CLINICAL INVESTIGATION PLAN (CIP)

Title of the clinical investigation/CIP:	**A prospective, open label, multicenter, post market study evaluating Princess® VOLUME Lidocaine for the correction of nasolabial folds**
Short title:	**VINO** (**V**olume LI**d**ocaine in **N**asolabial F**O**lds)
Investigation ID:	CPH-401-201258
CIP version:	3.0
CIP version date:	**31-OCT-2016**
Sponsor:	CROMA-PHARMA GmbH Industriezeile 6, 2100 Leobendorf, Austria Phone: +43 2262 684 680; Fax: +43 2262 6846 8165 E-mail: office@croma.at; Web: www.croma.at
Coordinating investigator:	[redacted]
Investigation site(s):	At least 3 sites located in Austria (an updated list of the sites, including names, addresses and positions of the corresponding Principal investigators, is kept separately from the CIP)
Medical monitor:	[redacted]
Other institutions involved:	An updated list of institutions that are involved in project management, monitoring, data management and statistics is kept separately from the CIP
CONFIDENTIAL	This clinical investigation plan is the property of CROMA-PHARMA GmbH and must be kept strictly confidential. Any unauthorized disclosure, copy or use of this document, or information contained herein, is prohibited.

Approval and signature pages

Clinical investigation plan agreed to by the Sponsor

_____ _____

[redacted]

_____ _____

[redacted]

Approval and signature pages

Clinical investigation plan agreed to by the Coordinating investigator

_____ _____

[redacted]

Approval and signature pages

Principal investigator agreement

I agree:

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

Investigator's name: _____

Investigator's address: _____

_____

Investigator's signature: _____

Date: _____

Synopsis

Investigation title	A prospective, open label, multicenter, post-market study evaluating Princess® VOLUME Lidocaine for the correction of nasolabial folds
Short title	**VINO** (**V**olume L**I**docaine in **N**asolabial F**O**lds)
Investigation ID	CPH-401-201258
Investigation sites	At least 3 sites located in Austria
Phase of development	Post-market clinical follow-up
Indication	Moderate to severe nasolabial folds
Planned duration	The duration of the clinical investigation will be 9 months for each participating subject. The total expected duration of the clinical investigation is about 13 months with an expected recruitment period of about 3-4 months
Objectives	• To evaluate the performance of Princess® VOLUME Lidocaine for the correction of nasolabial folds • To evaluate the safety of Princess® VOLUME Lidocaine when used for correction of nasolabial folds
Study design	A prospective, open label, multicenter, post-market investigation. Following informed consent and screening, eligible subjects with moderate to severe nasolabial folds will be treated with Princess® VOLUME Lidocaine, and will return for follow-up assessments 2, 4, 24 and 36 weeks after the treatment. A Touch-up treatment may be done at Week 2, if deemed appropriate by the investigator. The performance of the investigational device will be evaluated by the investigator by assessing severity of nasolabial folds using the Nasolabial Folds Severity Rating Scale (NLF-SRS) (4, 24 and 36 weeks after the treatment and in comparison to Day 0), global aesthetic improvement (4, 24 and 36 weeks after the treatment). The subject will evaluate pain intensity associated with the treatment (at Day 0 and at Week 2 (if Touch-up treatment occurred)), and satisfaction with the treatment 4, 24 and 36 weeks after the treatment. The safety will be evaluated based on occurrence of adverse events, which will be collected throughout the investigation.
Number of subjects	Up to 60 subjects will be included, to obtain the Week 24 performance data in at least 40 subjects.
Eligibility criteria	Inclusion criteria: 1. Male or female 18 years of age or older 2. Presence of two fully visible, approximately symmetrical nasolabial folds, with each of the folds scored 2-3 according to the 5-grade Nasolabial Folds Severity Rating Scale (NLF-SRS) as assessed by the investigator 3. Healthy skin in the facial area and free of diseases that could interfere in cutaneous aging evaluation 4. Willingness to abstain from any aesthetic or surgical procedures in the treatment area for the duration of the clinical investigation 5. Written signed and dated informed consent

	Exclusion criteria: 1. Pregnancy, lactation, planned pregnancy or unwillingness to use contraception at any time during the study (for women of child-bearing potential only) 2. History of mental disorders or emotional instability 3. History of allergic reaction or hypersensitivity to hyaluronic acid, lidocaine, or any amide-based anaesthetic 4. Presence of silicone implant or another non-absorbable substance (permanent fillers) in the nasolabial region 5. Facial surgery or implantation of dermal fillers, absorbable and non-absorbable sutures (thread), laser therapy, dermoabrasion, or botulinum toxin application in the nasolabial region within previous 12 months, or chemical peeling within previous 3 months, or planning to undergo such procedures in the treatment area during the study 6. Presence of infectious, inflammatory, or proliferative lesions in the nasolabial region 7. Cutaneous lesions in the treatment area 8. Known human immune deficiency virus-positive individuals 9. History of allergies against aesthetic filling products and recurrent herpes simplex 10. Tendency to hypertrophic scars and/or keloid formation 11. History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy 12. Diabetes mellitus or uncontrolled systemic diseases 13. Use of anticoagulant, antiplatelet or thrombolytic medication from 10 days pre- to 3 days post injection 14. Any medical condition which, in the investigator's opinion, prohibits the inclusion in the study 15. Current or previous (within 30 days of enrolment) treatment with another investigational drug and/or medical device or participation in another clinical study 16. Previous enrolment in this clinical investigation 17. 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 and mode of administration	Princess® VOLUME Lidocaine is a sterile, biodegradable, viscoelastic, transparent, isotonic and homogenized injectable gel implant formulated in a physiologic buffer to a concentration of 23 mg/mL, with addition of 0.3% lidocaine hydrochloride. Princess® VOLUME Lidocaine is administered by injection into the deep dermis or subcutis. The volume applied depends on the size of the area which requires correction and will be selected by the investigator, but will not exceed 10 mL in total per treatment.
Treatment duration	A single application, with optional Touch-up treatment after two weeks, if the desired level of correction has not been achieved with the initial application
Primary performance endpoints	• The average change versus baseline (Day 0) in the NLF-SRS grade of nasolabial folds at Week 24 as evaluated by the investigator • The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24
Secondary	• The average change versus baseline in the NLF-SRS grade at Week 4 and

performance endpoints	Week 36 as evaluated by the investigator • The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4 and Week 36 • The proportion of subjects with aesthetic improvement at Week 4, Week 24 and Week 36, as evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS) • Subjects' satisfaction with aesthetic outcome of the treatment at Week 4, Week 24 and Week 36, as evaluated by the subject • The average pain intensity during and after the treatment, as evaluated by the subject using an 11-point Numeric Pain Rating Scale (NPRS) immediately after the last injection and 15 min. thereafter, respectively • The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24 as evaluated by the independent reviewer of photographs.
Safety endpoints	Occurrence and frequency of adverse events
Statistical methods	All analyses will be done in the Intent-to-treat population, defined as all subjects who received the investigational device and have at least one post-treatment assessment. Individual NLF-SRS grades per visit will be calculated as the mean of grades assigned to the left and the right nasolabial fold, respectively. The absolute NLF-SRS change versus baseline will be computed by subtracting the value obtained on Day 0, and summarized by the visit using descriptive statistics. Additionally, the 95% confidence intervals of the mean will be given and proportions of the NLF-SRS change values ≥1 or ≥2, respectively, will be calculated. Adverse events will be summarised by preferred term and system organ class, and also by intensity, relationship to the investigational medical device or procedure, and seriousness.

Schedule of procedures and events

Table 1. Schedule of procedures and events

	VISIT 1 Baseline Visit*	VISIT 2 Week 2 Visit	VISIT 3 Week 4 Visit	VISIT 4 Week 24 Visit	VISIT 5 Week 36 Visit
Visit window	Day 0	Week 2 (± 2 days)	Week 4 (± 4 days)	Week 24 (± 7 days)	Week 36 (± 7 days)
Informed consent	x**				
Demographic data[a]	x**				
Medical history	x**				
Prior medication[b]	x**				
NLF-SRS grading of nasolabial folds[c]	x**		x	x	x
Urine pregnancy test[d]	x**				
Eligibility assessment	x**				
Treatment	x	x§			
Photography	x**	x§	x	x	x
Pain assessment[e]	x	xΩ			
GAIS assessment[f]			x	x	x
Subject satisfaction[g]			x	x	x
Adverse events[h]	x***	x	x	x	x
Concomitant medication[h]	x***	x	x	x	x

* Includes screening and treatment.
** Prior to application of the investigational device
*** From beginning of the treatment onwards
§ Optional, to be done at investigator's discretion
Ω To be performed only if Touch-up treatment occurred
a Includes date of birth, sex, and race
b All medication taken by the subject within the previous 10 days
c Performed by the investigator using the Nasolabial Folds Severity Rating Scale (NLF-SRS); the severity of the left and the right fold will be separately graded
d In females of child-bearing potential only, including women who are postmenopausal for less than 12 months
e Evaluated by the subject immediately after injection and approximately 15 min. thereafter using an 11-point Numeric Pain Rating Scale
f Evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS)
g Evaluated by the subject
h To be collected throughout the investigation, from beginning of the treatment until the last visit

List of abbreviations

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

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1 Background

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

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

Perception of age and health is critical in the judgement of attractiveness. Young faces are generally perceived to be more attractive than old faces, and estimated age is negatively correlated with perceived attractiveness[4,5]. Attractiveness influences both the self-perception and behaviour toward others, and is related to traits such as self-confidence and social acceptance. It is not surprising, therefore, that aesthetic interventions can improve the psychological well-being and quality of life in people who elect to undergo such procedures due to aging. Common positive changes include increased satisfaction with self-appearance, reduced depression or anxiety, improved emotional well-being and increased self-confidence[6].

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

2 Identification and description of the investigational device

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

2.1 Device description

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

The device packaging contains one prefilled syringe with 1.0 mL of the injectable gel implant, two 27G ½″ disposable sterile needles and a product leaflet. A set of two labels showing the batch number is situated at the bottom of the box.

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

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

The device is manufactured in compliance with EN ISO 13485:2003/AC:2009. No materials of human or animal origin are used during manufacture or as raw materials.

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

2.2 Manufacturer

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

Enclosed needles are manufactured by [redacted]

2.3 Intended use and mode of administration

Princess® VOLUME Lidocaine is a soft tissue filler, approved for use in adults (18 years and older) for the correction of deeper wrinkles and folds, augmentation or restoration of the volume of the face, remodelling of facial contours, and for medical reconstructive purposes in the treatment of, e.g., facial lipoatrophy, debilitating scars, or morphological asymmetry of the face.

The device is designed to be injected into the deep dermis or subcutis. The amount injected depends on the size of the area to be corrected and the desired level of soft tissue augmentation, but should not exceed 10 mL per treatment session or 20 mL per year. The injection technique, which is described in Section 6.2.2 Methods of use, is essential for success of the treatment. Therefore, Princess® VOLUME Lidocaine should be administered exclusively by physicians who have received specific training on its application and use in respective indications.

In the present clinical investigation, Princess® VOLUME Lidocaine will be used for correction of nasolabial folds.

2.4 Traceability

Each carton of Princess® VOLUME Lidocaine is identified and tracked by its batch 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 file and the other should be given to the subject to ensure traceability of the device.

3 Justification for the design of the clinical investigation

3.1 Non-clinical data and biocompatibility

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[9]. 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[10]. 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 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[11].

Lidocaine hydrochloride, an ancillary component of the device, is a well-known local anaesthetic. Lidocaine exerts its anaesthetic effects by blocking fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons, which prevents depolarization and inhibits the generation and propagation of nerve impulses[12]. Rapid release of lidocaine from hyaluronic acid gel, allowing for fast onset of action after injection, has been demonstrated *in vitro*[8].

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

3.2 Clinical data

Since the launch of the first BDDE-cross-linked hyaluronic acid dermal filler for aesthetic use in 1996, over 50 clinical studies have been conducted with this type of medical device, which included more than 9,000 subjects[11]. 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[10]. Over time, their use was extended to medical reconstructive purposes in the treatment of pathologic conditions like facial lipoatrophy, morphologic asymmetry of the face, and depressed scars. In order to improve the comfort of filler injections, novel formulations containing a local anaesthetic, lidocaine hydrochloride, have been developed to reduce procedural pain and to bypass the need for additional anaesthesia.

Lidocaine hydrochloride is a well-known local anaesthetic, which has been in clinical use for over 60 years. It is currently one of the most widely used local anaesthetics. When used for infiltrative anaesthesia, lidocaine hydrochloride has fast onset of action and moderate duration of effect lasting 1.5-2 h[13]. Absorbed lidocaine is metabolized in the liver and eliminated via the kidneys with a half-life of around 90 minutes[14]. 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[13,14].

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] and [redacted] has confirmed a statistically significant reduction in pain with formulations which contained lidocaine. The pain reduction was consistent across the studies, and present irrespective of the dermal filler tested. The frequency and severity of adverse events (AEs) was not different for dermal fillers with or without lidocaine, indicating no incremental safety risk[7,8].

Princess® VOLUME Lidocaine received the European Conformity (CE) mark in March 2016, based on equivalence with similar devices. While this device has not been tested in clinical trials so far, clinical data are available for Princess® VOLUME, which is virtually the same dermal filler, but without lidocaine. The safety and performance of Princess® VOLUME in the treatment of nasolabial folds has been evaluated in an open-label, uncontrolled, multicentre study, which enrolled 48 subjects with moderate-to-deep nasolabial folds. A significant immediate improvement of wrinkles was demonstrated after administration of the device, with the effect lasting for more than 9 months. Adverse device effects (ADEs) were short-term and characteristic for injection site reactions (i.e. swelling, redness, tenderness, pain and bruising). No long-term ADEs were reported and patient satisfaction rates were high[8,15]. This study confirmed the favourable risk-benefit ratio for Princess® VOLUME, ascertained in post-market surveillance between 2009 and 2015.

3.3 Justification for the clinical investigation

Princess® VOLUME Lidocaine has recently been approved for the correction of deeper wrinkles and folds, augmentation or restoration of the volume of the face, remodeling of facial contours, and for medical reconstructive purposes in the treatment of, e.g., facial lipoatrophy, debilitating scars, or morphological asymmetry of the face. The approval was based on similarity with other dermal fillers, which showed a favourable risk-benefit ratio in these indications. The current clinical investigation is designed to support the approval by obtaining clinical data on the performance and safety of Princess® VOLUME Lidocaine for the correction of nasolabial folds.

A prospective, open label, non-comparative design was selected because it allows for the most efficient collection of clinical data on the investigational device, in a manner which is appropriate to address the purpose and objectives of the present investigation. In the absence of spontaneous improvement of nasolabial folds, it is reasonable to assume that the treatment effect can be adequately assessed by comparing the post-treatment observations versus baseline, eliminating the need for a control group.

The primary performance endpoints is based on evaluation using a validated 5-point scale for assessment of severity of nasolabial folds, the Nasolabial Folds Severity Rating Scale (NLF-SRS), and is set at 6 months after administration of the device to address the minimum required durability of effect. Follow-up is, however, extended to 9 months, to get additional information on long-term effects. 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)[16].

Up to 60 subjects will be included in this investigation to obtain 6-month effectiveness data in at least 40 subjects. This sample size is arbitrarily selected, based on usual size of post-market clinical investigations, and is considered sufficient to provide robust estimations on performance and safety parameters in the study population.

4 Risks and benefits of the investigational device and clinical investigation

4.1 Anticipated clinical benefits

The treatment with Princess® VOLUME Lidocaine may remove or reduce a distressing aesthetic defect in subjects with moderate-to-severe nasolabial folds, thereby improving their psychological and social wellbeing. This is achieved by a minimally invasive procedure with a short downtime, which results in an immediate and long-lasting effect, persisting for 6-12 months.

4.2 Anticipated adverse device effects

The safety profile of BDDE-cross-linked 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[17]. Adverse effects that have been observed with devices similar to Princess® VOLUME Lidocaine are summarized in Table 2, on the following page.

Currently, there are no human safety data on Princess® VOLUME Lidocaine. There is, however, a considerable experience with Princess® VOLUME, which is essentially the same device, just without lidocaine. Almost 2 million (1,971,500) units of Princess® VOLUME (without lidocaine) have been sold worldwide from 2009 up to the end of 2015, and during the same period there were only 38 spontaneous ADE reports. Among these, 22 were cases of oedema, redness, inflammation, pain or swelling, which are commonly observed with any dermal filler. The remaining 16 comprised cases of nodules, lumps, burning, discoloration and a single report of an allergic reaction, all of which resolved shortly after occurrence[8].

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

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

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

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

In case impending tissue necrosis, which may occur with any dermal filler, a recent consensus statement on the treatment of 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[18].

4.3 Possible interactions with concomitant medical treatments

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

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

Sodium hyaluronate is incompatible with quaternary ammonium compounds such as benzalkonium chloride solutions. The device should never be placed in contact with these substances or with medical-surgical instruments that have been in contact with these substances.

4.4 Risk mitigation strategy

The risks will be mitigated by careful selection of the subjects and exclusion of those who may have an increased risk of developing certain types of AEs (see Section 6.3.5), proper injection technique (described in Section 6.2.2), appropriate training of the investigators to ensure correct application of

the device, and regular follow-up visits over the following 9 months, 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.

4.5 Risk-to-benefit rationale

Hyaluronic acid-based dermal fillers, such as Princess® VOLUME Lidocaine, are generally considered very safe and effective, and have been widely used for soft tissue augmentation worldwide. There is also no scientific evidence demonstrating adverse events of fillers or hyaluronidase in pregnant women. Observed adverse effects are mainly related to the injection procedure, are transient and mostly mild. While few serious adverse effects have been reported, these are very rare and not expected to occur when the device is correctly applied.This is supported by a remarkable safety track record of Princess® VOLUME (without lidocaine), with few ADEs reported among almost 2 million units sold since 2009, combined with favorable safety data from one clinical trial.

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

5 Objectives and hypotheses of the clinical investigation

5.1 Objectives

The objectives of this post-market clinical follow-up investigation are:

- To evaluate the performance of Princess® VOLUME Lidocaine for the correction of nasolabial folds.
- To evaluate the safety of Princess® VOLUME Lidocaine when used for correction of nasolabial folds.

5.2 Hypotheses

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

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

Princess® VOLUME Lidocaine has recently been approved for the correction of deeper wrinkles and folds, and other indications typical for hyaluronic acid dermal fillers. The approval was based on clinical experience with similar devices and 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 Princess® VOLUME Lidocaine with these products and available non-clinical safety data, it is anticipated that it will share the same safety profile, described in Section 4.2. All AEs and device deficiencies occurring during the investigation will be collected and reported.

6 Design of the clinical investigation

6.1 Design description

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

The investigation will consist of five visits: the baseline (Day 0) visit, which will entail informed consent, screening assessments, the treatment, and early post-treatment assessments, and follow-up visits 2,

4, 24 and 36 weeks after the treatment. Procedures to be performed at each visit are specified in Table 1. Schedule of procedures and events, which is located on page 8 and in section 6.1.4.

6.1.1 Primary performance endpoints

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

- The average change versus baseline (Day 0) in the NLF-SRS grade of nasolabial folds at Week 24 as evaluated by the investigator.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24

6.1.2 Secondary performance endpoints

- The average change versus baseline in the NLF-SRS grade at Week 4 and Week 36 as evaluated by the investigator.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 4 and Week 36
- The proportion of subjects with aesthetic improvement at Week 4, Week 24 and Week 36, as evaluated by the investigator using the Global Aesthetic Improvement Scale (GAIS)
- Subjects' satisfaction with aesthetic outcome of the treatment at Week 4, Week 24 and Week 36, as evaluated by the subject
- The average pain intensity during and after the treatment, as evaluated by the subject using an 11-point Numeric Pain Rating Scale (NPRS) immediately after the last injection and 15 min. thereafter, respectively.
- The proportion of subjects with the NLF-SRS grade reduced by ≥1 point versus baseline at Week 24 as evaluated by the independent reviewer of photographs.

6.1.3 Safety endpoints

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

- Occurrence and frequency of adverse events

6.1.4 Schedule of procedures and events

6.1.4.1 Baseline Visit (Visit 1)

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

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

6.1.4.2 Week 2 Visit (Visit 2)

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

- Photography (Optional)
- Touch-up treatment (optional)
- Pain assessment (only if Touch-up treatment performed)
- Adverse events
- Concomitant medication

6.1.4.3 Week 4 (Visit 3), Week 24 (Visit 4) and Week 36 (Visit 5) Visits

The following assessments will be performed respectively 4 weeks (± 4 days), 24 weeks (± 7 days) and 36 weeks (± 7 days) after Visit 1:

- Photography
- NLF-SRS grading of nasolabial folds
- GAIS assessment
- Subject satisfaction
- Adverse events
- Concomitant medication

6.1.5 Replacement of subjects

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

6.2 Investigational device

6.2.1 Packaging, labelling and storage

The investigational device will be obtained from the commercial manufacturing batch.

Each device will be provided in a folding box containing one syringe prefilled with 1.0 mL of the injectable gel implant, two 27G ½″ disposable sterile needles and a product leaflet. A set of two labels showing the batch number is situated at the bottom of the box. One of these labels should be attached to the subject's file and the other must be given to the subject to ensure traceability of the device.

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

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

6.2.2 Methods of use

The investigational device will be administered to eligible subjects on study Day 0.

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. Sensitive skin may be pre-treated with a local anesthetic patch or cream. If anesthetic is used, the type of anesthetic and exact time of application will be recorded on the case report form (CRF).

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

Injection technique

The injection technique used is essential for success of the treatment. Therefore, all investigators must complete a specific training in the injection technique, which will be documented in the Trial master file (TMF).

The investigational device should be injected into the deep dermis or subcutis. 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, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify that the needle is not intravascular.

Different injection techniques can be employed based on investigator's preference and characteristics of the defect under correction. These include:

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

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

The fan technique consists in introducing the needle as for the retrograde technique, and injecting the gel while withdrawing the needle, without removing its tip from the skin; then, changing the direction of the needle and injecting a new line. Repeating this process several times will achieve a fan pattern. This technique allows filling a large area and creating or restoring facial volume from a single injection point.

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

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

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

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

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

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

Completion of administration

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

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

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

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

- To refrain from application of make-up for 12 hours after injection;
- To avoid prolonged exposure to sunlight or ultraviolet (UV) radiation for 36 hours after injection;
- Not to massage the treatment site for one week following the injection, to avoid the possible risk of product mobility;

- To abstain from use of saunas or Turkish baths for one week after the injection.

6.2.3 Applied volume of the device

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

The maximum recommended dosage is up to 10 mL per treatment session and up to 20 mL per subject per year; these amounts include potential Touch-up treatments.

6.2.4 Touch-up treatment

A Touch-up treatment may be performed at the Week 2 visit at the investigator's discretion, if correction is not deemed satisfactory after the first injection. It will be documented in the CRF with the same level of details as the initial treatment.

6.2.5 Precautions

- The device must not be used if the expiry date has lapsed, or if the packaging or contents are damaged.
- The device should only be used with the needle and syringe provided by the manufacturer.
- The needle must not be manipulated or bent, if the needle is blocked, pressure on the plunger rod should not be increased, instead injection should be stopped and the needle replaced.
- After use the syringe, needle and remaining contents should be disposed appropriately and the device should never be re-used.
- The device should not be injected into blood vessels, bones, tendons, ligaments, nerves, muscles or naevi.
- Injections into the periorbital area (crow's feet, eye circle, eye lids), glabellar region and nasal alae are not recommended.
- Overcorrection should be avoided.
- The device should never be placed in contact with quaternary ammonium compounds (such as benzalkonium chloride solutions) or with medical-surgical instruments that have been in contact with these substances.

6.2.6 Rescue medication

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

6.2.7 Investigational device accountability

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

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

At the end of the clinical investigation, all remaining supplies, including empty boxes of investigational devices that have been used, must be returned to the Sponsor for accurate accounting of the investigational device. Empty or used syringes will not be returned to the Sponsor, but will be destroyed by the investigation site, in line with their routine procedure for medical waste disposal.

Considering the number of subjects to be enrolled, the average volume of the device administered in the clinical investigation of Princess® VOLUME (0.9 mL per fold), and potential additional Touch-up

treatment, it is anticipated that approximately 300 units of the investigational device will be used during this clinical investigation.

6.3 Subjects

6.3.1 Number of subjects and duration of the clinical investigation

Up to 60 subjects with moderate to severe nasolabial folds will be enrolled and treated with the investigational device in order to obtain the Week 24 performance data in at least 40 subjects.

Each subject will participate in the study for 9 months. Taking into account the anticipated recruitment period of 3-4 months, the total expected duration of the clinical investigation will be 13 months.

6.3.2 Recruitment strategy

The recruitment over the study will be competitive and will be stopped as soon as 60 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 for nasolabial folds. The investigator may also offer participation in the study to potential candidates identified in their subject database. In case of an unexpectedly low recruitment rate, the investigation may be advertised. In such case, the advertising strategy and materials will be submitted to the Ethics Committee (EC) for prior review and approval.

6.3.3 Subject identification

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

6.3.4 Inclusion criteria

A subject must meet <u>all</u> of the following criteria to qualify for participation in this investigation

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

6.3.5 Exclusion criteria

Subjects meeting <u>any</u> of the following criteria should not be enrolled:

1. Pregnancy, lactation, planned pregnancy or unwillingness to use contraception at any time during the study (for women of child-bearing potential only)
2. History of mental disorders or emotional instability
3. History of allergic reaction or hypersensitivity to hyaluronic acid, lidocaine, or any amide-based anaesthetic
4. Presence of silicone implant or another non-absorbable substance (permanent fillers) in the nasolabial region
5. Facial surgery or implantation of dermal fillers, absorbable and non-absorbable sutures (thread), laser therapy, dermoabrasion, or botulinum toxin application in the nasolabial region within

previous 12 months, or chemical peeling within previous 3 months, or planning to undergo such procedures in the treatment area during the study

6. Presence of infectious, inflammatory, or proliferative lesions in the nasolabial region
7. Cutaneous lesions in the treatment area
8. Known human immune deficiency virus-positive individuals
9. History of allergies against aesthetic filling products and recurrent herpes simplex
10. Tendency to hypertrophic scars and/or keloid formation
11. History or presence of any autoimmune or connective tissue disease, or current treatment with immune therapy
12. Diabetes mellitus or uncontrolled systemic diseases
13. Use of anticoagulant, antiplatelet or thrombolytic medication from 10 days pre- to 3 days post injection
14. Any medical condition which, in the investigator's opinion, prohibits the inclusion in the study
15. Current or previous (within 30 days of enrolment) treatment with another investigational drug and/or medical device or participation in another clinical study
16. Previous enrolment in this clinical investigation
17. 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)

6.3.6 Withdrawal criteria and procedures

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

1. Occurrence of an AE which requires a premature termination of the treatment or precludes follow-up of the subject
2. A major CIP deviation, which may interfere with evaluation of the treatment outcome (e.g., additional aesthetic correction of the defect during the course of the study, use of prohibited medication, or similar)
3. Investigator's decision, triggered by safety, behavioural or administrative reasons
4. Informed consent withdrawal

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

Reasons, circumstances and findings related to early withdrawal should be fully described on the CRF respecting the subject's rights. Attempts should be made to perform an early termination visit, which should consist of the assessments planned for the Week 24 visit. In the event that the withdrawal is caused by an AE, the procedures stated in Section 14.6 must be followed.5

6.3.7 Life-style and other restrictions

Contraception

The safety of Princess® VOLUME Lidocaine for use during pregnancy has not been established, so females of childbearing potential should use contraception or avoid unprotected sexual intercourse throughout the clinical investigation. Any pregnancy occurring during the subject's participation in the investigation will be reported as an AE and followed-up as described in Section 14.6.

Other restrictions

The following restrictions apply to all subjects:

- Make-up should not be applied for 12 hours after injection;
- Prolonged exposure to sunlight or UV radiation must be avoided for 36 hours after injection; day care with UV protection should be used daily throughout the entire clinical investigation;
- To minimise the risk of product mobility, the subject should be advised to avoid massaging the treatment site or applying pressure to this area for one week following the injection;
- Subjects should abstain from frequent solarium visits;
- Subjects should abstain from alcohol on injection days.
- Use of saunas or Turkish baths is prohibited for one week after the injection.

6.3.8 Medical care upon termination of the clinical investigation

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

6.3.9 Screening/baseline failures

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

6.3.10 Subject confidentiality

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

Personal subject data will be kept confidential in compliance with the European Data Protection Directive and other applicable international and national requirements.

The investigator must ensure that anonymity of the study participants will be maintained and that their identities are protected from unauthorized parties. On the CRF or any other documents submitted to the Sponsor or Sponsor's representative, subjects must be identified only by their identification codes; use of names, initials, addresses, telephone numbers, electronic addresses or similar information is prohibited. The investigator will keep the original of the Subject Identification Log (including complete name and date of birth of each subject) in his/her file. The investigator must maintain these documents in strict confidence.

To allow compliance with good clinical practice (GCP), all subjects will be asked for consent regarding the access to their personal clinical study-related data for monitoring, audits, and inspections as well as regarding transmission and storage of their anonymous data for the duration defined in the current GCP regulation; a respective statement will be part of the Informed consent form (ICF). Professionals with access to source data for monitoring, audits and inspections are bound to preserve strict confidentiality.

6.4 Assessments and procedures

Assessments and procedures that will be performed during the investigation are described below. The exact timing of each assessment is indicated in Table 1. Schedule of procedures and events and in section 6.1.4.

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 medical device, and AEs.

6.4.1 Demographic data

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

6.4.2 Medical history

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

6.4.3 Pregnancy test

In females of childbearing potential, including women who are postmenopausal for less than 12 months, a urine pregnancy test will be performed using a dipstick test with sensitivity of ≤20 mLU of human chorionic gonadotropin per mL. The result will be recorded in the subject's medical record and the CRF.

6.4.4 Photography

Photographs of the subjects are taken as part of routine practice at the clinical site before the application of the medical device at the Baseline visit and after the intervention.

6.4.5 NLF-SRS grading of nasolabial folds

NLF-SRS is a validated, 5-point rating scale ranging from Grade 0 (none) to Grade 4 (extreme) as outlined in

Table 3 and 4. The severity of nasolabial folds will be evaluated by the investigator according to the NLF-SRS. The left and right nasolabial fold will be separately graded, and the assigned grades will be recorded in the subject's record and the CRF.

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

Table 4 CROMA - NLF Severity Rating Scale (NLF-SRS)

CROMA NLF-	Description

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

6.4.6 Aesthetic improvement/GAIS assessment

The aesthetic improvement after correction of nasolabial folds will be evaluated at Week 4, 24 and 36 by the investigator using the Global Aesthetic Improvement Scale (GAIS)[19], presented in **Table 5**, and recorded in the CRF.

Table 5. 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.

6.4.7 Pain assessment

After initial administration and optional Touch-up treatment of the investigational device, the subject will be asked by the investigator to quantify the pain associated with the procedure by means of a semi-quantitative 11-point Numeric Pain Rating Scale (NPRS), where 0 corresponds to no pain, and 10 to the worst pain imaginable[16]. 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 in the Pain assessment form and the CRF. To avoid over-reporting of pain, a non-leading question *„How do you feel?"* should be asked prior to pain assessment. Only spontaneously reported pain, or pain graded ≥4 will be recorded as an AE.

6.4.8 Subject's satisfaction assessment

Each subject will be asked to grade their satisfaction with the treatment using one of the following categories: "Very unsatisfied", "Unsatisfied", "Neither unsatisfied nor satisfied", "Satisfied", or "Very satisfied".

The statement selected by the subject will be recorded in the Subject's satisfaction form and the CRF.

6.4.9 Outcome evaluation by the independent reviewer of photographs

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

6.4.10 Safety monitoring

The safety of the investigational device will be monitored throughout the investigation, from Day 0/visit 1 until the final visit (visit 5). AEs will be collected at each visit. In addition, the subjects will be instructed to immediately contact the investigator by phone in case of occurrence of any untoward event between the visits. The procedure for collection, recording and reporting of AEs is described in Section 14.

6.4.11 Prior and concomitant medication and non-drug therapies

Prior medication is defined as all medication taken within 10 days (whether continuing or not) prior to Day 0. Concomitant medication is defined as all medication taken from Day 0 (including medication taken immediately pre-injection and post-injection) until the Week 36 visit.

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

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

Prohibited medication and aesthetic treatments

- Immune therapy, i.e., treatment with biologics designed to boost the body's natural defences (from Day 0 until the end of the clinical investigation)
- Anticoagulant, antiplatelet, or thrombolytic drugs (from 10 days pre- until 3 days post-injection)
- Facial surgery or implantation of dermal fillers other than the investigational device (from 12 months prior to Day 0 until the end of the clinical investigation)
- Absorbable and non-absorbable sutures (thread), laser therapy or dermabrasion (from 12 months prior to Day 0 until the end of the clinical investigation)
- Botulinum toxin treatment in the area treated with the investigational device (from 12 months prior to Day 0 until the end of the clinical investigation)
- Chemical peeling (from 3 months prior to Day 0 until the end of the clinical investigation)
- Skin needling or mesotherapy (from Day 0 until the end of the clinical investigation)

6.4.12 Factors that may compromise the outcome

There are no foreseeable factors that may significantly compromise the outcome. A substantial body weight change could possibly affect the results in individual subjects. Since this is a 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.

6.5 Monitoring plan

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

Prior to initiation of the clinical investigation at any of the investigation sites, the Monitor will discuss the CIP and the CRF with the investigator and their staff. The site must not enroll any study participant before this initiation visit. During the investigation, further monitoring visits will be performed according to ISO 14155:2011, the applicable standard operating procedures, and local regulations. The CRF will be reviewed against source data for adherence to the CIP, as well as for completeness, accuracy and consistency of data. Additionally, the Monitor will check the progress of enrolment, and will ensure that the investigational device is stored, dispensed and accounted for according to the respective specifications. Key study personnel must be available to assist the Monitor during these visits. The Monitor will inform the investigator or their authorized designee of any CRF entry error, omission, or illegibility. The Monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or their authorized designees.

The investigator and their institution must permit the monitoring of the investigation, and provide the Monitor direct access to those portions of the subject's primary medical records, which directly concern this clinical investigation.

7 Statistical considerations

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

7.1 Sample size

Up to 60 subjects with moderate to severe nasolabial folds will be enrolled in order to obtain the 24-week performance and safety data from at least 40 of them. If less than 60 subjects will be recruited at the point when at least 40 subjects complete the Week 24 assessment, a decision to continue the recruitment up to 60 subjects in total will be made by the Sponsor.This sample size is arbitrarily selected and is considered appropriate for the post-market follow-up clinical investigation and sufficient to provide robust estimations on performance and safety parameters in the study population. With a sample size of 60, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.076 from the observed proportion for an expected proportion of 0.900. Thus, a robust estimation of the success rate at week 24 can be derived..

7.2 Analysed data sets

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

7.3 Missing data

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

7.4 Methods of analysis

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

Demographic data, use of additional anaesthetic, initial amount of the filler applied, and occurrence of the Touch-up treatment with the amount of the filler applied will be listed by subject and summarized

using descriptive statistics. Other data collected will be listed per subject and summarized as described in the SAP.

7.4.1 Performance endpoints

As two facial folds of each subject will be considered, there are two measurements per subject for NLF-SRS. No great differences between the folds are expected, thus the mean of both measurements will be used for analyses. Individual NLF-SRS grades per visit will be calculated as the mean of grades assigned to the left and the right nasolabial fold, respectively. The absolute NLF-SRS change versus baseline will be computed by subtracting the value obtained on Day 0 from that of the corresponding visit. Absolute NLF-SRS change from baseline will be summarized by the visit using descriptive statistics and additionally the 95% confidence intervals of the mean will be given. In addition, the proportion of the NLF-SRS change values ≥1, or ≥2, respectively, will be calculated.

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

7.4.2 Safety endpoints

AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) and listed by subject. Incidence of AEs will be summarised by preferred term (PT) and system organ class (SOC), and also by intensity, relationship to the investigational medical device or procedure, and seriousness.

8 Data management

8.1 Case report forms

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

A web-based standardized electronic CRF (eCRF) will be used to document the subjects' data during the course of the study. The eCRF is designed to accommodate the specific features of the study design. All data obtained after the subject has given informed consent must be recorded in the eCRF. The investigator will assure that all data are entered promptly, completely, and accurately according to the eCRF instructions, and conform to source documents. Data for all subjects screened for study have to be documented on a respective form (see Section 6.3.9) but no eCRF entry for screening/baseline failures will be made.

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

The investigator or designee has to carefully answer queries issued by Data Management in the eCRF.

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

8.2 Data management procedures

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

Regarding self-evident corrections (such as spelling and header corrections) if applicable, investigator's agreement will be obtained that these will be made by the Data Manager and documented in the audit trail.

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

8.3 Data retention

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

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

8.4 Report of the clinical investigation

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

9 Amendments to the clinical investigation plan

Any change to the CIP concerning the purpose of the study, the study design or the subject's eligibility can only be made in form of a written amendment to the CIP. Such amendments have to be discussed and signed by the Sponsor, the Coordinating Investigator, and the other investigators before implementation.

Amendments that might have an impact on study procedures to be performed and/or the well-being of the subjects require additional informed consent, which has to be given in writing by all subjects enrolled in the clinical investigation who are affected by the amendment.

10 Deviations from the clinical investigation plan

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

Under emergency circumstances, deviations from the CIP may proceed without prior approval by the Sponsor and favorable opinion of the EC if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the Sponsor and the EC as soon as possible in accordance with national regulations.

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

11 Device accountability

Investigational device accountability is described in Section 6.2.7.

12 Statements of compliance

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

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

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

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

A prior regulatory approval will also be sought, if required by national regulations.

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

13 Informed consent process

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

The investigator or their authorized designee must give each subject complete and adequate verbal and written information about the investigation. The investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical investigation. Before consenting, the subject must be left with ample time to consider and ask questions. It must be emphasized that participation is voluntary and that the subject has the right to withdraw from the clinical investigation at any time without any justification and without prejudice. The subject must then sign and date the ICF prior to the conduct of any study procedures. The consent taker (investigator or study team member) must sign and date the ICF as well.

A copy of the Subject information Sheet and ICF will be given to the subjects for their records. The rights and welfare of the study participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this clinical investigation or in case of withdrawal of their consent during the clinical investigation.

If amendments to the final CIP affect the subject's participation in the clinical investigation (e.g. a change in any procedure), the Subject information Sheet and the ICF must be updated to incorporate this modification, and the subject must sign the amended ICF indicating that they re-consent to participate in the clinical investigation.

14 Adverse events, adverse device effects and device deficiencies

14.1 Definitions

Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

- For study subjects this definition includes events related to the procedures involved, as well pregnancy in females.

- For users or other persons this definition is restricted to events related to the investigational medical device.

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

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

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

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

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

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

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

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

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

14.2 Method of detecting AEs

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

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

In addition, the subjects will be instructed to immediately contact the investigator/study site in case of occurrence of any untoward event between visits.

14.3 AE/SAE documentation

For each AE the following must be reported:

- description of the event (event term)
- start date
- start time (for events occurring on the treatment day)
- outcome
- end date (if applicable)
- severity
- action taken (none, medical and/or surgical)

- the relationship to the investigational device, the relationship to the procedure
- seriousness criteria.

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

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

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

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

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

Any medication necessary for the treatment of an AE must be recorded on the “Concomitant Medication” page of the CRF.

14.4 AE/SAE assessment

All AEs will be assessed in terms of:

- seriousness (yes, no)
- severity
- relationship to the investigational medical device or study procedures
- outcome.

14.4.1 Severity assessment

The severity of an AE/SAE will be graded as follows:

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

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

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

14.4.2 Causality assessment

The investigator is obligated to estimate the relationship between each AE/SAE and the investigational medicinal device or study procedure. Clinical judgement should be used and the relevant documents like IB consulted. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. The relationship should be determined using one of the following causality levels[20]:

Definite: The AE/SAE is associated with the investigational device or with procedures beyond reasonable doubt when it is a known side effect of the product category the device belongs to, or of similar devices and procedures; has a temporal relationship with investigational device use/application or procedures; involves a body-site or organ that the investigational device or procedures are applied to or have an effect on; follows a known response pattern to the medical device (if the response pattern is previously known); the discontinuation of medical device application (or reduction of the level of exposure), when clinically feasible, and reintroduction of its use (or increase of the level of exposure) impact on the event; other possible causes (e.g. an underlying or concurrent

illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; and/or harm to the subject is due to error in use.

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

Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained, should also be classified as possible.

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

Not related: Relationship to the device or procedures can be excluded when the AE/SAE is not a known side effect of the product category the device belongs to or of similar devices and procedures; has no temporal relationship with the use of the investigational device or the procedures; does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; the discontinuation of medical device application or the reduction of the level of exposure, when clinically feasible, and reintroduction of its use (or increase of the level of exposure) do not impact on the event; involves a body-site or an organ not expected to be affected by the device or procedure; can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); and/or harm to the subject are not clearly due to use error.

14.4.3 Outcome assessment

The outcome of an AE will be assessed as follows:

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

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

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

Fatal: The subject died due to the event.

Unknown: If outcome is not known or not reported.

14.5 AE/SAE reporting requirements and contact details

For any AE (including a SAE) all appropriate sections of the CRF must be completed.

Any SAE must be reported by the investigator to the Medical Monitor within 24 hours of awareness of the event via eCRF. Only in case of any problem with the eCRF the SAE must to be reported via fax:

[redacted]

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

Information about an SAE will be collected and recorded on the SAE Report Form. The investigator will be requested to supply as much detailed information as possible regarding the SAE that is available at the time of the initial contact. The investigator should also complete missing or requested information and submit follow-up reports to the Medical Monitor until the SAE has resolved or, in the case of permanent impairment, until the SAE has stabilized.

The Medical Monitor will inform the sponsor about all SAEs without undue delay after receipt of the respective report from the Investigator.

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

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

14.6 AE/SAE follow-up

The investigator will take all appropriate and necessary measures required for resolution of the AE.

All AEs must be followed-up by the investigator until recovery, or until the investigator determines that the subject's condition is stable, or until the last day of the clinical investigation at the site, whichever occurs first.

Any pregnancy must be followed-up until the pregnancy outcome. If it is still on-going at the end of the clinical investigation, follow-up will be continued outside of the context of clinical investigation and pregnancy outcome (including pregnancy duration and health status of a newborn or cause of premature termination, as applicable) will be reported to the Sponsor.

All SAEs judged to be related to the investigational medical device (SADEs) must be followed by the investigator until the subject has recovered, recovered with sequelae, died, or until the investigator determines that the subject's condition is stable, whichever occurs first.

14.7 Foreseeable AEs and anticipated ADEs

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

14.8 Device deficiency reporting requirements

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

Device deficiencies should be reported by the investigator to the Medical Monitor within 24 hours after the site became aware of the device deficiency. Contact information is provided in Section 14.5.

The Medical Monitor will forward the deficiency report to the Sponsor within 24 hours after receipt of the respective report from the investigator.

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

14.8.1 Handling of deficient medical devices

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

14.9 Data monitoring committee

Not applicable.

15 Vulnerable populations

Vulnerable populations will not be included in this clinical investigation.

16 Suspension or premature termination of the clinical investigation

The Sponsor reserves the right to terminate the clinical investigation for any reason (e.g. safety, new data on the risk/benefit, ethical or administrative reasons). Written notice, outlining the reasons for the termination, will be submitted to the investigators in advance of such termination. The Sponsor will provide instructions if assessments beyond the regular per protocol procedures should be necessary.

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

The investigator, EC, or regulatory authority (if applicable) may also suspend or prematurely terminate the clinical investigation at the investigational sites for which they are responsible.

If the clinical investigation is prematurely terminated, the Sponsor or the Sponsor's representative will promptly inform the relevant authority (if applicable) of the termination and its reason(s); the investigator or the Sponsor (or representative) will promptly inform the EC, as specified in applicable regulations.

17 Publication policy

The results of the clinical investigation may be published and/or presented at scientific meetings. The results, however, should not be published without prior written consent by the Sponsor and such consent will not be unreasonably withheld. All manuscripts and abstracts, which refer to data originating from the clinical investigation, must be submitted to the Sponsor for comments at least 90 days prior to submission for publication.

If the proposed publication contains any invention related to the clinical investigation, the Sponsor is entitled to file respective patent applications and - on this ground - to delay the submission for publication or presentation of medical results for at least 6 months after receipt of the manuscript or abstract.

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