FILLER Lidocaine was shown to be safe and well tolerated when used for correction of nasolabial folds (see section 4.2.1 for details on safety).[11]

However, there are no own data for use of Saypha® FILLER Lidocaine for bilateral lip augmentation available yet.

3.3 Justification for the clinical investigation

Saypha® FILLER Lidocaine has been approved for use in adults (EU: 18 years and older) for the correction of moderate to severe facial wrinkles and folds and to increase lip volume, and for medical reconstructive purposes in the treatment of, e.g., facial lipoatrophy, debilitating scars, or morphological asymmetry of the face. The current clinical investigation is designed to evaluate the effectiveness, safety and long-term safety of Saypha® FILLER Lidocaine for bilateral lip augmentation and to assess the duration of the aesthetic effect of the device.

A prospective, open label 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 deficiency of lip volume, 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 primary performance endpoint is based on evaluation using a 5-point scale for assessment of deficiency of lip volume validated Lip Fullness Scale (LFS) and is set at six weeks after initial administration of the device to address the minimum required durability of effect. Follow-up is, however, extended to 18 months at a maximum, to get additional information on long-term effects. In case it is observed by the investigator that no aesthetic effect is any more visible the study can be terminated after 12 months.

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]

Approximately 110 subjects will be included in this investigation to have 100 evaluable subjects. This sample size is considered sufficient to provide robust estimations on performance and safety parameters in the underlying overall study population as well as the IMD manufacturing site subgroups (subjects will be randomized 1:1 to IMD from either site 'C1' ('IMD-C1') or site 'HQ' ('IMD-HQ')).

4 Risks and benefits of the investigational device and clinical investigation

4.1 Anticipated clinical benefits

The treatment with Saypha® FILLER Lidocaine may remove or reduce a distressing aesthetic defect in subjects with volume deficiency of lips (“very thin” lip shows to “moderately thick” lip shows, see section 6.4.7), 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 anticipated to last up to nine months after treatment.

4.2 Anticipated adverse device effects

The safety profile of BDDE-cross-linked hyaluronic acid 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® FILLER Lidocaine are summarized in Table 4.

Additional information on AEs, especially serious events like arterial occlusion and necrosis is provided in the IB.[11] Physicians must inform the subject that there are potential side effects and/or incompatibilities associated with implantation of this device, which may occur immediately or may be delayed.

***Table 4**. Adverse effects of cross-linked hyaluronic acid dermal fillers (with or without lidocaine)*

Commonly reported treatment related AEs (also refer to Section 8.2.1 of the IB)	**Rare AEs** (also refer to Section 8.2.2 of the IB)	**Very rare SAEs (device related)** (refer to Section 8.2.3 of the IB)
• Redness • Erythema • Swelling • Edema • Pain • Itching • Tenderness • Bruising • Hematoma • Bleeding	• Abscess* • Angioedema* (antibody-mediated edema) • Bacterial infections • Burning • Beading, lumpiness • Discomfort • Discoloration • Dispigmentation • Delayed erythema* • Firmness • Granuloma • Herpes reactivation* • Hypersensitivity • Induration • Implant visibility, implant site mass, mass formation, migration • Inflammation • Irritation • Nodules* (inflammatory and non-inflammatory) • Malar edema* • Numbness • Paresthesia* • Puncture marks • Scar sarcoidosis • Scleromyxedema (generalized) • Teleangiectasia • Vasculitis • Vasospasm • Vasovagal reaction during injection	• Vascular Compromise/Arterial Occlusion† • Retinal artery / vein occlusion† • Necrosis†
These events are typically managed with the application of ice. These events are typically mild in intensity and should resolve within one to two days after injection.		These very rare device-related serious adverse events (SADEs) have been reported after use with similar HA dermal fillers.
	* for more details refer to Section 8.2.2 of the IB	† for more details refer to Section 8.2.3 of the IB

4.2.1 ***Saypha® FILLER (without lidocaine)***

Saypha® Filler (without lidocaine) obtained the CE mark in 2008. FLASH1 (CPH-410-201259) was a post-market clinical follow-up study evaluating performance, tolerability and safety of Saypha® FILLER for the correction of facial lipoatrophy, morphological asymmetry or debilitating scars. A total of 53 subjects were split up into the three study indications: facial lipoatrophy (23 subjects), morphological asymmetry (17 subjects) and debilitating scars (13 subjects). A total of 13 AEs were documented in eleven subjects (20.8%). Neither deaths, nor other serious AEs (SAEs) occurred during the

investigation. Out of these 13 AEs, seven AEs (in 9.4% of the subjects, n=5) were classified as ADE, all being classified as procedure-related and four additionally as investigational device-related. There were three cases of injection site hematoma, two events of injection site pain and two events of headache. All ADEs were assessed as of mild (42.9% of ADEs) or moderate (57.1% of ADEs) severity and had been resolved at the end of the clinical investigation.

4.2.2 *Saypha® FILLER Lidocaine*

Saypha® FILLER Lidocaine differs from Saypha® FILLER only by the inclusion of lidocaine and a slightly altered buffer formulation.

Saypha® FILLER Lidocaine received the CE mark in 2016. Post-market surveillance data from 2016 to end of June, 2018 confirm the safety and effectiveness of the device. Overall, more than 205,714 units of Saypha® FILLER Lidocaine were released (complaint ratio of 0.0112%).

FINO (CPH-401-201324) was a prospective, open label, multicentre, post-marketing clinical follow-up study evaluating Saypha® FILLER Lidocaine for correction of NFLs. Overall 60 subjects were included. 31 AEs reported by 26 subjects (43.3%) were assessed as definitely related to the procedure and therefore classified as ADEs. These were mostly injection site hematoma (reported in 16 subjects), injection site pain (in 12 subjects), and injection site swelling (in 2 subjects). Reported AEs were mostly mild or moderate and had resolved within a maximum of 25 days of their onset. Two AEs were serious, of which one subject reported a severe AE (papillary thyroid gland carcinoma) and the other a moderate hematoma infection. However, these AEs were not related to the IMD or the procedure.

4.3 Possible interactions with concomitant medical treatments

No studies on drug interactions with Saypha® FILLER 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 (also see Exclusion Criterion (ExC) #16, section 6.3.4).

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 4.2), appropriate training of the investigators to ensure correct application of the device, and regular follow-up visits, which will allow for timely recognition and management of potential AEs. Furthermore, the subjects will be instructed to immediately contact the investigator in case of occurrence of any AE between the scheduled visits.

Aspiration technique will be used as injection technique, to mitigate the subject's risk. I.e. 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 (also see section 6.2.2),

4.5 Risk-to-benefit rationale

Hyaluronic acid-based dermal fillers, such as Saypha® FILLER (with and without) Lidocaine, are generally considered very safe and effective, and have been widely used for soft tissue augmentation worldwide. The benefits and risks of the clinical use of Saypha® FILLER Lidocaine were evaluated based on a review of relevant scientific literature and post-marketing safety data of other well established CE marked and FDA approved medical devices (see sections 6.1 (Data from Clinical Studies) and 8.2 (Adverse Events) of the IB[11] for details).

Furthermore, when using of Saypha® FILLER Lidocaine, only a very low number of product quality and adverse event complaints compared to the total number of devices sold have been reported since

its first market entry (see section 4.2.2). All adverse events mentioned above are described in the instructions for use[16] as commonly reported after use of dermal fillers.

Subjects in this study will be treated with IMD from 2 different manufacturing sites (see section 2.2). The implementation of the new manufacturing site is not considered to impact the safety and effectiveness of the IMD.

Considering the potential benefits of correction, in particular the immediate and long lasting improvement of distressing aesthetic defect, it was concluded that the therapeutic benefits of Saypha® FILLER Lidocaine outweigh the potential risks. The overall residual design, manufacturing, and use risks, and the benefit/risk ratio of the device when used on subjects by experienced and trained physicians, according to the manufacturer's instructions for use, are fully acceptable.

5 Objectives and hypotheses of the clinical investigation

5.1 Objectives

The main objectives of this investigation are:

- To evaluate the effectiveness, safety and long-term safety of Saypha® FILLER Lidocaine for lip augmentation;
- To assess the duration of the aesthetic effect of Saypha® FILLER Lidocaine for lip augmentation.

Additional objectives:

- To compare the effectiveness of Saypha® FILLER Lidocaine ('IMD-HQ' and 'IMD-C1') produced in the two different manufacturing sites ('HQ' and 'C1').
- To compare the IMD injection techniques 'retrograde technique' and 'bolus technique'
- To compare the injection equipment used: '27G ½″ needle' versus cannula ('25G x 50mm cannula' or '22G x 70mm cannula')

5.2 Hypotheses

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

5.3 Claims and intended performance of the IMD to be verified

Saypha® FILLER Lidocaine has recently been approved for the correction of moderate to severe facial wrinkles and folds and to increase lip volume.[11] The approval was based on clinical experience with similar devices. In the meantime, more than 205,714 units of Saypha® FILLER Lidocaine were released and data on safety were obtained (see section 4.2.2). Besides, a prospective, open-label, multicentre, post-market clinical follow-up study evaluating Saypha® FILLER Lidocaine for the correction of nasolabial folds (FINO; CPH-401-201324) was conducted showing that Saypha® FILLER Lidocaine is effective in reducing nasolabial folds. Furthermore, Saypha® FILLER Lidocaine was shown to be safe and well tolerated. Reported AEs were mostly mild or moderate. One severe AE and the two reported serious AEs were not related to the IMD or the procedures. The present investigation is undertaken to support these claims.

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

The safety profile of lidocaine-containing hyaluronic acid dermal fillers is well established. Based on the equivalence of Saypha® FILLER Lidocaine with these products and available non-clinical and clinical safety data of the IMD under investigation (as well as of Saypha® FILLER *without* lidocaine), it is anticipated that it will share the same safety profile (details described in section 4.1). All AEs and device deficiencies occurring during the investigation will be collected and reported.

6 Design of the clinical investigation

6.1 Design description

This is a prospective, open-label, multicentre, randomized investigation to evaluate the effectiveness, safety and long-term safety of Saypha® FILLER Lidocaine for bilateral lip augmentation and to assess the duration of the aesthetic effect of the device. 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 comprises of six on-site visits within 18 months (76 weeks):the Screening/Baseline visit (Visit 1/Day 0) and 5 follow-up visits at 3 weeks (Visit 2), 6 weeks (Visit 3), 6, 12, and 18 months after initial treatment (Visits 4, 5 and 6). Visit 6 at Month 18 is an optional visit. In case it is observed by the investigator at the 12 months visit (Visit 5) that no aesthetic effect is any more visible the study can be terminated at Visit 5. Subjects will randomly be assigned to one of the two IMDs at a 1:1 ratio ('IMD-HQ' : 'IMD-C1').

The Screening/Baseline visit (Visit 1) will entail informed consent and screening assessments as specified in section 6.5.1. During this visit the investigator will determine the inclusion of subjects based on inclusion/exclusion criteria (see sections 6.3.3 and 6.3.4).

Eligible subjects will be randomized to one of the IMDs ('IMD-HQ' or 'IMD-C1') and undergo bilateral lip augmentation treatment with Saypha® FILLER Lidocaine in order to correct moderate to severe deficiency of lip volume at Visit 1 (Day 0). In addition to this initial treatment an optional touch-up treatment can be performed at Visit 2 (Week 3) in order to achieve optimal cosmetic corrections (in the discretion of the investigator). The injection volume will be recorded at each treatment visit (i.e., Visit 1 and Visit 2) (see section 6.4.6). 24 hours after each treatment a telephone visit will be performed for safety evaluation (Visit 1a and Visit 2a in case of touch-up treatment; see sections 6.5.2 and 6.5.4).

Baseline severity of lip volume deficiency will be determined at Visit 1 by the investigator using a validated 5-point Lip Fullness Scale (LFS) before the initial treatment. The LFS will be repeated 6 weeks and 6, 12 and optional 18 months after the initial IMD treatment. Independent photographic reviews will be performed at the same time points using LFS on photographs (see section 6.4.7).

Subject's pain during treatment and recovery from treatment will be evaluated by means of a numerical pain rating scale (NPRS) immediately and 15 minutes after each IMD administration (see section 6.4.8).

Global aesthetic improvement (GAIS) relative to baseline photographs will be evaluated by both - the investigator and the subject - at 6 weeks and 6, 12 and optional 18 months after initial IMD treatment (see section 6.4.9).

Subject´s satisfaction with the outcome of the treatment will be assessed with the Face-Q™ questionnaires "Satisfaction with Outcome" (see section 6.4.10) and "Satisfaction with Lips" (see section 6.4.11) at 6 weeks and 6, 12 and optional 18 months after initial treatment.

Assessment of the aesthetic effect of injection of Saypha® FILLER Lidocaine will be performed by the investigator at 6 weeks and 6, 12 and optional 18 months after initial treatment (see section6.4.12).

The safety will be evaluated based on occurrence of adverse events, which will be collected at each visit throughout the clinical investigation, beginning immediately after start of initial treatment until the last visit. In order to identify potential adverse events post-administration a safety evaluation after 15 minutes needs to take place (see section 6.4.13).

A detailed schedule of procedures is given in section 6.5 and Table 1; Description of assessments can be found in section 6.4.

6.1.1 *Criteria for evaluation (endpoints)*

Primary performance endpoints

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

- The proportion of subjects ('responders') with the lip volume improved by ≥1 point versus baseline value at 6 weeks after initial treatment based on the investigator live assessment using the validated Lip Fullness Scale (LFS).

  'Responder' is defined having at least ≥ 1 grade improvement as evaluated with the 5 point-validated LFS at a given visit relative to Baseline score. Individual LFS grades per visit will be calculated separately for the upper and the lower lip.

Safety endpoints

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

- Occurrence and frequency of adverse events

Secondary performance endpoints

- The percentage of responders, based on the investigator live assessment at 6, 12 and optional 18 months after the initial treatment using the validated LFS.
- The percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS.
- The percentage of subjects with an improvement relative to baseline photographs, (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on the investigator assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment using the 5-point GAIS.
- The percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as "very much improved" or "much improved" or "improved"), based on subject assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment, using the 5-point GAIS.
- The extent of subject´s satisfaction with overall outcome of the treatment, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Outcome".
- The extent of subject's satisfaction with augmentation of lips, at Week 6, Month 6, 12 and optional Month 18 after initial treatment, assessed by the subject using the Face-Q™ Questionnaire "Satisfaction with Lips".
- Subject's perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable.
- Percentage of subjects demonstrating an aesthetic effect at Week 6, Month 6, 12 and optional Month 18 based on the investigator's life assessment.
- Injection volume (initial and touch-up) required for an optimal augmentation of the lips with Saypha® FILLER Lidocaine.

6.1.2 *Randomization*

Subjects providing written informed consent and having met all inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the two IMDs (either IMD from manufacturing site 'HQ' or 'C1') (see section 2.2 for details). The site staff can perform the randomization via the eCRF sytem and distribute the respective IMD ('IMD-HQ' and 'IMD-C1') to the subjects accordingly.

6.1.3 *Blinding*

Not applicable.

6.1.4 *Discussion of clinical investigation design*

This clinical investigation is undertaken to evaluate the effectiveness, safety and long term safety of Saypha® FILLER Lidocaine for lip augmentation and to assess the duration of the aesthetic effect after implantation.

The primary and one of the secondary performance endpoints (see section 6.1.1) is based on the 5-grade LFS (Lip Fullness Scale), a validated instrument for semi-quantitative assessment of lip fullness (see section 6.4.7). Difference of one grade on this scale is considered to be clinically meaningful since it can be visually recognized by various observers as demonstrated during validation of the scale.

In view of multicenter conduct of the investigation, the LFS assessment will be also evaluated centrally, by an experienced independent photographic reviewer (see section 6.4.7). This will allow for unified assessment of treatment responses across the sites and checking if any bias was introduced by inter-observer variability between the sites.

The clinical relevance of the investigation will be also supported by several secondary endpoints (see section 6.1.1), related to global aesthetic improvement (by using the GAIS) and subject's satisfaction with outcome (overall and the lips by using Face-Q^{TM} scales).

A randomization to IMD produced by one of the manufacturing sites 'HQ' and 'C1' will be done. It shall be shown that there is no difference in effectiveness and safety of the two IMDs between the two manufacturing sites.

Safety and long term safety of Saypha® FILLER Lidocaine for lip augmentation will be monitored by documentation of safety parameters (AEs and device deficiencies) (see section 6.4.13).

6.2 Investigational medical device (IMD)

6.2.1 *Packaging, labelling and storage*

Each device will be provided in a folding box containing one glass syringe prefilled with 1.0 mL of the injectable gel implant and two 27G ½″ disposable sterile needles, and a product leaflet (Instructions for Use; IFU[16]). Additionally. cannulas (25G x 50mm and 22G x 70mm) will be provided.

Two labels showing the batch number are attached to the boxes. One of these should be attached to the subject's medical record. IMDs from the two different manufacturing sites (see section 2.2) can separately be identified and differentiated by investigator. The IMD is labeled according to applicable guidelines and national legal requirements indicating that the device is exclusively for use in a clinical investigation.

The IMD must be stored in the original box, at 2-25°C (36-77 °F) in a dry place, protected from light, heat and frost. The shelf life of finished sterilized Saypha® FILLER Lidocaine is 24 months at the specified storage conditions.

The investigator must ensure that upon receipt of the IMD 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*

Prior to administration

- Prior to administration, the subjects should be evaluated for any possible contraindications or risks and should be informed of all possible risks and warnings associated with treatment (also refer to section specified in the IB[11]).

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 / cannula firmly attached. The needle / 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 (IFU).

Injection technique

The IMD should be injected into the submucosa of the lips[23]. 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 / cannula, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular.

The 27G ½″ needle or either 25G x 50mm cannula or 22G x 70mm cannula, which are provided with the kit, have to be used. A minimum of 30 subjects will be treated either with 27G ½" needle or cannula (25G x 50mm or 22G x 70mm cannula).

The technique used is essential for the success of the treatment. The following injection techniques should be employed based on investigator's preference and characteristics of the defect under correction.

These include:

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

Bolus technique: deposition of a small bolus just before withdrawing the needle. Placing the bolus on mucosa in the white portion of the lip and under the muscle is absolutely necessary. The bolus injections are placed subdermal from the white portion of the lip directly into the mucosa. 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 device should be injected slowly with the least amount of possible pressure for the same reason.

If the needle / cannula is blocked, the pressure on the plunger rod should not be increased, but the injection stopped and the needle /cannula replaced.

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

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.[19]

In case of any other adverse event the Expert Consensus Recommendations for treatment of Soft Tissue Filler Complications[19] should be followed in the discretion of the investigator. More details are provided in section 6.2.6.

The remainder of the IMD from the same syringe after application to one lip can be used for the application to the other lip of the same subject at the same visit but not for any other subject or any other visit of the same subject. Note: If the remaining IMD from one syringe will be used for the application to the other lip, the injection volume for the first lip must be documented beforehand (see section 6.4.6).

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 and after subject's pain assessment has been performed (see section 6.4.8) is optional and may reduce redness and swelling.

In order to identify potential AEs (e.g., possible blanching caused by arterial occlusions) post-administration a safety evaluation by the investigator after 15 minutes needs to take place. Therefore, the subject should be requested to stay on site for at least 15 minutes after the injection.

Prior to discharge the subject should be advised to follow restrictions specified in section 6.3.7 and to inform their investigator as soon as possible about any unwanted event, especially inflammatory reactions persisting for more than one week or any other occurring secondary effect (also refer to section 14).

6.2.3 *Applied volume of the device*

Saypha® FILLER Lidocaine is administered by injection into the lips. The volume applied depends on the size of the area which requires correction and will be selected by the investigator. A maximum volume of 2 mL for both lips in total (i.e., for upper plus lower lip)[23] might be needed per treatment (i.e., initial treatment and touch-up treatment, respectively) but the maximum recommended volume is up to 10 mL per treatment session and up to 20 mL per subject per year; these amounts include potential touch-up treatments (also see section 6.4.6).

6.2.4 *Touch-up treatment*

A touch-up treatment may be performed at the Week 3 visit (Visit 2) at the investigator's discretion, if correction is not deemed satisfactory after the first injection at Visit 1.

If applicable, it will be documented in the subject's records and the eCRF with the same level of details as the initial treatment (see section 6.4.6 for details).

6.2.5 *Precautions and warnings for the investigator*

Refer also to the current IB[11] (esp. sections 8.1.5 and 8.1.6) and to the IFU[16]:

- The device must only be used by qualified medical healthcare personnel trained on the respective injection technique.
- The device must be injected into non-inflamed, disinfected, healthy skin.
- After use the syringe, needle /cannula and remaining contents should be disposed after use in a special container and the device shall never be re-used.
- The device should not be re-used; quality and sterility can only be guaranteed for a syringe in its original package; Re-use of the device creates potential infection risk for subjects or users.
- Verify the integrity of the syringe and expiry date before use. The device must not be used if the expiry date has lapsed, or if the packaging or contents are damaged. Syringes with an open or shifted tip cap within the protective packaging must not be used. In such case follow instructions given in section 14.8.
- The device should only be used with the syringe, the needle or the additionally provided cannula provided by the manufacturer.
- The needle / cannula must not be manipulated or bent. If the needle / cannula is blocked, do not increase the pressure on the plunger rod but stop the injection and replace the needle. Discard the needle /cannula in a special container
- There are no available clinical data (effectiveness, tolerance) about injecting the device into an area which has already been treated with another filling product.
- The device should not be injected into blood vessels, bones, tendons, ligaments, nerves, muscles or naevi. The treating physicians should be familiar with the face's vascular anatomy to avoid the incidence of arterial inclusion. During the pretreatment planning phase, proximity of susceptible

vessels to common treatment areas should be considered, being aware that anatomical location of blood vessels can vary between different subjects.

- 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.
- The device shall not be used in women who are pregnant or breastfeeding (see section 6.3.7 for more information).
- Subjects should be advised to follow *restrictions* as given in section 6.3.7.
- Subjects must be advised to inform their investigator as soon as possible about any unwanted event. Special focus should be on inflammatory reactions persisting for more than one week or any other occurring secondary effect. The investigator should treat these side effects appropriately[11] and document as AE in the subject's medical record and in the eCRF (see section 14 for more details).

6.2.6 ***Rescue medication***

Any rescue medication / procedure applied should be documented in the subject´s medical record and in the eCRF as concomitant medication/prodcedure (see section 6.4.3).

Use of Hyaluronidase

In case of overcorrection or occurrence of nodules (see IB[11], section 8.2.2) or vascular compromise (see IB, section 8.2.3), a commercially available hyaluronidase injection (e.g. [redacted], or similar) may be used at the discretion of the investigator.

In case impending tissue necrosis, which may occur with any dermal filler, a recent consensus statement on the treatment of hyaluronic acid filler-induced impending necrosis recommends immediate treatment with high doses of hyaluronidase (e.g., at least 200 units of [redacted] 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. If no improvement or progression of necrosis is observed, the above regimen of hyaluronidase, nitroglycerin paste and aspirin should be repeated daily, typically for 2-3 days.[19]

In case of any other adverse event the Expert Consensus Recommendations for treatment of Soft Tissue Filler Complications 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.[19]

6.2.7 ***Investigational medical device accountability***

The IMD must not be used outside the context of this clinical investigation plan (CIP) and the Instructions for Use (IFU). The IMD must be handled in accordance with the Sponsor's instructions (see section 6.2.2 to 6.2.5 and refer to the current version of the IB[11] / IFU[16]).

Considering the number of subjects to be enrolled, the average volume of the device administered in the clinical investigation of Saypha® FILLER Lidocaine (maximum volume of 2 mL for both lips in total), and potential additional touch-up treatment, when including 110 subjects it is anticipated that up to 440 units (à 1 mL) of the IMD may be used during this clinical investigation.

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

At the end of the clinical investigation, all remaining supplies, including empty boxes of IMD that have been used, must be returned to the Sponsor for accurate destruction and accounting of the IMD.

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

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

6.2.8 *Handling of deficient investigational medical devices*

Any IMD alleged to be deficient must not be used by the investigator and must be returned to the Sponsor. Instructions in section 14.8 must be followed.

6.3 Subjects

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

Approximately 110 subjects with moderate to severe volume deficiency of lips (defined as grade 1 grade 3 within LFS) will be enrolled and treated with the IMD.

Each subject will participate in the study for up to 18 months. Taking into account the anticipated recruitment period of 2-3 months, the total expected duration of the clinical investigation will be about 21 months.

6.3.2 *Recruitment strategy*

The recruitment over the study will be competitive and will be stopped as soon as 110 subjects are enrolled in the study.

The study subjects will be recruited by the investigator, among subjects who attend the investigation site seeking the corrective treatment of volume deficiency of their lips.

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 *Inclusion criteria*

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

1. Adult female or male subjects 18 years of age at Screening/Baseline visit (Visit 1)
2. Presence of approximately symmetrical “very thin” lips (minimal red lip shows) to “moderately thick” lips (moderate red lip shows) as assessed with the LFS (severity grade of 1 to 3 on both lips) as determined by the investigator at Visit 1
3. For females of childbearing potential only: negative urine pregnancy test at Visit 1, and must agree to use an highly effective method of contraception for the duration of the clinical investigation (see section 6.3.7 for details)
4. Healthy skin in the treatment area and free of diseases that could interfere in evaluation of treatment
5. Willingness to abstain from any cosmetic or surgical procedures in the treatment area for the duration of the clinical investigation
6. Willingness to take part in this clinical investigation documented by a personally signed/dated informed consent.

6.3.4 *Exclusion criteria*

A subject who meets **ANY** of the following criteria is **NOT ELIGIBLE** for the study and must 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)History of mental disorders or emotional instability
2. History of allergic reaction or hypersensitivity to hyaluronic acid, lidocaine or any amide-based anaesthetic
3. Prior surgery, scars or tattoo to the upper or lower lip or lip line; surgery and tattooing are prohibited until end of clinical investigation
4. Tooth gap, overbite, beard longer three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator
5. Presence of any abnormal lip structure, such as a scar or lump or severe lip asymmetry, as judged by the investigator
6. Previous tissue augmenting therapy in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) with HA or collagen filler, or laser treatment, chemical peeling, dermabrasion or mesotherapy within 12 months before Visit 1 and until end of clinical investigation
7. Previous permanent implant or treatment with non-HA or non-collagen filler in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) and until end of the investigation
8. Previous toxin treatment in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) within 9 months before Visit 1 and until end of clinical investigation
9. Presence of cutaneous lesions, inflammatory and/or infectious processes (e.g. acne, herpes, etc.) or proliferative lesions in the treatment area
10. Known human immune deficiency virus-positive individuals
11. History of allergies against aesthetic filling products and recurrent (3 times a year) herpes simplex in the treated area
12. Tendency to hypertrophic scars, keloid formation and/or pigmentation disorders
13. History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy
14. Uncontrolled systemic diseases (such as diabetes mellitus)
15. Use of anticoagulant, antiplatelet or thrombolytic medication (e.g. acetylsalicylic acid) from 10 days pre- to three days post IMD injections
16. Planned dental/oral surgery or modification (bridge-work, implants) within two weeks prior to initial IMD injection and to a minimum of four weeks post IMD injections
17. Any medical condition which, in the investigator’s opinion, prohibits the inclusion in the study
18. Current or previous (within 30 days of enrolment) treatment with another investigational drug and/or medical device or participation in another clinical study
19. Previous enrolment in this clinical investigation
20. Any dependent relationship of the subject with the investigator, investigation site or Sponsor (e.g. employees or relatives)
21. 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)

6.3.5 *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. Pregnancy
5. 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. If the subject is unreachable, a corresponding note should be provided in the subject´s medical record.

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

Attempts should be made to perform an early termination visit, which should consist of the assessments planned for the Month 18 visit (Visit 6; also see section 6.5.6). In the event that the withdrawal is caused by an AE, the procedures stated in section 14.6 must be followed.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening/baseline failure" or "dropout" as specified in section 6.3.10.

6.3.6 *Replacement of subjects*

Subjects withdrawn from the investigation or lost for follow-up will not be replaced. No re-screening is allowed.

6.3.7 *Life-style and other restrictions*

Contraception

The safety of Saypha® FILLER Lidocaine administration in pregnancy has not been established. Non-clinical studies on reproductive and developmental toxicity of Saypha® FILLER Lidocaine have *not* been conducted. No studies on the effect of Saypha® FILLER Lidocaine on lactation have been conducted. So women of childbearing potential participation should not be pregnant and should use highly effective contraception or avoid unprotected sexual intercourse throughout the clinical investigation. Any pregnancy occurring in study subjects during the investigation (i.e., from date of ICF signature until the last scheduled visit) should be reported as AE and followed-up as described in section 14.

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

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

Other restrictions

The following restrictions apply to all subjects:

- Make-up should not be applied for 12 hours after each IMD injection;
- Prolonged exposure to sunlight or ultraviolet (UV) radiation must be avoided for one week after each IMD injection; lip 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 each IMD injection (exception: a light massage may be applied after injection of the device for uniform distribution of the filler by the investigator – see section 6.2.2);
- Use of saunas or Turkish baths is prohibited for one week after each IMD injection.
- Beard longer three-day beard, or excessive facial hair that could interfere in evaluation of treatment as judged by the investigator (see ExC#5)

6.3.8 *Prohibited medication and aesthetic treatments*

The following medications and treatments are prohibited prior to start of the investigation and during the entire investigation, if not stated otherwise below (also refer to the respective ExC in section 6.3.4):

- Prior surgery or tattoo to the upper or lower lip or lip line (see ExC#4)
- Previous tissue augmenting therapy in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) with HA or collagen filler, or laser treatment, chemical peeling, dermabrasion or mesotherapy within 12 months before Visit 1 (see ExC#7)
- Previous permanent implant or treatment with non-HA or non-collagen filler in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) (see ExC#8)
- Previous toxin treatment in the lip area (including lips, oral commissures, nasolabial folds, marionette and perioral lines) within 9 months before Visit 1 (see ExC#9)
- History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy (see ExC#14)
- Anticoagulant, antiplatelet, or thrombolytic drugs (e.g. acetylsalicylic acid) from ten days pre- until three days after each injection of the device (see ExC#16)
- Planned dental/oral surgery or modification (bridge-work, implants) within two weeks prior to initial IMD injection and to a minimum of four weeks post IMD injections (see ExC#17)
- Current or previous (within 30 days of enrolment) treatment with another investigational drug and/or medical device or participation in another clinical study (see ExC#19)
- If no aesthetic effect is present anymore new injections for lip augmentation might be placed after 3 months in general (see section 6.4.12).
- According to IB (see section 8.1.5) sensitive skin may be pre-treated using a local anaesthetic patch or cream. However, a pre-treatment with local anaesthetics is not allowed in this investigation to not falsify the pain assessment (as collected via Numerical Pain Rating Scale; see section 6.4.8).

6.3.9 *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.

In case no aesthetic effect is present anymore new injections might be placed at previously injected locations after 3 months in general (see section 6.4.12).

6.3.10 *Screening/Baseline failures and dropouts*

Data for screening/baseline failures (eligible subjects who did not receive investigational device for whatever reason) will be documented in appropriate forms (e.g., Subject Screening/Enrolment Log). Screening data for these subjects will be kept in the Investigator's File. The type of data to be entered in the eCRF, if any, will be defined in the eCRF Completion Guidelines.

Subjects who prematurely discontinue the investigation after receiving at least one dose of the IMD will be defined as dropouts.

6.3.11 *Subject identification, privacy and 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 format of the codes will be defined in the eCRF Completion Guidelines. The investigator will assign the codes in ascending order, in line with the order of the informed consent date and time.

The investigator must ensure that anonymity of the subjects will be maintained and that their identities are protected from unauthorized parties. In the eCRF or any other document submitted to the Sponsor or Sponsor's representative, subjects must be identified only by their identification codes; use of names, initials, complete birthdates, addresses, telephone numbers, electronic addresses or similar information is prohibited. The investigator will keep the Subject Identification Log (including complete name, date of birth, and contact details of each subject) in their medical record. 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 8.4. Professionals with access to subjects' data for monitoring, audits and inspections are bound to preserve strict confidentiality.

This CIP, other investigation-related documentation, collected data and all other information generated will be held in strict confidence. No information concerning the clinical investigation or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

Clinical photography and assessment of the independent photographic reviewer and use of photographs for publication purposes

Besides assessment by the investigator on site, lip fullness will additionally be assessed by an independent photographic reviewer using photographs (see section 6.4.7). Subject's eyes will not appear on the photographs, i.e., only anonymized pictures will be sent to the independent photographic reviewer. Should there be attributes visible on the photographs that could identify a subject (e.g., characteristic scars, tattoos), the photographs will be anonymized for that purpose (i.e., the identifying features will be obscured by a black bar). The same applies to photographs used for publication purposes. However, subjects will be explicitly informed about this matter when obtaining written informed consent.

6.4 Assessments and procedures

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

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

6.4.1 *Demographic data*

Information on subject's year of birth, gender and race will be collected. In addition, the smoking habits (current, former, never smoked, unknown) will be collected. In case the subject is a current smoker (less than 3 months smoking cessation), the average number of cigarettes or other tobacco products per day must be recorded.

All demographic data will be documented in the subject´s medical record and in the eCRF.

6.4.2 *Medical history and aesthetic procedures history*

Medical history will be collected at Day 0 (Visit 1) prior to application of the IMD, from subject interview and medical records (if available). Special attention should be paid to diseases and conditions relevant for exclusion criteria with particular reference to facial aesthetic or surgical procedures.

Any medical condition that is present at Screening/Baseline prior to start of application of the IMD should be considered as medical history.

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

If such condition, however, deteriorates after the IMD administration, at any time during the investigation, it should be documented as an AE (see Section 14).

6.4.3 *Prior and concomitant medication and non-drug therapies*

Prior medication and procedures (e.g. surgeries or aesthetic procedures) are as all medication taken or procedures performed within ten days (whether continuing or not) prior to Visit 1 (Day 0).

Concomitant medication / procedure is defined as all medication taken or procedures performed from Visit 1 (including medication taken immediately pre-injection and post-injection of the IMD) until the final visit (Visit 5 or 6, if applicable).

At each visit the subject will 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 IMD.

Prior and concomitant medication and non-pharmacological procedure applied (e.g. surgeries or aesthetic procedures) will be documented in the subject's medical record and in the eCRF classified by drug generic name / trade name or active substance (in case that no generic name is available).

Prohibited concomitant medications and non-pharmacological procedure (e.g. surgeries or aesthetic procedures) are listed in section 6.3.7.

6.4.4 *Pregnancy test*

In females of childbearing potential, including women who are postmenopausal for less than twelve 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.

6.4.5 *Photography*

Photographs of the subject´s lips will be taken by the investigator or their designee using a digital camera before the application of the medical device at Visit 1 (Day 0) and at each follow-up visit except Week 3 visit.

A standardized procedure, which will be described in a photography manual, will be applied to ensure consistency of the background, camera settings, lighting, and subject position between the visits and across the sites. An excessive or distracting makeup (especially of the lips) has to be removed.

A review of all photographs will be performed by an independent photography reviewer who will evaluate the severity of volume deficiency as described in section 6.4.7.

The photographs will also be used for the investigator´s and subject´s assessment of aesthetic improvement using the Global Aesthetic Improvement Scale (GAIS) (see section 6.4.9).

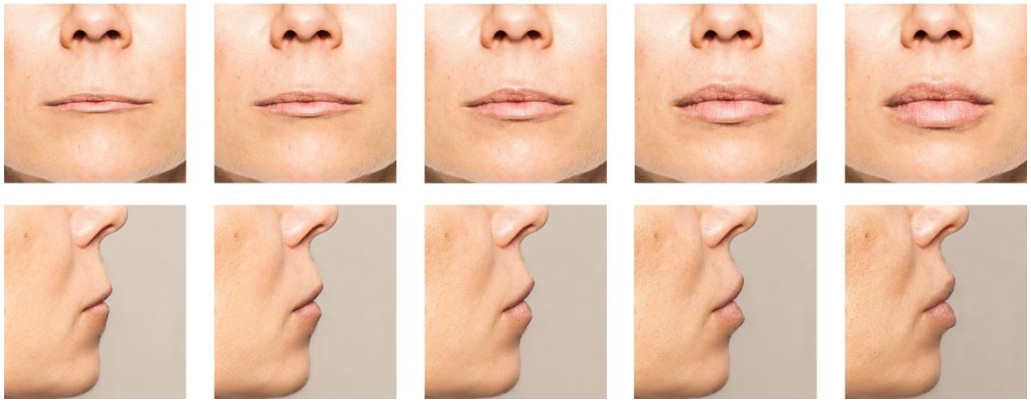
6.4.6 *Injection volume, injection technique and injection equipment*

The actual injection volume (initial and touch-up) required for an optimal augmentation of lips with Saypha® FILLER Lidocaine will be documented separately for upper and lower lips in the subject´s medical record and the in eCRF. The volume injected into each lip will be read off the syringe by the investigator. The actual volume injected will be read of the device by the investigator and recorded in the eCRF, together with information on injection technique (i.e., retrograde technique or bolus technique), the injection equipment used (i.e., needle or cannula), area of application, date, and exact start time and end time of injection.

6.4.7 *Lip Fullness Scale (LFS) - Grading of lip volume deficiency*

Lip Fullness Scale (LFS) is a validated 5-point rating scale ranging from Grade 1 (minimal) to Grade 5 (very significant) as outlined in Table 5. The upper and lower lip will be separately graded, and the assigned grades will be recorded in the subject's record and the eCRF.

Table 5. *Croma - Lip Fullness Scale (LFS)*

Croma LFS - grade	**1 (Minimal)**	**2 (Slight)**	**3 (Moderately thick)**	**4 (Thick)**	**5 (Full)**
Description	Minimal red lip shows Flat contour.	Slight red lip shows May have minimal lip pout or nearly flat contour	Moderate red lip shows May have slight lip pout	Significant red lip shows May have moderate or significant lip pout or may be curved.	Very significant red lip shows May have significant/very significant lip pout or may be very curved
Visual guide					

Investigator

The severity of volume deficiency of the lips will be evaluated by the investigator according to the LFS.

At the Visit 1 (Day 0) the LFS grading will be performed *before* the IMD treatment, and the grade assigned at this visit will represent the baseline value for derivation of the responder status. Subjects can be included only if Inclusion criterion #2 is met (refer to 6.3.3).

The LFS grading results of the investigator will be recorded in the subject´s medical record and in the eCRF.

Independent photographic reviewer

The severity of volume deficiency will additionally be assessed by an independent photographic reviewer using LFS on photographs.

This assessment is performed after the photo has been uploaded. The independent photographic reviewer will be dislocated from the investigation sites and will not discuss any findings with the investigators during the trial. Further details will be described in a separate manual.

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

After initial administration and touch-up treatment of the IMD, 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 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 on the Pain Assessment Form. The subject will be provided with the appropriate questionnaire in local language.

Completed subject's Pain Assessment Form will be considered as source documents and archived in the subject's medical record. The results will be transferred into 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 according to the procedures described in section 14.

6.4.9 *Global Aesthetic Improvement Scale (GAIS) - "Aesthetic improvement"*

The aesthetic improvement after correction of hypotroph lips will be independently evaluated by the investigator and the subject using the Global Aesthetic Improvement Scale (GAIS)[20], a widely-used instrument presented in Table 6. The upper and lower lip will be graded separately.

Table 6. *Global Aesthetic Improvement Scale (GAIS)*

Category	Description
Very much improved	Optimal aesthetic result for the implant in this patient.
Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this patient. A Touch-up would slightly improve the result.
Improved	Obvious improvement in appearance from the initial condition, but a Touch-up or retreatment is indicated.
No change	The appearance is essentially the same as the original condition.
Worse	The appearance is worse than the original condition.

Investigator

The investigator will perform live assessment and will evaluate the aesthetic improvement against subject's photographs obtained at the Visit 1 (Day 0). Results will be recorded in the subject´s medical record and in the eCRF.

Subject

For subject's assessment, the subject will get the GAIS Questionnaire Form and review the photographs taken at the current and the Baseline visit. The subject will be asked to evaluate the aesthetic improvement by comparing the appearance on current photographs against Visit 1 (Day 0).

The assessment will be done at the beginning of the visit (but after clinical photography was conducted) to avoid potential influence of investigator's comments on subject's perception of improvement. The investigator´s answer should not be disclosed to the subject prior to his/her assessment to avoid potential influence.

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

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

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

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

The questionnaire is a validated instrument for evaluation of subject´s satisfaction with the overall outcome of the treatment.[21] It comprises 6 positively worded items that ask the subjects to indicate how they feel about the result of their most recent facial aesthetic procedure.

Four response options are provided (i.e., definitely agree, somewhat agree, somewhat disagree, and definitely disagree). For each statement, the subject may circle only one answer. The upper and lower lip will NOT be graded separately. The scale is described in Table 7 below.

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

The assessment should preferably be conducted at the beginning of the visit to avoid potential influence of subject's perception of improvement by investigator's comments.

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

6.4.11 *FACE-Q™ Questionnaire – "Satisfaction with lips"*

Subject's satisfaction with lips will be evaluated using the respective FACE-Q™ Questionnaire (Appearance appraisal scale: Lips).

The questionnaire is a validated instrument for evaluation of subject´s satisfaction with lips. It comprises 10 items.This scale measures the appearance of the lips with items that ask about size, shape and fullness, as well as how their lips suit their face and how the lips look when smiling.

Four response options are provided (i.e., answers very dissatisfied, somewhat dissatisfied, somewhat satisfied, very satisfied). For each statement, the subject may circle only one answer. The upper and lower lip will NOT be graded separately.The scale is described in Table 8 below.

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

The assessment should preferably be conducted at the beginning of the visit to avoid potential influence of subject's perception of improvement by investigator's comments.

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

6.4.12 *Assessment of aesthetic effect*

At each follow-up visit, the investigator will evaluate the aesthetic effect. The presence of an aesthetic effect at a given visit relative to baseline will be recorded as either „YES" or „NO" in the subject´s medical record and in the eCRF.

The duration of the clinical investigation is planned for 18 months at a maximum and depends on the assessment of the aesthetic effect. In case it is observed by the investigator that no aesthetic effect is any more visible the study can be terminated at Month 12 (Visit 5) for the respective subject.

If no aesthetic effect is present anymore new injections for lip augmentation might be placed at previously injected locations after 3 months in general.

6.4.13 *Safety monitoring*

The safety of the subjects will be monitored throughout the investigation, from Visit 1 (Day 0) beginning immediately after start of initial treatment until the final visit (Visit 5 or 6, if applicable).

At visits IMD will be applied, special focus will be paid on potential AEs occuring within 15 min after each IMD application.

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. Special focus should be on inflammatory reactions persisting for more than one week or any other occurring secondary effect.

Device deficiencies will be documented as well at each IMD treatment.

The procedure for collection, recording and reporting of AEs and device deficiencies is described in section 14.

6.5 Schedule of procedures

The "schedule of procedures and assessments" in **Table 1** gives an overview of study procedures during study conduct. The following sections tabulate the procedures to be performed by visit.

6.5.1 *Visit 1 -Screening / Baseline Visit - Day 0*

- Assessments prior to IMD administration:
    - Provide subject information / Obtain written informed consent (see section 13)
    - Assign the subject number (see eCRF Completion Guidelines)
    - Collect demographic data (see section 6.4.1)
    - Record medical history (including information on prior facial aesthetic or surgical procedures) (see section 6.4.2)
    - Record prior and concomitant medication and procedures (see section 6.4.3)
    - Review and evaluate inclusion/exclusion criteria (see section 6.3.3 and 6.3.41) including wash out periods for prohibited treatment (see section 6.3.7)
    - Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4)
    - Instruct female subjects of childbearing potential about highly effective methods of contraception (see section 6.3.7)
    - Perform photography (see section 6.4.5)
    - Lips fullness assessment (LFS) – investigator (see section 6.4.7)
    - Lips fullness assessment (LFS) – independent photographic reviewer; Note: This assessment is performed after the photo has been uploaded (see section 6.4.7).
- IMD administration:
    - see Section 6.2 for detailed instructions for injection
    - Document information on injection (see section 6.4.6)
    - Place the one peel-off label of the outer carton box in the subject´s medical record and provide the other label to the subject to ensure traceability of the device (see section 2.5)
- Pain assessment (during treatment) using the NPRS by subject immediately after IMD administration (see section 6.4.8)

- Pain assessment (during recovery from treatment) using the NPRS by subject 15 min after administration of the IMD (see section 6.4.8)
- Record AEs from beginning of the first IMD administration procedure onwards (see section 14):
    - The subject should be kept at the investigation site and observed for at least 15 min after IMD administration in order to identify potential AEs post-administration
    - Special focus should be laid on inflammatory reactions persisting for more than one week or any other occurring secondary effect (see section 6.4.13).
- Advise the subject prior to discharge to follow restrictions specified in section 6.3.7 and to inform the investigator especially about inflammatory reactions persisting for more than one week or any other occurring secondary effect (see section 6.4.13).
- Record any device deficiencies (see section 14.8)

6.5.2 *Visit 1a - Telephone Visit - Day 1 (24h after 1st injection)*

- Ask for any changes in AEs and new AEs (see section 14)
- Ask for changes in concomitant medication and procedures (see section 6.4.3)

In case of an AE an unscheduled on-site visit should be performed (see section 6.5.7).

6.5.3 *Visit 2 – Week 3 (after Visit 1) ± 2 days*

- Record any new AE or changes of AEs (see section 14) with special focus on inflammatory reactions persisting for more than one week or any other occurring secondary effect (see section 6.4.13).
- Record changes in concomitant medication and procedures (see section 6.4.3)

Optional Touch-up IMD administration (see Section 6.2):

The touch-up treatment is optional and will be conducted at investigator's discretion, if full correction was not achieved after initial IMD treatment (i.e., at Visit 1). If the investigator decides to conduct a touch-up treatment, the following assessments must be conducted for the respective subjects:

- Document information on injection (see section 6.4.6)
- Place the one peel-off label of the outer carton box in the subject´s medical record (see section 2.5)
- Pain assessment (during treatment) using the NPRS by subject immediately after IMD administration (see section 6.4.8)
- Pain assessment (during recovery from treatment) using the NPRS by subject 15 min after administration of the IMD (see section 6.4.8)
- The subject should be kept at the investigation site and observed for at least 15 min after IMD administration in order to identify potential AEs post-administration
- Re-advise the subject prior to discharge to follow restrictions specified in section 6.3.7 and to inform the investigator especially about inflammatory reactions persisting for more than one week or any other occurring secondary effect (see section 6.4.13).
- Record any device deficiencies (see section 14.8)

6.5.4 *Visit 2a - Telephone Visit - Day 1 (24h after touch-up) – only in case of touch-up treatment*

- Ask for any changes in AEs and new AEs (see section 14)
- Ask for changes in concomitant medication and procedures (see section 6.4.3)

In case of an AE an unscheduled on-site visit should be performed (see section 6.5.7).

6.5.5 *Visit 3 to 6 – Week 6 to Month 18 (after Visit 1)*

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

- Visit 3 – Week 6 (± 5 d) after Visit 1
- Visit 4 – Month 6 / Week 26 (± 7 d) after Visit 1
- Visit 5 – Month 12 / Week 52 (± 7 d) after Visit 1
- Visit 6 – Month 18 / Week 76 (± 7 d) after Visit 1 – optional

The following assessment will be performed through these follow-up visits:

- Record any new AE or changes of AEs (see section 14)
- Record changes in concomitant medication and procedures (see section 6.4.3)
- Women of child-bearing potential: Urine dipstick pregnancy test (see section 6.4.4)
- Lips fullness assessment (LFS) – investigator (see section 6.4.7)
- Lips fullness assessment (LFS) – independent photographic reviewer; Note: This assessment is performed after the photo has been uploaded (see section 6.4.7).
- GAIS assessment – investigator (see section 6.4.8)
- GAIS assessment – subject (see section 6.4.8)
- FACE-Q™ – Satisfaction with overall outcome of treatment (see section 6.4.10)
- FACE-Q™ – Satisfaction with lips (see section 6.4.11)
- Assessment of aesthetic effect (see section 6.4.12). In case it is observed by the investigator that no aesthetic effect is any more visible the study can be terminated at Month 12 (Visit 5) for the respective subject; otherwise a visit for optional Month 18 (Visit 6) should be scheduled.

6.5.6 *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 6.5.5).

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

- Record any new AE or changes of AEs (see section 14)
- Record changes in concomitant medication and procedures (see section 6.4.3)
- Lips fullness assessment (LFS) – investigator (see section 6.4.7)

6.5.7 *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. Special focus should be on inflammatory reactions persisting for more than one week or any other occurring secondary effect. The investigator should treat these side effects appropriately.[19]

In case the unscheduled visit results in early termination of the subject, the assessments for the Early Termination Visit should be performed (see section 6.5.6). Details of the event are to be recorded in the subject's records and in the eCRF.

6.6 Factors that may compromise the outcome

There are no foreseeable factors that may significantly compromise the outcome. Subject eligibility criteria and prohibition of concomitant medications and aesthetic procedures that may affect the outcome are carefully defined.

A substantial body weight change could possibly affect the results in individual subjects. Since this is an interventional post-market 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.

6.7 Monitoring plan

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

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

During the investigation, further monitoring visits will be performed according to ISO 14155:2011, the applicable standard operating procedures, and local regulations. At each visit the monitor will check the progress of enrolment, will review source data for adherence to the CIP, review eCRFs against source data for completeness, accuracy and consistency, and will also check if the IMD have been stored, dispensed and accounted for according to respective specifications.

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

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

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

6.8 Audits

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

Audits of the clinical investigation may be conducted by the Sponsor or external organizations designated by the Sponsor to evaluate compliance with the CIP, written procedures, ISO 14155:2011 and the applicable regulatory requirements.

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

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

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

Confidence Interval calculation has been performed for the primary performance endpoint "The proportion of subjects ('responders') with the lip volume improved by ≥1 point versus baseline value at 6 weeks after initial treatment based on the investigator live assessment using a validated Lip Fullness Scale (LFS)". A responder is defined having at least ≥ 1 grade improvement compared to baseline values on the 5 point-validate lip fullness scale" (see section 6.1.1).

Approximately 110 subjects with moderate to severe volume deficiency of lips will be enrolled in order to obtain performance and safety data.

This sample size is arbitrarily selected and is considered sufficient to provide robust estimations on performance and safety parameters in the overall study population and in the subgroups regarding IMD manufacturing site. With a sample size of 100 a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend by 0.059 in the overall population and 0.083 in the two manufacturing site subgroups from the observed proportion for an expected proportion of 0.900 (i.e., responder rate of 90%; calculated with nQuery Advanced 8.2.1.0). In order to cover subjects' drop-out or lost to follow-up the sample size will be increased by 10%. 110 subjects will be enrolled (with 55 subjects per manufacturing site). Thus, a robust estimation of the success rate at week 6 can be derived.

7.2 Analysed data sets

Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all subjects who received at least one administration of the investigational medical device (IMD).

Full Analysis Set (FAS)

The Full Analysis Set (FAS) comprises all subjects who received at least one administration of the IMD and who had at least one post-treatment evaluation of the LFS.

Per-Protocol Set (PPS):

The Per-Protocol Set (PPS) includes all subjects of the FAS who have no major protocol deviations.

Subjects with major protocol deviations will be excluded from the PPS. For this purpose, protocol deviations that could interfere with the objectives of the study, use of prohibited concomitant medications/procedures or deviation of the inclusion/exclusion criteria etc. will be assessed as 'minor' or 'major' in collaboration with the sponsor in the Data Review Meeting (DRM). The criteria for this assessment will be defined before analysis in the SAP. Listings will be prepared to assess the eligibility of all subjects during the DRM.

All safety analyses will be based on the SAF. The primary data set for effectiveness analysis will be the FAS and PPS. Certain sensitivity analyses may be also done in the PPS.

7.3 Methods of analysis

All statistical analyses will be done using descriptive statistics. All summary tables and subject data listings will be prepared by visit if applicable.

Summary statistics (mean, standard deviation, minimum, first quartile, median, third quartile, and maximum) will be provided for continuous variables, and the number and percentage of each category will be provided for categorical data. If applicable and unless otherwise specified statistical tests will be non-parametric and 2-sided at 0.05 level of significance.

Two-sided 95% confidence intervals for the percentages of responders and mean LFS improvement at various time points will be given and proportions for the LFS improvements of ≥1 point will be calculated. Individual LFS grades per visit will be calculated as the mean of grades assigned to the upper lip and lower lip, respectively.

All statistical analyses including will be outlined in detail in the SAP including all aspects of the interim analysis (IA), tables, figures and subject data listings. Any changes in the original statistical methodology will be documented in the SAP as well.

All data collected will be presented in subject data listings.

7.3.1 *Interim analysis*

An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit at Month 6 (Visit 4). Summary tables and subject data listings will be provided for the SAF and the FAS and all variables that are outlined in detail in the IA section of the final SAP. The SAP has to be finalized prior to the IA database lock. The IA database will be cleaned and a data base lock prior to export for data analysis will be done. The interim analysis will be done on the 'overall population' (see section 7.3.10 for more information).

7.3.2 *Final analysis*

Final analysis will be done after completion of the investigation by all subjects. All primary, secondary and safety endpoints will be tabulated by visit, if applicable, and summarized using descriptive statistics only. The final analysis will be done for the 'overall population' and for several defined subgroups (see section 7.3.10 for more information).

7.3.3 *Subject disposition*

Summary tables will be provided for the following subject characteristics:

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

Subjects who prematurely discontinue the investigation after receiving at least one dose of the IMD will be defined as dropouts, see section 6.3.10.

7.3.4 *Demographics and baseline characteristics*

Summary statistics for demographic and baseline characteristics, including age, gender, race, and other relevant study entry criteria will be prepared for the SAF.

7.3.5 *Medical and aesthetic procedures history*

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

7.3.6 *Prior and concomitant medication and non-pharmacological procedures*

Prior and concomitant medication / non-pharmacological procedures will be coded using the World Health Organization (WHO) Drug Dictionary. All recorded medication for the SAF will be presented in subject data listings according to anatomical area, therapeutic area and preferred term.

7.3.7 *Performance endpoints*

As two lips of each subject will be considered, there are two measurements per subject for LFS. Differences between the lips are expected, thus both measurements will be separately used for analyses.

Individual LFS grades per visit will be calculated separately to the upper and the lower lip, respectively. The absolute LFS change versus baseline will be computed by subtracting the value obtained on Day 0 from that of the corresponding visit. Absolute LFS change from baseline will be summarized by the visit using descriptive statistics. In addition, the proportion of the LFS change values ≥1 and its 95% confidence interval will be calculated.

Individual GAIS grades, subjects' satisfaction with the overall outcome of the treatment, subject's satisfaction with augmentation of lips, the pain ratings, investigator´s evaluation of aesthetic effect and the injection volume (initial and touch-up) will be summarized and tabulated by visit using descriptive statistics.

7.3.8 *Safety endpoints*

AEs will be coded by the 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.

Urine pregnancy tests will be listed only. All other safety data will be statistically summarized for all subjects dosed (SAF).

7.3.9 *Multicentre trial*

This study will take place in up to three investigation sites, however, due to the limited number of subjects no site stratification is planned.

7.3.10 *Analysis of subgroups*

Besides the 'overall population' (including all subjects enrolled in the investigation), which includes all enrolled subjects, the following subgroups will descriptively be analyzed:

- **IMD from manufacturing sites: 'HQ' and 'C1'**

  In this study, IMD from two different manufacturing sites ('C1' and 'HQ') will be used and subjects will be randomly assigned in a 1:1 ratio to 'IMD-C1' or 'IMD-HQ', respectively.

  This subgroup analysis will compare both IMDs ('IMD-HQ' or 'IMD-C1') and separately analyze the results for the 'IMD-C1' and 'IMD-HQ' subgroups.

- **Injection technique: 'retrograde technique' and 'bolus technique'**

  It is planned to descriptively analyze the performance of the IMD separated by injection technique.

  The corresponding subgroup analysis will separately analyze the results for subjects treated with the two different injections techniques.

- **Injection equipment: '27G ½″ needle' versus cannula ('25G x 50mm cannula' or '22G x 70mm cannula')**

  It is planned to analyze the performance of the IMD separately for the injection equipment used (27G ½″ needle versus cannula (25G x 50mm cannula or 22G x 70mm cannula)). Therefore it is planned to treat a minimum of 30 subjects either with needle or cannula (25G x 50mm cannula or 22G x 70mm cannula).

  The corresponding subgroup analysis will separately analyze the results for subjects treated by means of the different injection equipment.

All subgroup analyses are planned to be performed for the primary performance endpoint and the main secondary performance endpoints.

The following secondary performance endpoints are planned to be analyzed:

- The percentage of responders, based on the investigator live assessment at 6, 12 and optional 18 months after the initial treatment using the validated LFS.
- The percentage of responders based on the independent photographic reviewer´s assessments before initial treatment and at Week 6, Month 6, 12 and optional Month 18 after initial treatment, based on photographs and using the validated LFS.
- The percentage of subjects with an improvement relative to baseline photographs, (subjects who have been rated as “very much improved” or “much improved” or “improved”), based on the investigator assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment using the 5-point GAIS.
- The percentage of subjects with an improvement relative to baseline photographs (subjects who have been rated as “very much improved” or “much improved” or “improved”), based on subject assessment at Week 6, Month 6, 12 and optional Month 18 after initial treatment, using the 5-point GAIS.
- Subject’s perception of pain after initial and touch-up treatment with Saypha® FILLER Lidocaine using the 11-point Numeric Pain Rating Scale (NPRS), where 0 is no pain and 10 is the worst pain imaginable.

7.4 Subject data listings

All recorded data will be presented in subject data listings.

7.5 Missing data

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

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

7.6 Software used for statistical analysis

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

7.7 Deviations from the planned statistical analysis

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

8 Data handling and data management

8.1 Source documents and other records maintained by the investigator

It is the investigators’ obligation to assure documentation of all relevant data in the subject’s medical record, such as the dates of informed consent and enrolment into the clinical investigation, medical history, prior and concomitant medications, visit dates, clinical observations including AEs (incl. reporting and follow-up of AEs), results of all assessments including clinical photographs, information related to medical device application, and the date of subject’s exit from the investigation, including the reason.

Any form completed by the subject is also considered as a source document and must be kept in the subject’s medical record.

In addition, the investigator must maintain all other essential documents pertaining to the clinical investigation as defined by ISO 14155:2011 and applicable regulatory requirements.

8.2 Case report forms

A CRF will be completed for each subject enrolled in the investigation who received the investigational device. Data on each subject enrolled in the investigation will be recorded pseudonymously in the web-based validated electronic CRF (eCRF), which is designed to accommodate the specific features of the clinical investigation design and complies with regulatory requirements on electronic data transfer.

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

For the formal interim analysis (see section 8.3), the addition of a second eSignature page will be for the Investigator agreeing and confirming that all clinical data recorded through the Month 6 visit is correct and accurate. This page will be associated only with the Screening/Baseline through Month 6 pages (but not with the pages documenting AEs, medical history, prior and concomitant medications and procedures; the ability of the last visits to be entered will not be restricted). Once signed, no changes can be made without stripping the eSignature.

Any subsequent change, deletion or addition will be recorded by an audit trail system, which will require re-signing of the eCRF by the Investigator or their authorized designee. The investigator must assure that all data are entered promptly, completely, and accurately according to the eCRF instructions, and is ultimately responsible for conformance of eCRF entries with source documents.

8.3 Data management procedures

All data management activities will be conducted by the Sponsor's representative following their standard operating procedures. They will build the database and handle the data cleaning process, including logical checks, medical checks, and query process. Details on data handling and data cleaning will be described in the Data Management Plan (DMP).

Procedures for verification, validation and securing of electronic clinical data systems

The database application development occurs on a validated clinical data management system. The validation requirement for a database is satisfied through the following components:

- The data entry screen testing and edit check testing serve as evidence of a database that performs for its intended use of capturing and cleaning of clinical data.
- The User Acceptance Testing Plan serves as the summary of the testing documenting the validation process, findings and resolutions.
- All validation is performed on the project development/test environment of the database which is an exact replica of the production database, reserved primarily for testing.

Procedures for Data Cleaning

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

Upon completion of data collection and all data cleaning activities, i.e., when the database is considered complete and accurate, it is considered soft locked and reviewed by the Sponsor together with the clinical investigation team during the Data Review Meeting. The database will be hard locked after Sponsor’s approval. All changes will be tracked by audit trail. Once hard locked the final clean datasets will be exported for final statistical analysis.

Interim analysis

An interim analysis (IA) assessing the safety and effectiveness will be performed after all subjects have completed the follow-up visit at Month 6 (Visit 4). For the interim analysis the database will be cleaned and a data base lock prior to export for data analysis will be done.

8.4 Data retention

The investigator shall retain all clinical investigation records (including all individual subject-related documents (e.g., subject´s questionnaires and ICF), device-related records, investigation-related correspondence, and all other documents contained in the Investigator's File) 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, or the time period specified in the contract between the Sponsor and the investigator, whichever is longer. In any case, the investigator must contact the Sponsor in writing prior to destruction of any records pertaining to the clinical investigation, to get confirmation that these no longer need to be retained. In addition, the Sponsor should be informed in writing if the investigator plans to leave the site or chooses to store the records at a different physical address than the site address, to ensure traceability of the records and appropriate arrangements for the transfer of custody.

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

8.5 Report of the clinical investigation

Following completion of the clinical investigation, the results will be evaluated, and the Clinical Investigation Report (CIR) 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 relevant authorities as appropriate, within the timeframes defined per national regulation or to the Ethics committee (EC).

After the interim analysis an interim Report will be generated.

9 Amendments to the clinical investigation plan (CIP)

Any change of this CIP can only be made in form of a written amendment. Such amendment must be discussed, agreed upon and signed by the Sponsor and the investigator before implementation.

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

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

10 Deviations from the clinical investigation plan

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

Under emergency circumstances, deviations from the CIP may proceed without prior approval by the Sponsor and favourable opinion of the 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.

11 Device accountability

Investigational medical device accountability is described in section 6.2.7.

12 Statements of compliance

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

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

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

The clinical investigation will not commence until a favorable opinion from the respective EC[H] 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. It must be emphasized that participation is voluntary and that the subject has the right to withdraw from the clinical investigation at any time without any justification and without prejudice. They also must be informed that the quality of their medical care will not be adversely affected if they decline to participate in the investigation or in case of subsequent consent withdrawal. Before consenting, the subject must be left with ample time to consider and ask questions.

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

The investigator will document in the subject´s medical record and the eCRF that s/he has informed the subject and that the subject and the investigator have signed the ICF. A signed and dated copy of the ICF will be given to the subject for their records. The other copy of the signed and dated ICF will remain in the Investigator´s File.

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

[H] The Ethics Committee (EC) is an independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation. For the purposes of this CIP, "ethics committee" is synonymous with "research ethics committee", "independent ethics committee" or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region (also see ISO14155:2011, section 3.18).

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 IMD.

- For subjects taking part in the clinical investigation 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 IMD.

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

- 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 IMD. 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 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;
- Foetal distress, foetal death, a congenital abnormality or birth defect.

Planned hospitalization for pre-existing condition or a procedure required by the CIP without a serious

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 an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the Investigator´s Brochure (IB).

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

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

In order to identify potential AEs post-administration of IMD (initial treatment and touch-up treatment) a safety evaluation 15 minutes after the IMD administration needs to take place (see section 6.4.13).

To avoid over-reporting of pain, a non-leading question „*How do you feel?*“ should be asked prior to pain assessment via NPRS at Visit 1 and – if applicable – at Visit 2 (see section 6.4.8). Spontaneously reported pain, or pain graded ≥4 during or after treatment will be recorded as an AE according to the procedures described in section.

In addition, the subjects will be instructed to immediately contact the investigator/investigation site in case of occurrence of any untoward event between visits and an unscheduled visit will be performed (see section 6.5.7). Special focus should be on inflammatory reactions persisting for more than one week or any other occurring secondary effect. The investigator should treat these side effects appropriately.[19]

Throughout the entire investigation the investigator should also verify results of all assessments with respect to possible AEs.

14.3 AE/SAE documentation

For each AE the following must be reported:

- Description of the event (event term)
- Seriousness
- Start date, including start time for events occurring on the day of IMD administration
- Intensity
- Action taken (none, medical and/or surgical)
- Outcome
- End date (if applicable)
- The relationship to the IMD and procedure, respectively

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

Each AE has to be documented, even if the investigator feels that it is not connected with the IMD or procedure.

The AE will be described in precise, standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information (including affected body site(s)). In such cases, the diagnosis will be documented as the AE and not the individual signs/symptoms. In case of any local reaction the exact location (e.g., upper or lower lips) should be clearly noted.

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

Adverse events will be documented beginning immediately after start of initial treatment until the last visit. Events occurring after provision of informed consent and prior to start of application of the IMD 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. If such condition, however, deteriorates after the IMD administration, at any time during the investigation, it should be reported as an AE.

If the intensity or seriousness of an AE changes over time, the most severe intensity or seriousness of the AE will be recorded and included in the analysis. No separate AEs will be recorded for each intensity level.

Changes in causality assessment should also be clearly documented. AEs related to the IMD as well as to investiation procedure must be documented. Any medication and non-pharmacological procedure necessary for the therapy of an AE must be recorded on the respective page of the eCRF.

Adverse events in users or other persons

- For any AE in users or other persons the Adverse Event (AE) Documentation Form for Users / Other Persons must be completed according to the Instructions for Completion.
- If the AE fulfills one of the criteria for seriousness the SAE Report Form must be completed, additionally and reporting responsibilities have to be fulfilled (see section 14.5).
- If the AE is related to a device deficiency, the corresponding Device Deficiency Form has to be completed, too (see section 14.8).

14.4 AE assessment

All AEs will be assessed in terms of seriousness, intensity, relationship to the IMD or clinical investigation procedures, and outcome.

14.4.1 *Seriousness*

The seriousness of an AE is assessed by comparing AE features against the SAE definition provided in section 14.1.

14.4.2 *Intensity*

The intensity of an AE will be graded as follows:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and/or requires medical intervention.

14.4.3 *Causality*

The investigator is obligated to estimate the relationship between each AE/SAE and the IMD or clinical investigation procedure. Clinical judgement should be used and relevant documents like Instructions for Use or Investigators Brochure 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 IMD 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 IMD use/application or procedures; involves a body-site or organ that the IMD or procedures are applied to or have an effect on; follows a known response pattern to the IMD (if the response pattern is previously known); the discontinuation of IMD 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 IMD 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 IMD 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 IMD 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 IMD 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 IMD or the procedures; does not follow a known response pattern to the IMD (if the response pattern is previously known) and is biologically implausible; the discontinuation of IMD 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 IMD 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.

For the final analysis all AEs assessed with the relationship “unrelated” or “unlikely” will be classified as “not related” and AEs assessed with “possible”, “probable” or “definite” will be classified as “related”.

14.4.4 *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 Sponsor’s representative within 24 hours of awareness **of the event via Email**. 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 subjects taking part in the investigation or the conduct of the investigation.

Information about an SAE will be collected and recorded on the SAE Reporting 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 until the SAE has resolved or, in the case of permanent impairment, until the SAE has stabilized. Any pregnancy must be notified to the contact given above within the same timelines as an SAE (within 24 hours after being made aware of the pregnancy) on a Pregnancy Notification Form. The pregnant subject should be withdrawn immediately from the clinical investigation upon confirmation.

The Sponsor's representative will inform the Sponsor about any SAEs without undue delay after receipt of the respective SAE report from the investigator.

At the end of the clinical investigation, a reconciliation of all reported SAEs will take place and be enclosed as a list in the Clinical Investigation Report.

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

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 subject's last day of the clinical investigation at the site, whichever occurs first.

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 IMD (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.

14.8 Device deficiency reporting requirements

All IMD deficiencies will be recorded on a Device Deficiency Reporting Form.

Device deficiencies should be reported by the investigator to the Sponsor's representative within 24 hours after the site became aware of the deficiency using the same contact as for SAEs (see section 14.5).

The Sponsor's representative will forward the Device Deficiency Reporting Form to the Sponsor within 24 hours after receipt of the respective report from the investigator.

If a device deficiency is associated with an AE, the corresponding AE documentation (see section 14.4) and reporting procedures (see section 14.5) must be adhered to as well.

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 within a time period specified in the contract between the sponsor and the investigator prior to submission for publication.

If the proposed publication contains any invention related to the clinical investigation, the Sponsor is entitled to file respective patent applications and - on this ground - to delay the submission for publication or presentation of medical results within a time period specified in the contract between the sponsor and the investigator after receipt of the manuscript or abstract.

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19 Protocol Amendments

19.1 Protocol Amendment 1

The changes and corresponding rationales are described within a separate document.