Prospective, controlled, randomized, blinded evaluator, monocentric, split-face clinical study to evaluate the efficacy and safety of injectable implant based on hyaluronic acid hydrogel with lidocaine versus injectable implant based on hyaluronic acid hydrogel without lidocaine for the treatment of moderate to severe nasolabial folds.

CLINICAL INVESTIGATION PLAN

Test Medical Device	injectable hyaluronic acid+lidocaine
Clinical Investigation Plan (CIP) Code	HA28L/MD01/20
Study Phase	Medical Device pre CE-marking investigation
Investigation title	Prospective, controlled, randomized, blinded evaluator, monocentric, split-face clinical study to evaluate the efficacy and safety of injectable implant based on hyaluronic acid hydrogel with lidocaine versus injectable implant based on hyaluronic acid hydrogel without lidocaine for the treatment of moderate to severe nasolabial folds.
Investigation Sponsor	Matex Lab Switzerland SA 12 Route de la Galaise 1228 Plan les Ouates Geneve (Switzerland) phone : +39 335 7077476/5 mail : rd.neauvia@neauvia.com
Investigation Manager	Prof. Nicola Zerbinati Centro Medico Polispecialistico Via M. Ponzio 15 27100 Pavia Phone number : +39 0382 556680 Fax number: +39 0382 558790 E-mail address: nzerbinati@centro-medico.it
Principal Investigator	Prof. Marco Romanelli, MD, PhD Dermatology Clinic Department of Clinical and Experimental Medicine, University of Pisa, Italy; Via Roma 67, 56126 Pisa, Italy Phone number: +39 050 992 436; Fax number: +39 050 551 124 E-mail address: m.romanelli@med.unipi.it
Protocol version No.	Final 1
Date	December 10, 2020

This investigation will be performed in compliance with UNI EN ISO 14155:2020 (Clinical investigation of medical devices for human subjects - Good Clinical Practices) and with ICH-GCP when applicable, including the archiving of essential documents, and updates

The information contained in this document is confidential and will not be disclosed to others without written authorization from the Sponsor except to the extent necessary to obtain informed consent from those persons to whom the investigational medical device may be administered or for discussions with local regulatory authorities, independent Ethic Committees, or persons participating in the conduct of the investigation

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SIGNATURES FOR THE APPROVAL

PRINCIPAL INVESTIGATOR

Prof. Marco Romanelli, MD, PhD
Dermatology Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy

Signature _____ *Date* _____

SPONSOR INVESTIGATION MANAGER

Prof. Nicola Zerbinati
Study dermatology consultant
Centro Medico Polispecialistico
Via M. Ponzio 15 27100 Pavia

Signature _____ *Date* _____

As consequence of the ongoing SARS-CoV-2 (Covid-19) pandemic, the circulation of the individuals and of the things is heavily restricted. Therefore both the Authors above are kindly asked to:

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As soon as possibile, the original pages and the scanned printed copies will be attached to the hard copy of this protocol.
The e-scans will be employed for the EC and the Italian Ministry of Health application.

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DECLARATION PAGE FOR THE PRINCIPAL INVESTIGATOR

Medical Device: injectable hyaluronic acid+lidocaine

CIP CODE: HA28L/MD01/20

TITLE: Prospective, randomized, blinded evaluator, monocentric, split-face clinical study to evaluate the efficacy and safety of injectable implant based on hyaluronic acid hydrogel with lidocaine versus injectable implant based on hyaluronic acid hydrogel without lidocaine for the treatment of moderate to severe nasolabial folds.

PRINCIPAL INVESTIGATOR: Prof. Marco Romanelli, MD, PhD

INVESTIGATIONAL SITE: Dermatology Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy
Via Roma 67, 56126 Pisa, Italy

I have read this protocol and I agree to conduct the investigation according to this protocol, to the Ethical Principles for Medical Research Involving Human Subjects adopted by the Helsinki Declaration, as well as applicable parts of the ICH-GCP guidelines, UNI EN ISO 14155:2020 and updates and to applicable regulatory requirements. I have read and agree to comply with the Investigator obligations reported in the protocol. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of subjects.

I have read and understood the information in the Investigator's Brochure, including the potential risks and adverse event profile of the medical device.

I agree to conduct in person or to supervise the investigation. I agree to ensure that all who assist me in the conduct of the investigation have access to the investigation protocol and are aware of their obligations.

Principal Investigator's Signature: _____ **Date:** _____

As consequence of the ongoing SARS-CoV-2 (Covid-19) pandemic, the circulation of the individuals and of the things is heavily restricted. Therefore Prof. Marco Romanelli is kindly asked to:

- *Print, date and sign this page;*
- *Scan the printed, dated and signed page;*
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PROTOCOL SUMMARY

Title	Prospective, controlled, randomized, blinded evaluator, monocentric, split-face clinical study to evaluate the efficacy and safety of injectable implant based on hyaluronic acid hydrogel with lidocaine versus injectable implant based on hyaluronic acid hydrogel without lidocaine for the treatment of moderate to severe nasolabial folds.
CIP Code	HA28L/MD01/20
Investigation Sponsor	Matex Lab Switzerland SA 12 Route de la Galaise, 1228 Plan les Ouates Geneve (Switzerland)
Principal Investigator	Prof. Marco Romanelli, MD, PhD Dermatology Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy
Investigation Phase	Medical Device pre CE-marking study
Investigation Site	The investigation will be conducted in one single investigational study site in Italy: Dermatology Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy.
Number of subjects	A total of 52 both gender outsubjects aged 18-75 years with moderate to severe nasolabials folds is extimated for data analysis. A maximum number of 55 subjects may be recruited to account for a rate of non-evaluable subjects up to 5%.
Investigation Objectives	<u>Primary objective</u> The primary objective of this investigation is to assess and compare the pain experienced by subjects during and immediately after injections (recording times: within 1 min and 15-30-45-60 minutes after the injection) of the product under investigation (hyaluronic acid PEG-cross-linked formulated with 0.3% lidocaine: HAL) versus the same product WITHOUT lidocaine (HA), admnistered to subjects with moderate to severe nasolabial folds. <u>Secondary objectives</u> • To assess and compare the safety of HAL and of HA; • To assess and compare and the efficacy of HAL and of HA injection. Clinical efficacy will be determined by the o Global Aesthetic Improvement Scale (GAIS), done by the subject at weeks 2, 12 and 24; o Wrinkle Severity Rating Scale (WSRS), done by the blinded evaluating investigator at at the entry and a the weeks 12 and 24; o blinded evaluating investigator and subject satisfaction done at week 24; o digital photography done before treatmente and at weeks 2, 12 and 24.
Indication	Correction of moderate to severe nasolabial folds

Investigation Population	Inclusion Criteria: 1. Outsubjects of either gender aged ≥ 18 and ≤ 75 yrs; 2. Presence of moderate to severe nasolabials folds (WSRS grade 3-4); 3. Reasonable potential benefit from correction; 4. Subjects able to understand the full nature and the purpose of the investigation, including possible risks and side effects, able to cooperate with the Investigator and to comply with the requirements of the entire investigation (ability to attend all the planned investigation visits according to the time limits included) based on Investigator's judgement; 5. Subjects must voluntarily give written, informed consent, adhere to the protocol and report events and concomitant medication for the entire duration of investigation. Exclusion Criteria: 1. Pregnant (as determined by a urine pregnancy test at the screening visit) or lactating women. For the entire duration of the investigation, female subjects of childbearing potential (i.e., not permanently sterilised - post hysterectomy or tubal ligation status – or not postmenopausal from at least one year) must adopt an appropriate method of contraception according to the definition of Note 3 of ICH M3 Guideline*; 2. Prior therapy (e.g., other permanent or biodegradable injectable fillers or surgical correction such as a face-lift, etc.) within 3 months prior to entry into the study or planned to undergo such therapy during the study; 3. Previous tissue augmentation with permanent implants (e.g., silicone) in the area to be treated; 4. Presence of active inflammation, infection (acne, herpes, dermatitis, etc.) or unhealed wound of the face; 5. Presence of varices in the area to be treated; 6. History of hypertrophic scarring; 7. Medical history or clinical examination positive for metabolic or endocrine serious diseases (e.g. uncontrolled diabetes or diabetes complications), anaphylaxis, severe allergies, immune disorders affecting the skin or other local or systemic concomitant diseases that may interfere with healing or with protocol evaluation parameters; 8. Use of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, antiplatelets and anticoagulants in the week before treatment; 9. Use of any other treatment or medication that, according to its pharmacological properties and in the opinion of the Investigator, can alter the perception of pain, started in the week before the screening visit; 10. Use of narcotic agents, antineoplastics, immunosuppressants or any other agent that may interfere with wound healing in the 4 weeks before the screening visit; 11. Neurological or psychiatric diseases that may threaten the obtaining of informed consent or the adherence to investigation procedures; 12. Ongoing neoplastic (including skin cancer) and/or immunodepressive diseases; 13. Subjects with known allergy or hypersensitivity to at least one component of

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	any of the investigational medical devices; 14. Ongoing or scheduled during the study radiation, laser, ultrasound, chemical peels treatment in the target area; 15. Known hypocoagulability state; 16. History of drugs and/or alcohol abuse; 17. Subjects unable to measure pain properly by means of a visual analogue scale (VAS); 18. Subjects considered to be unsuitable to participate, in the investigators opinion, for any other reason; 19. Planned relocation during the study, which would make follow-up visits impossible; 20. Concomitant participation in other clinical investigations or participation in the evaluation of any investigational drugs/devices during 3 months before this investigation or previous participation in the same investigation. **Note: According to the definition of Note 3 of ICH M3 Guideline a highly effective method is defined as those which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Highly effective birth control methods include: combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence.*
Investigation Design	This will be a pre CE-mark controlled, prospective, randomized, blinded evaluator, single centre, split-face clinical investigation. Each subject will receive both medical devices under investigation, one (HAL) on the one side of the face, the other (HA) on the other side, in randomized fashion. The products will be administered by the Investigator/Co-Investigator (Treating Investigator), while the clinical evaluation will be done by a Co-Investigator not aware of the side type treatment (Blinded Evaluator). The investigational plan include a Visit 1, during which subjects will screened for entry (inclusion/exclusion) criteria; eligible subjects will be treated with the medical devices and followed for the next hour for pain and safety evaluation. Visit 2, 3 and Visit 4 are schedule after 2 (± 2 days), 12 (± 10 days) e 24 weeks (± 10 days) for the assessment of safety and clinical efficacy. Subjects prematurely discontinued from the investigation after the treatment period will perform an 'Early termination visit', in which procedures schedule for Visit 4 (24 weeks, final visit) will be performed. In case of premature discontinuation of the investigation, the Investigator will duly record the reason for premature withdrawal in the appropriate section of the case report form (CRF). Visit 4 (or the 'Early termination Visit') will represent the conclusion of subject's participation in the investigation. Adverse events will be recorded during the entire investigational period by investigator's assessment and subjects' spontaneous reporting. Vital signs (blood pressure and heart rate) will be measured at each visit in the investigational site. The extimated total duration of the investigation for each subject will be 24 weeks. This time frame has been selected basing on literature data related to dermal fillers based on hyaluronic acid.

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Treatment	Investigational medical devices: a) Test medical device (1 mL filler): PEG cross-linked hyaluronic acid hydrogel (28 mg/mL) plus lidocaine 0,3 %; b) Reference medical device (1 mL filler): PEG cross-linked hyaluronic acid hydrogel (28 mg/mL); Study devices will be administrated using linear threading, multiple punctate pools, and/or fan-like injection technique. The depth of injection will be at the discretion of the Treating Investigator; however, for a given subject, both devices will be injected at the same depth and with the same technique. In all subjects the first injection will be done in the right side of the face, the second in the left side. Doses: the minimum amount must be at least 0.5 ml per side, the maximum 2 ml per side, per each implant. The Treating Investigator will decide the dose to obtain the optimal correction of defect per each patient implant.
Concomitant treatments	Permitted treatments: With the exception of those products listed among non-permitted medications, participants will be allowed to use any concomitant medication (necessary for the treatment of pre-existing concomitant pathologies or for intercurrent diseases), that do not interfere with the investigation evaluation parameters. Non-permitted treatments: Chemical (drugs, medical devices, homeopathics, cosmetics, peeling ecc..) and/or physical (for example laser or massage) topical treatments at the the injections site are not admitted from visit 1 to final visit. Subjects will be warned to avoid the prolonged exposure to strong sun light and to tanning lamps in the same time lapse.
Investigation Endpoints	Primary performance endpoint: The primary performance endpoint of this investigation will be the pain severity experienced by subjects during and immediately after injections. Pain severity associated with injection will be measured within 1 min and 15-30-45-60 minutes after the injection, separately for each site (right/left), using a 100-mm Visual Analogue Scale (VAS).
	Secondary performance endpoint: • The secondary performance endpoint of this investigation will be to assess and compare the efficacy of HAL and of HA injection. The aesthetic results of the treatment will be evaluated by the subject, separately for each site (right/left), 2, 12 and 24 weeks after treatment ; evaluation will be done by means of the Global Aesthetic Improvement Scale (GAIS). The blind investigator will evaluate the risults at visit 1, 3 and 4 by the WSRS, separately for each side. At the final visit both the blind investigator and the subject will express a global satisfaction assessment (GSA) on corrective procedure (for each side of the face) Safety endpoints The safety endpoints of this investigation will be; • Incidence of local and systemic adverse events; • Changes from baseline in vital signs (blood pressure and heart rate).

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Sample size calculation	A sample size of 52 subjects will achieves 81% power to detect a mean of paired differences of 1.0 with an estimated standard deviation of differences of 2.5 and with a significance level (alpha) of 0.05 using a two-sided paired t-test. A maximum number of 55 subjects may be recruited to account for a rate of non-evaluable subjects of about 5%
Statistical analysis	All statistical analyses will be performed using Stata version 16.1. The software used to perform the statistical analysis, as well as the data management activities, is fully validated. The following describes the statistical analysis as it is foreseen at the time of planning the investigation. A detailed statistical analysis plan (SAP) will be issued before database lock. The contents of the SAP will include the investigation's objectives, type of primary analysis, clear specification of all primary and secondary endpoints, full and detailed descriptions of the statistical methods for data analysis and will address special issues such as definition of major protocol violators, definition of subjects and data included in or excluded from each analysis, and exploratory analyses. The plan will be reviewed and may be updated before the start of the statistical analysis, which will start only at the end of data management activities and after the description and discussion of protocol deviations by the clinical team during a data review meeting. During the meeting subjects will be confirmed in the respective analysis populations. Subjects' exclusion from each of the analysis populations will be documented and justified in a Data Review Report. All data obtained in this investigation and documented in the CRFs will be listed and summarized with statistics or frequency tables as appropriate. Statistical testing will be two-sided. All p-values will be rounded to the first two significant (different from zero) decimal digits, or to one significant digit if lower than 0.001. Statistical significance will be declared if the p-value will be less than 0.05. Two-sided 95% confidence intervals (CI) for outcome variables will be calculated, unless otherwise specified. For quantitative safety and performance variables, analysis within sequence groups will be also presented. <u>Investigation Populations</u> The following populations are defined for this investigation: • Enrolled population: all subjects who sign the informed consent and are enrolled in the investigation after evaluation of all inclusion and exclusion criteria; • Intention-to-treat (ITT) population: all subjects who received almost one of the investigational device; • Modified ITT (mITT) population: all subjects of the ITT population who have at least one valid post-treatment record per treatment; • Per-Protocol (PP) population: all subjects of the mITT population who meet all inclusion/exclusion criteria and who do not have any major protocol deviation (e.g. use of forbidden concomitant medications, inadequate or poor compliance to investigation procedures, etc.). • Safety population: all subjects of the ITT population who receive at least one application of the investigational medical devices; The analysis of safety endpoints will be performed in the safety population. The analysis of performance endpoints will be conducted in the mITT population and

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	repeated in the PP population. The results obtained in the PP population will be seen as confirmative of those observed in the mITT population. Descriptive Statistics: Descriptive statistics will be provided in summary tables by treatment group according to the type of variable. Continuous variables will be summarized by number of observations, mean and standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts of subjects and percentages. All data collected will be presented in the listings. Subject accountability: Disposition of subjects, subject status and subjects excluded from different analysis sets will be summarized. Baseline characteristics: Demographic and baseline characteristics will be summarized by means of descriptive statistics. No formal statistical tests will be performed to verify the homogeneity of the sequence groups at baseline visit (intra-subjects study). Performance endpoints Primary performance endpoint will be the mean pain score experienced by the subject in the first hour after each treatment. The pain measurement will be obtained from the VAS scores. Based on these VAS scores, the area under the curve from treatment until 1 hour after will be calculated and this area under the curve will be divided by time. This resulted in a mean VAS score that will be compared between sequence with a paired t-test. For secondary endpoint a two-sided Wilcoxon signed-rank test will be done. Safety endpoints AEs which occurred before and those which started after the application of the investigational device (treatment-emergent AEs, TEAEs) will be presented separately. All AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) after medical coding using the most recent MedDRA thesaurus version. The primary SOC and the PT will be used for the analysis of the frequency distribution in the two groups. The number of TEAEs (i.e. AEs started after the start of treatment), treatment-emergent SAEs, TEAEs related to the medical device under investigation, treatment-emergent SAEs related to the medical device, and the number and proportion (with exact 95% CI) of subjects with at least one TEAE, treatment-emergent SAE, TEAE related to the medical device and treatment-emergent SAEs related to the medical device will be presented by treatment group. The incidence of TEAEs in the two sequence groups will be compared by means of McNemar test. Risk ratios and odds ratios with 95% CIs, Fisher's exact test and logistic regression will be considered to compare proportions between treatment groups.The results of changes from baseline in vital signs (blood pressure and heart rate) will be presented as descriptive statistics.
Starting and ending date	AS CONSEQUENCE OF THE ONGOING COVID 19 PANDEMIC, SEVERAL ACTIVITIES (SOCIAL, ECONOMICS AND HEALTHCARE) ARE DELAYED OR STOPPED. THEREFORE, TO HYPOTHESIZE THE ACTUAL TIMES OF THE STUDY IS DIFFICULT. AS SUPPOSITION, MAY BE THAT THE STUDY WILL START (FIRST PATIENT IN) DURING THE FIRST HALF YEAR 2021 AND WILL END (LAST PATIENT OUT) DURING THE FIRST HALF YEAR 2022.

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
ATC	Anatomical Therapeutical Classification
BDDE	Butane Diol Diglycidyl Ether
CE	Communauté Européenne
CI	Confidence Interval
CIR	Clinical Investigation Report
CIP	Clinical Investigation Protocol
CRF	Case Report Form
DD	Device Deficiency
EC	European Community
EN	European Norm
EU	European Union
FSCAs	Field Safety Corrective Actions
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic Acid
HAL	Hyaluronic Acid plus Lidocaine
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ISF	Investigator Study File
ISO	International Organization for Standardization
ITT	Intention-to-treat
IUD	Intrauterine Device
IUS	Intrauterine System
L	Lidocaine
MEDDEV	Medical Devices guidelines
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
NA	Not Applicable
NAV	Not Available
ND	Not Detected
NLF	NasoLabial Fold
NOR	Nothing Of Relevance
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
PEG	Poly Ethylen Glycol
PEGDE	Poly Ethylen Glycol Diglycidyl Ether
PP	Per Protocol
PT	Preferred Term
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOPs	Standard Operating Procedures
TEAE	Treatment-emergent Adverse Event
UNI	Ente Nazionale di Unificazione
USA	United States of America
USADE	Unanticipated Serious Adverse Device Effect

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UV	Ultra Violet (rays)
VAS	Visual Analogue Scale
WSRS	Wrinkle Severity Rating Scale

TABLE OF CONTENTS

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1. INTRODUCTION

1.1 Background information

The skin is the largest organ in the whole human body and may represent up to 16% of the body weight. It is a poly-functional structure that is substantially aimed at protecting from chemical, physical and biological external noxious agents, and at maintaining homeostasis[1]. Moreover, it exerts an important role of social interface for an individual, both in terms of non-verbal communication and of evaluation by the group (a 'nice skin' is considered as a positive characteristic, especially among females). The biological ageing is an ubiquitous, continuous and progressive, to which the cutaneous mantle cannot escape. Ageing of the organ is a consequence of both endogenous changes and of exogenous damages[2]. The endogenous change is part of the natural process of organic decline, whereas the exogenous ageing is caused by external factors, mainly the sunlight exposition (photoageing), cigarette smoking and environmental pollution[3,4]. The endogenous ageing is due to a reduction of cellular turnover (turnover of epidermic cells, which in young people is about 28 days, requires up to 40-60 days in elderly people) and to structural changes of derma and of subcutaneous tissue; it is characterised by appearance of laxity, thin wrinkles and enhancement of facial mimic[5]. Conversely, typical damages due to exogenous agents are discolouration and hyperpigmentation (age spots), deep wrinkles, cutaneous atrophy and coriaceous appearance; typical characteristics of exogenous damage are elastosis (accumulation of amorphous elastin, with consequent reduction of elasticity) and thinning and fragmentation of collagen fibrils[6,7]. Environmental factors not only reduce the level of antioxidant substances and increase free radicals, thus damaging structural proteins, but also induce the hyper-expression of collagen-degrading metalloproteases and of elastin fibres[8], and increasing the levels of inflammatory mediators through the NF-kB pathway[9]. Furthermore, UV rays may directly damage the skin causing the rupture of cross-linking at level of nucleic acids and of nuclear structural proteins (with consequent possibility of onset of cutaneous tumors) and the accumulation of glycated catabolites[10,11].

Cutaneous damages may also be a consequence of systemic diseases (such as renal failure, hepatic failure, sclerodermia, Cushing syndrome etc..) or of pharmacological treatments (such as glycoactive corticosteroids). The cutaneous deterioration may therefore assume a para-physiological or clearly pathological profile as a function of the general life and health context of each individual.

Endogenous changes take place mainly in the derma, mostly made of a dense extracellular matrix that is rich of collagen fibres, which represents the support of the cellular component and

[1] Venus M, Waterman J, McNab I. *Basic physiology of the skin*. Surgery 2011; 9 (10): 471-474

[2] Baumann I. *Skin ageing and its treatment*. J Pathol 2007; 211 (2): 241-251

[3] Petitjean J et al. *Effect of cigarette smoking on the skin of women*. J Dermatol Scie 2006; 42: 259-261

[4] Frances C. *Smoker's wrinkles: epidemiological and pathogenic considerations*. Clin Dermatol 1998; 16: 565-570

[5] Khavkin J, Ellis DA. *Aging skin: histology, physiology and pathology*. Facial Plast Surg Clin North Am 2011; 19(2): 229-234

[6] Montagna W, Kirchner S, Carlisle K. *Histology of sun-damaged human skin*. J Am Acad Dermatol 1989; 21 (5); 907-918

[7] Fitzpatrick RE, Rostan EF. *Reversal of photodamage with topical growth factor: a pilot study*. J Cosmet Laser Ther 2003; 5 (1); 25-34

[8] Sardi M. *Role of matrix metalloproteinases in skin ageing*. Connet Tissue Res 2009; 50(2).132-138

[9] Kammeyer A, Luiten RM. *Oxidation events and skin aging*. Ageing Res Rev 2015; 21: 16-29

[10] Thurstan SA, Gibbs NK, Langton AK et al. *Chemical consequences of cutaneous photoageing*. Chem Cent J 2012; 6(1): 34

[11] Gkogkolou P, Bohm M. *Advanced glycation end products: key players in skin aging?* Dermatoendocrinol 2012; 4(3): 259-270

contributes to cutaneous resistance and elasticity[12]; elastic fibres – made of elastin and microfibers of fibrillin – are a second key component for elasticity, mechanic resistance and resistance to tension [13] (Fig. 1). Important changes also take place at the epidermidis level, where the accumulation of corneocytes determines a rough and withered appearance of the skin [14].

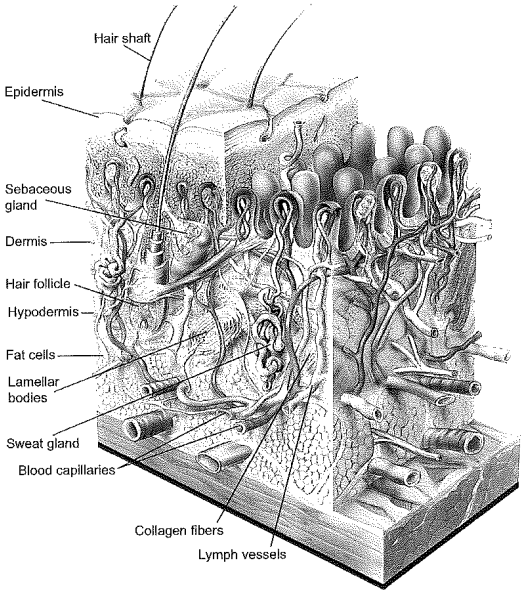

Figure 1 Structure of human skin.
Notes: The outer layer of the epidermis, the external layer of human skin, is made up primarily of corneocytes which provide a barrier function. Underlying the corneocytes are viable keratinocytes, which migrate outward and terminally differentiate to become corneocytes. The epidermis is organized into extensions called rete ridges that project between dermal papille (pink) into the underlying connective tissue. Underlying the epidermis is the dermis, which is primarily made up of collagen, elastin fibers, and other extracellular matrix components. Collagen and elastin fibers are synthesized by fibroblasts to provide tensile strength, firmness, and elasticity to the skin. The innermost layer of the skin, the hypodermis, is composed largely of fat cells, which helps provide structure to the skin. Blood capillaries, lymph vessels, sweat glands, sebaceous glands, hair follicles, and lamellar bodies lie within the dermis and hypodermis. Illustration: © www.julius-ecke.de; source: www.skin-care-forum.basf.com.

Figure 1. Structure of human skin

Moreover, the reduction of vascular texture and subcutaneous structural changes contribute to ageing. At the extracellular substance level, the involutive process is associated with a thinning of collagen fibres and a structural disorganisation of the collagen itself, mainly due to a reduction of the synthesis of type I collagen[15].

The normal process of deterioration, although it appears later, starts at around 20 years [16]. The water content is reduced, the collagen production slows down and elastin, the protein that allows to the skin to resume the normal conformation after the stretching, became less elastic. Therefore, ageing determines a thinning of the skin, the loss of elasticity, a decrease in water content and also a decrease of subdermic fat [17] (Fig. 2).

[12] Quan T, Fisher GJ. *Role of age-associated alterations of the dermal extracellular matrix microenvironment in human skin aging.* Gerontology 2015; 61 (59: 427-434

[13] Sherrat MJ. *Tissue elasticity and the ageing elastic fibre.* Age 2009; 31 (4): 305-325

[14] Rittie I, Fisher GI. *Natural and sun-induced aging of human skin* . Cold Spring Harb Perspect Med 2015; 15 (1): a015370

[15] Uitto J. *The role of elastin and collagen in cutaneous aging: intrinsic aging versus photoexposure*. J Drugs Dermatol 2008; 7(2): S12-S16

[16] Baumann L. *Skin ageing and its treatment*. J Pathol 2007; 211: 241-251

[17] Mc Cullough JL, Kelly KM. *Prevention and treatment of skin aging*. Ann NY Acad Sci 2006; 1067:323-331

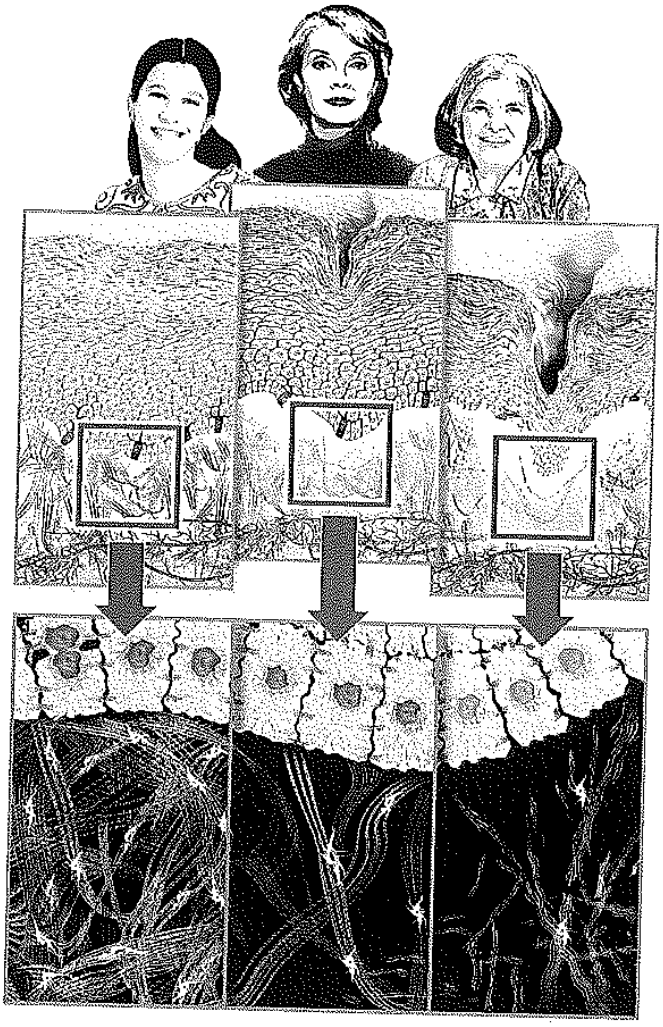

Figure 2 Changes in the skin with age.
Notes: As the skin ages, several changes occur in the epidermis and dermis. In the epidermis, corneocytes (terminally differentiated keratinocytes) accumulate, giving the skin a rough and dull appearance. In the dermis, the collagen content decreases and collagen and elastin fibers become disorganized and fragmented. This weakens the structure underlying the epidermis, leading to wrinkles. Illustration: © Kleinhans RED, source: www.skin-care-forum.basf.com.

Fig. 2 Change in the skin with age

Although it is clearly impossible to stop the biologic watch, actually the branch of the dermatologic science aimed at treating the visible aspect is able to antagonize and in part to prevent or slower down the appearance of the manifestations that characterize the ageing of our skin, which are often socially considered and imperfections and thus undesirable. There are different approaches, from the systemic ones to those of local characteristic[18,19,20]. The anti-ageing treatment is based on the

[18] Aldag C, Teixeira DN, Leventhal PS. *Skin rejuvenation using cosmetics products containing growht factors, cytokines and matrikines: a review of the literature.* Clin Cosm Invest Dermatol 2016; 9: 411-419

[19] Dumoulin M, Gaudot D, Lemaire B. *Clinical effects of an oral supplement rich in antioxidants on skin radiance in women.* Clin Cosm Invest Dermatol 2016; 9: 315-324

[20] Laurino C, Palmieri B, Coacci A. *Efficacy, safety and tolerance of a new injection technique for high- and low-molecular-weight hyaluronic acid hybrid complexes.* ePlasty 2015; 427-437

use of specific substances (biocompatible and absorbable) aimed at favouring the restoration of physiological characteristics that are typical of young skin (tone, compactness, hydration).

1.2 Rationale; investigational medical device

Hyaluronic acid (HA), also known as hyaluronan, is the most abundant glycosaminoglycan in the human dermis and is widely distributed in the skin, eye, joint and cartilage. HA is a naturally occurring polysaccharide of the extracellular matrix in human tissues -including skin- and it is chemically, physically, and biologically similar exhibiting no species or tissue specificity[21]. In its naturally occurring form, HA has a short half-life (typically 1–2 days) and is eliminated by the lymphatic system and liver[22]. Out of the many strategies that have been made to stabilize HA, to control its degradation rate, and to obtain a more stable material - while maintaining its properties - there are cross-linking and conjugation. In cross-linking, HA reacts with a cross-linking agent that can create covalent bonds between HA chains. Therefore, chemical cross-linking of HA is necessary to extend its residence time in the dermis. Cross-linked HA is a biodegradable, biocompatible, non-toxic and non-immunogenic polymer. HA has been used for many years in medicine in a variety of applications (scaffolding for tissue engineering, visco-supplementation for osteoarthritis treatment, ophthalmic surgery, etc.) and in the last decades it is used as the principal component of many biomedical devices. HA is present on the market in several pharmaceutical forms including nanoparticles, nanocomplexes, matrices and hydrogels. The reference HA planned for this study is a PEG cross-linked hydrogel HA[23] already in the italian market (*Neauvia Intense filler*, prefilled siringes containing HA 28 mg, authorization code 907900450; MatexLab, Brindisi). The PEG linking is a patended method.

The use of soft tissue augmenting agents to correct soft tissue defects has increased significantly over the past years and hyaluronic acid fillers have become the most frequently used soft tissue augmentation agents over the past several years[24,25]**.** Next to botulinum toxin injection, the injection of soft tissue fillers is the second most frequent minimally invasive procedure performed in the USA. The overall number of procedures in the USA using soft tissue fillers increased 190% in the last decade[23]. Non-surgical treatments, such as injectable dermal fillers, can reduce or eliminate facial lines, wrinkles, and folds giving the subject a younger appearance by restoring facial volume. Dermal fillers are a common minimally invasive option for the non-permanent treatment of age-related facial wrinkles, nasolabial folds (NLF) [26], marionette lines, and cheek hollowness. Unlike invasive surgical interventions, dermal fillers produce immediate benefits, requiring very minimal downtime, allowing individuals to return to work and their normal daily lives almost immediately after treatment [21].

Although HA fillers are effective and have many advantages, they are associated with notable pain upon injection and subjects consider pain to be a significant factor with injectable implants. Pain

[21] Levy P M, De Boulle K, Raspaldo H. *A split-face comparison of a new hyaluronic acid facial filler containing pre-incorporated lidocaine versus a standard hyaluronic acid facial filler in the treatment of naso-labial folds*. J Cosmet Laser Ther 2009;11**,** 169–173

[22] Monheit G. D. *et al. Reduced pain with use of proprietary hyaluronic acid with lidocaine for correction of nasolabial folds: a patient-blinded, prospective, randomized, controlled trial*. Dermatol Surg 2010; 36**,** 94–101

[23] Zerbinati N, Esposito C, Cipolla G. *et al. Chemical and mechanical characterization of hyaluronic acid hydrogel cross-linked with polyethylen glicol and its use in dermatology*. Dermatol Ther 2020 May 31: e13747 doi: 10.1111/dth.13747.

[24] Kouba D J *et al. Guidelines for the use of local anesthesia in office-based dermatologic surgery*. J Am Acad Dermatol 2016; 74,1201–1219 (

[25] Smith L, Cockerham K. *Hyaluronic acid dermalfillers: can adjunctive lidocaine improve patient satisfaction without decreasing efficacy or duration*? Patient Prefer Adherence 2011; 5**,** 133–139

[26] Fagien S, Monheit G, Derek Jones D *et al*. *Hyaluronic acid gel with (HARRL) and without lidocaine (HAJU) for the treatment of moderate-to-severe nasolabial folds: a randomized, evaluator-blinded, phase III study*. Dermatol Surg 2017; 0, 1–8

management usually requires some form of anaesthesia to be administered before treatment. Topical formulations, percutaneous injections and nerve blocks using lidocaine are most widely used [22] [23]. Moreover, topical anaesthesia is often insufficient at completely eliminating pain and requires an extended period of time of onset. Local anaesthesia adequately controls pain but can distort the area of treatment, making it more difficult to determine the end point of treatment [27]. Nerve blocks are effective, but their prolonged duration of action and transient cosmetic side effects are often unsatisfactory to subjects. In some cases, nerve block procedures should be avoided as in the case of nasolabial fold correction: infraorbital nerve block injection could add volume to the NLF, hampering a correct estimate of the filler volume needed [28]. In addition, many doctors are unfamiliar with performing nerve blocks [29]. Moreover, the separate administration of the anaesthesia can be associated with adverse events such as bruising, ecchymosis, and edema [30] [31]. Consequently, a number of physicians routinely add lidocaine solution to the available fillers in order to avoid injectable anaesthesia. Not only does this practice prompt questions of sterility, consistency, and quality of the final mixture, but it can change the product's flow characteristics and effectiveness by diluting the HA concentration with the lidocaine solution. Therefore, the ability to reduce pain by combining lidocaine with the dermal fillers represents one target for the advancement of current HA fillers. The lidocaine is added at 0.3% during the manufacturing process as a dry/powder substance and therefore does not dilute or increase the volume of the soft tissue filler [28]. Several studies that examined and compared HA fillers with and without lidocaine revealed significantly less pain and, in some, less erythema, swelling, and bruising with adjunct lidocaine [21] [22] [27] [28] [32] [33] [34] [35]. Pre-incorporated lidocaine in collagen fillers is shown to cause less bruising and swelling after injection, which could translate to HA fillers [36]. Lidocaine is also shown to function as an antihistamine in lower concentrations, inhibiting its release from mast cells [37]. Furthermore, returning to the previously injected area for optimal results frequently causes no more pain. It appears that the reduction and/or the absence of pain during the procedure may contribute to the injection of the lidocaine version versus the lidocaine free version being perceived as easier to perform by some injectors.

Levy et al. demonstrated that the lidocaine version provides superior comfort not only during the injection, but also while massaging, sculpting and after the injection compared to the HA free lidocaine version, when assessed by both injectors and participants [21].

A concern, besides the reduction of the efficacy and/or durability of adding lidocaine to dermal fillers, is the possibility that subjects may have an allergic reaction to lidocaine. A review of the

[27] Weinkle S . *et al. A multi-center, double-blind, randomized, controlled study of the safety and effectiveness of Juvéderm injectable gel with and without lidocaine.* J Cosmet Dermatol 2009; 8**,** 205–210

[28] Levy P M, De Boulle K, Raspaldo H. *Comparison of injection comfort of a new category of cohesive hyaluronic acid filler with preincorporated lidocaine and a hyaluronic acid filler alone*. Dermatol Surg 2009; 35 Suppl 1, 332–336; discussion 337

[29] Huang W, Vidimos A. *Topical anesthetics in dermatology*. J Am Acad. Dermatol 2000; 43**,** 286–298

[30] Grekin R, Auletta M J. *Local anesthesia in dermatologic surgery*. J Am Acad Dermato 1988; l19**,** 599–614

[31] Wahl G. *European evaluation of a new hyaluronic acid filler incorporating lidocaine*. J Cosmet Dermatol 2008; 7, 298–303

[32] Ballin AC, Cazzaniga A, Brandt F S. *Long-term efficacy, safety and durability of Juvéderm® XC.* Clin Cosmet Investig Dermatol 2013; 6, 183–189

[33] Beasley KL, Weiss M. Weiss RA. *Hyaluronic acid fillers: a comprehensive review*. Facial Plast Surg 2009; 25, 86–94

[34] Lupo MP, Swetman G, Waller W. *The effect of lidocaine when mixed with large gel particle hyaluronic acid filler tolerability and longevity: a six-month trial*. J Drugs Dermato 2010; l9,1097–1100

[35] Baumann L. *Dermal fillers*. J Cosmet Dermato 2004; l3**,** 249–250

[36] Librowski T, Pytka K, Szaleniec M. *Antihistaminic activity of caranederivatives in isolated guineapig ileum.* Pharmacol Rep 2009; 61**,** 1211–1215

[37] Bhole MV, Manson A, Seneviratne SL *et al. IgE-mediated allergy to local anaesthetics: separating fact from perception; a UK perspective*. Br J Anaesth 2012; 108**,** 903–911

literature published in 2012 showed that the incidence of true allergic reaction to local anaesthetic agents (including lidocaine and other products) was about 1% (0.97%) [38]. The majority of documented cases of allergy to lidocaine has been attributed to preservatives (such as methylparaben) present in the vials of lidocaine rather than to lidocaine itself. Data from clinical evaluation report the same profile of safety and the same effectiveness in terms of aesthetic result for two HA dermal filler formulations (with and without lidocaine)[39]. In addition, results showed that the adding of 0.3% of lidocaine does not affect the longevity of HA dermal filler. Studies of characterization of HA gel with lidocaine showed that the presence of lidocaine does not affect the properties of the product being freely released. In fact, in vitro kinetics studies the lidocaine contained in the dermal filler is rapidly released from the gel following injection and then it is metabolized, leaving the remaining product exactly equivalent to the HA dermal filler without lidocaine, and so with equivalent performance and longevity [40]. A comprehensive review and metanalysis on hyaluronic acid plus lidocaine was recently published[41]**.** Studies of characterization of HA dermal filler with lidocaine and kinetic of lidocaine HCl release have been also performed by manufacturer of PEG-linked HA. Lidocaine HCl was immediately released from hyaluronan hydrogels crosslinked by BDDE and by PEG when immersed in aqueous medium with the same kinetic for both hydrogels. Lidocaine HCl did not interact with hyaluronic acid and the release increased with the time of the incubation. Different concentration in hyaluronan or different cross-linkers (BDDE or PEG) did not interfere with the release of lidocaine. The anaesthetic effect of lidocaine added to medical device gradually declined during the first hour, indicating most lidocaine has been released from the HA gel. This short lasting effect may provide additional subject comfort by alleviating the "frozen face" effect, common after application of dental blocks, which can last longer than 2 hours [22].

The usefulness of lidocaine as ancillary substance is supported also by safety data.

In the clinical evaluation, have been observed the same adverse events for the two type of HA dermal filler formulations (with and without lidocaine). Therefore, they have the same safety profile. Most of the adverse events reported had mild or moderate severity with the same frequency for both formulations of fillers. The only difference is reported in terms of pain intensity: less pain was reported in subjects treated with HA containing lidocaine. Lidocaine HCL is added in small amount in the final device (0.3% maximum) as an ancillary substance for reducing pain and distress due to the injection. It is released immediately when the medical device is immersed in an aqueous medium. It does not interact with hyaluronic acid and its release increased with the incubation time. Chemical and mechanical characterization of the HA dermal fillers containing lidocaine, showed that its presence does not modify the properties of the product being freely released.

Several lidocaine-containing HA fillers are already available worldwide (Restylane lidocaine, Juvederm lidocaine etc..) as medical devices.

The test filler under investigation in this study will be a PEG cross-linked hyaluronic acid hydrogel containing lidocaine, a degradable injectable medical device submitted to Notify Body evaluation for EC-marking certification, according to the REGULATION (EU) 2017/745, for the treatment of moderate to severe nasolabial folds.

[38] Prager W *et al. A prospective, split-face, randomized, comparative study of safety and 12-month longevity of three formulations of hyaluronic acid dermal filler for treatment of nasolabialfolds.* Dermatol Surg 2012; 38, 1143–1150 (

[39] Raspaldo H, De Boulle K, Levy P M. *Longevity of effects of hyaluronic acid plus lidocaine facial filler*. J Cosmet Dermatol 2010; 9**,** 11–15

[40] Sobanko J, Miller CJ, Alster T S. *Topical anesthetics for dermatologic procedures: A Review.* Dermatologic Surgery 2012; 38**,** 709–721

[41] Wary C, Luan S, Panayi AC et al. *Effectiveness and safety of hyaluronic acid gel with lidocaine fo the treatment of nasolabial folds: a sistematic review and metanalysis*. Aesthetic Plast Surg 2018; 42(4):1104-1110.

1.3 Summary of the preclinical data

Below a summary of the recent preclinical studies, showing the safety of the product.

Tests	Tests report no.	Results
CYTOTOXICITY DIRECT CONTAC on "Hyaluronic acid hydrogels crosslinked by PEGDE with lidocaine"	Eurofins -BIOLAB Report N°: STULV19AA2725-1 GLP	Not citotoxic
SYSTEMIC TOXICITY TEST on "Hyaluronic acid hydrogels crosslinked by PEGDE with lidocaine"	Eurofins -BIOLAB Report N°: STULV19AA2731-1 GLP	Doesn't cause toxic symptoms and satisfies the requirements of the tests
DELAYED HYPERSENSITIVITY TEST - GUINEA PIG MAXIMISATION TEST on "Hyaluronic acid hydrogels crosslinked by PEGDEwith lidocaine"	Eurofins -BIOLAB Report N°: STULV19AA2731-1 GLP	Not sensiting
SUBCUTANEOUS IMPLANTATION TEST ON "Hyaluronic acid hydrogels crosslinked by PEGDE with lidocaine" - Local and systemic effects (4 weeks)"	Eurofins -BIOLAB Report N°: STULV19AA3839-1 GLP	Causes slight local effects compared to the negative control, 4 weeks after implantation in subcutaneous tissue. Doesn't cause significantly different systemic effects compared to the control, 4 weeks after implantation in subcutaneous tissue.
SUBCUTANEOUS IMPLANTATION TEST ON "Hyaluronic acid hydrogels crosslinked by PEGDE with lidocaine" - Local and systemic effects (13 weeks)"	Eurofins -BIOLAB Report N°: STULV19AA3420-1 GLP	Causes slight local effects compared to the negative control, 13 week safter implantation in subcutaneous tissue. Doesn't cause significantly different systemic effects compared to the control, 13 weeks after implantation in subcutaneous tissue.
SUBCUTANEOUS IMPLANTATION TEST ON "Hyaluronic acid hydrogels crosslinked by PEGDE with lidocaine" - Local and systemic effects (52 weeks)"	Eurofins -BIOLAB Report N°: STULV19AA2734-1 GL	Causes minimal local effects compared to the negative control, 52 weeks after implantation in subcutaneous tissue. Doesn't cause significantly different systemic effects compared to the control, 52 weeks after implantation in subcutaneous tissue.

1.4 Potential risks and benefits

Risks associated with hyaluronic acid

Hyaluronic acid containing fillers are generally well tolerated. The most common adverse events are local pain, brusing, ecchimosys, erythema and bleeding - generally mild and transient. Serious adverse events are rare. Early adverse reactions to hyaluronic acid fillers include vascular infarction and compromise; inflammatory reactions; injection-related events; and inappropriate placement of filler material. Among late reactions are nodules, granulomas, and skin discoloration. Most adverse events can be avoided with proper planning and technique. Detailed understanding of facial anatomy, proper patient and product selection, and appropriate technique can further reduce the risks[42].

Risks associated with lidocaine

Large data on lidocaine toxicity are available on database as TOXNET, MEDLINE, RTECS (Register of toxic effects of chemical substances). The incidence of side effects is directly proportional to the total dose of local anaesthetic agent injected; low doses are generally well tolerated. The initial symptoms of anaesthetic induced toxicity include light-headedness, circumoral numbness, diplopia, and tinnitus. These effects are generally mild and short-lasting. Serious events include slurred speech, tremors, seizure and respiratory depression.

There are no expected serious risks or complications that may emerge from the administration of the two investigational medical devices (HA and HA+lidocaine) according to treatment schedule defined in this investigational protocol. Therefore, it is expected that benefits from the participation in this investigation will outweigh the theoretical risks.

[42] Signorini M, Liew S, Sundaram H et al. *Global Aesthetics Consensus: Avoidance and Management of Complications from Hyaluronic Acid Fillers—Evidence- and Opinion-Based Review and Consensus Recommendations*. Plast Reconstr Surg. 2016; 137(6): 961–971.

2. INVESTIGATION OBJECTIVES

2.1 Primary objective

The primary objective of this investigation is to assess and compare the pain experienced by subjects during and immediately after injections (recording times: within 1 min and 15-30-45-60 minutes after the injection) of the product under investigation [hyaluronic acid PEG-cross-linked formulated with 0.3% lidocaine: HAL] versus the same product WITHOUT lidocaine [HA], admnistered to subjects with moderate to severe nasolabial folds.

2.2 Secondary objectives

The secondary objectives of this investigation are:

- To assess and compare the safety of HAL and of HA;
- To assess and compare and the efficacy of HAL and of HA injection. Clinical efficacy will be determined by the
    - Global Aesthetic Improvement Scale (GAIS), done by the subject at weeks 2, 12 and 24;
    - Wrinkle Severity Rating Scale (WSRS), done by the blinded evaluating investigator at weeks 12 and 24;
    - blinded evaluating investigator and subject satisfaction done at week 24;
    - digital photography done before treatment and at weeks 2, 12 and 24.

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3. INVESTIGATION DESIGN

This will be a pre-CE mark controlled, prospective, randomized, blinded evaluator, single centre, split-face clinical investigation.

Each subject will receive both medical devices under investigation, one (HAL) on the one side of the face, the other (HA) on the other side, in randomized fashion.

The products will be administered by the Investigator/Co-Investigator (Treating Investigator), while the evaluations will be done by a Co-Investigator not aware of the side type treatment (Blinded Evaluator).

The investigational plan include a Visit 1, during which subjects will be screened for entry (inclusion/exclusion) criteria; eligible subjects will be treated with the medical devices and followed for the next hour for pain and safety evaluation.

Visit 2, 3 and Visit 4 are schedule after 2 (± 2 days), 12 (± 10 days) e 24 (± 10 days) weeks for the assessment of safety and clinical efficacy.

Subjects prematurely discontinued from the investigation after the treatment will perform an 'Early termination visit', in which procedures scheduled for Visit 4 (24 weeks, final visit) will be performed (whenever feasible). In case of premature discontinuation of the investigation, the Investigator will duly record the reason for premature withdrawal in the appropriate section of the case report form (CRF).

Visit 4 (or the 'Early termination Visit') will represent the conclusion of subject's participation in the investigation.

Adverse events will be recorded during the entire investigational period by investigator's assessment and subjects' spontaneous reporting. Vital signs (blood pressure and heart rate) will be measured at each visit in the investigational site.

The total duration of the investigation for each subject will be 24 weeks. This time frame has been selected basing on literature data related to dermal fillers based on hyaluronic acid.

4. SUBJECTS SELECTION CRITERIA

4.1 Subjects recruitment

Subjects will be recruited among the subjects attending the Unit as consequence of whatever reason.

A total of 52 both gender outsubjects aged 18-75 years with moderate to severe nasolabials folds is extimated for data analysis. A maximum number of 55 subjects may be recruited to account for a rate of performance non-evaluable subjects (no records after treatment) up to 5%.

The investigation will be conducted in one single investigational site in Italy: Dermatology Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy. Prof. Marco Romanelli, head of the Unit, will be the Principal Investigator.

Subjects to be enrolled in the investigation will be evaluated at the investigational site and, after the signature of the Informed Consent Form, will be screened for inclusion. If eligible, will be recruited to partecipate to the study. All subjects screened will be recorded in the investigation Subjects Screening Log.

The Principal Investigator and/or a co-investigator in the investigational site will verify the suitability of each subject for the participation in the investigation based on acceptable medical history and findings in the clinical examination which comply with the inclusion/exclusion criteria detailed in Section 4.2 and 4.3, respectively.

As soon as the number of subjects defined in the protocol will be achieved, no further subjects will be enrolled in the investigation.

To minimize the event of possible photosensitization, treatment should be avoided in the months with strong sunlight (in Italy, approximately, July and August).

STUDY TIMELINES: AS CONSEQUENCE OF THE ONGOING COVID 19 PANDEMIC, SEVERAL ACTIVITIES (SOCIAL, ECONOMICS AND HEALTHCARE) ARE DELAYED OR STOPPED. THEREFORE, IS NOT EASY TO HYPOTHESIZE THE ACTUAL TIMES OF THE STUDY. AS SUPPOSITION, MAY BE THAT THE STUDY WILL START (FIRST PATIENT IN) DURING THE FIRST HALF YEAR 2021 AND WILL END (LAST PATIENT OUT) DURING THE FIRST HALF YEAR 2022.

4.2 Inclusion criteria

Subjects will be enrolled at Visit 1 (Day 1) if they meet all the following criteria:

1. Outsubjects of either sex aged ≥ 18 and ≤ 75 yrs;
2. Presence of moderate to severe nasolabials folds (WSRS grade 3-4);
3. Reasonable potential benefit from correction;
4. Subjects able to understand the full nature and the purpose of the investigation, including possible risks and side effects, able to cooperate with the Investigator and to comply with the requirements of the entire investigation (ability to attend all the planned investigation visits according to the time limits included) based on Investigator's judgement;
5. Subjects must voluntarily give written informed consent, adhere to the protocol and report events and concomitant medication for the entire duration of investigation.

4.3 Exclusion criteria

Subjects will **no**t be enrolled at Visit 1 (Day 1) if they meet any of the following criteria:

1. Pregnant (as determined by a urine pregnancy test at the screening visit) or lactating women. For the entire duration of the investigation, female subjects of childbearing potential (i.e., not permanently sterilised - post hysterectomy or tubal ligation status – or not postmenopausal from at least one year) must adopt an appropriate method of contraception according to the definition of Note 3 of ICH M3 Guideline*;
2. Prior treatment of the face (e.g. other permanent or biodegradable injectable fillers or surgical correction such as a face-lift, etc.) within 3 months prior to entry into the study or planned to undergo such therapy during the study;
3. Previous tissue augmentation with permanent implants (e.g., silicone) in the area to be treated;
4. Presence of active inflammation, infection (acne, herpes, dermatitis, etc.) or unhealed wound of the face;
5. Presence of varices in the area to be treated;
6. History of hypertrophic scarring;
7. Medical history or clinical examination positive for metabolic or endocrine serious diseases (e.g. uncontrolled diabetes or diabetes complications), anaphylaxis, severe allergies, immune disorders affecting the skin, other local or systemic concomitant diseases that may interfere with healing or with protocol evaluation parameters;
8. Use of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, antiplatelets and anticoagulants in the week before treatment;
9. Use of any other treatment or medication that, according to its pharmacological properties and in the opinion of the Investigator, can alter the perception of pain, started in the week before the screening visit;
10. Use of narcotic agents, antineoplastics, immunosuppressants or of any other agent that may interfere with healing in the 4 weeks before the screening visit;
11. Neurological or psychiatric diseases that may threaten the obtaining of informed consent or the adherence to investigation procedures;
12. Ongoing neoplastic (including skin cancer) and/or immunodepressive diseases;
13. Subjects with known allergy or hypersensitivity to at least one component of any of the investigational medical devices;
14. Ongoing or scheduled during the study radiation, laser, ultrasound, chemical peels treatment in the target area;
15. Known hypocoagulability state;
16. History of drugs and/or alcohol abuse;
17. Subjects unable to measure pain properly by means of a visual analogue scale (VAS);
18. Subjects considered to be unsuitable to participate, in the investigators opinion, for any other reason;
19. Planned relocation during the study, which would make follow-up visits impossible;
20. Concomitant participation in other clinical investigations or participation in the evaluation of any investigational drugs/devices during 3 months before this investigation or previous participation in the same investigation or planned to receive other investigational products during the study .

**Note: According to the definition of Note 3 of ICH M3 Guideline a highly effective method is defined as those which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.*

Highly effective birth control methods include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence.

5. TREATMENTS

5.1 Reference and Test investigational medical devices

Reference device: HA (PEG cross-linked hyaluronic acid hydrogel)

Prefilled sirynge 1 mL.

Packaging: carton box containing one sterile syringe, one 21Gx16 mm needle and a 22Gx50 mm cannula.

Composition: gelatinous, transparent, colourless, cross-linked hydrogel with 2.8% of Hyaluronic Acid and Non-pyrogenic water 97.2% (containing Glycine and L-Proline < 2%).

Handling and storage: the shelf life of the medical device is three years and the products must be protected from damage, freezing and sunlight and stored at a temperature between + 4° C and 27° C.

Test device : HAL (PEG cross-linked hyaluronic acid hydrogel plus lidocaine)

Prefilled sirynge 1 mL.

Packaging: carton box containing one sterile syringe, one 21Gx16 mm needle and a 22Gx50 mm needle.

Composition: gelatinous, transparent, colourless, cross-linked hydrogel with 2.8% of Hyaluronic Acid and Non-pyrogenic water 96.9% (containing Glycine and L-Proline < 2%) and 0.3% lidocaine.

Handling and storage: the shelf life of the medical device is three years and the products must be protected from damage, freezing and sunlight and stored at a temperature between + 4° C and 27° C.

Both devices are manifactured and will be provided by Matex Lab S.p.A. (Via Carlo Urbani 2 angolo Via E. Fermi, 72100 Brindisi, Italy. Phone: +039 0831 572103).
Matex Lab S.p.A. is a company established in 2012 with wide experience in the field of biomedical technologies, specializing in the development of hydrogels for medical purpose.

5.2 Dosage and administration

The investigational medical devices must be administered only to subjects selected for taking part in the investigation according to the protocol.

Duration of treatment

Single admnistration of each device (one on right side and the other on the left side of the face).

Dosage and mode of treatment

- study devices will be administered using linear threading, multiple punctate pools, and/or fan-like injection technique. The technique of injectiom and the depth of injection will be at the discretion of the Treating Investigator; however, for a given subject, both devices will be injected at the same depth and with the same technique.
- in all subjects the first injection will be done in the right side of the face, the second in the left side.
- doses: the minimum amount must be at least 0.5 ml per side, the maximum 2 ml per side, per each implant. The Treating Investigator will decide the dose to obtain the optimal correction of defect per each patient implant.

5.3 Packaging and labelling

The labelling of the investigational product will be performed in accordance with the ISO 14155 guideline for medical devices and all local requirements.

Each single box will be labelled with almost the following information:

- clinical investigational plan code, sponsor's references,
- study site identification,
- Principal Investigator's name,
- product identification,
- batch number and expiry date
- storage conditions,
- the statement '*for clinical study only*',
- the statement '*keep out from children*',
- place to write the subject code,
- place to write the administration date .

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Example:

Clinical Trial HA28L/MD01/20	
Matex Lab Switzerland SA,12 Route de la Galaise1228 Plan les Ouates - Switzerland-	
phone: +39 335 7077476/5	
Study site	*Clinica Dermatologica, Dipartimento di Medicina Clinica e Sperimentale* *Azienda Ospedaliera Universitaria Pisana* *Via Roma, 67 - 56126 Pisa*
Principal Investigator	*Prof. Marco Romanelli*
Product	*(HA or HAL)*
batch number/expiry date	*xxx/xxxx**
Subject n° _____	
Date of admnistration _____	
For clinical study only. Keep out from children . Protect from damage, freezing and sunlight; store at a temperature between + 4° C and 27°	

Each siringe will be labelled almost with the product identification, the study code and a place to write the subject code.

An autoadesive flag label reporting the same data (to be sticked on CRF) is foreseen.

The Investigator and/or Hospital Pharmacist will be responsible for the correct storage and distribution of the investigational medical device, as well as of its accountability.

The Sponsor of the investigation will be responsible for the investigational medical device shipment to the Hospital Pharmacy.

An adequate amount of investigational devices will be supplied to the investigational site. Reserve units will be supplied in case of damaging of the scheduled units.

At the end of the investigation, following a final reconciliation on products accountability, both the used and the unused investigational medical devices will be sent to the Sponsor or locally destroyed at the investigational study site according to the local standard operating procedures (SOPs).

5.4 Treatment code

A computer-generated randomization list (specifying the type of medical devices to be injected in the right and the left side of the face) will be available.

Each subject included in the investigation will be coded by the Investigator through a 2-digit progressive *Screening number* as they present themselves for the investigation at the screening visit (Visit 1), starting from code 01 preceded by the letter "S" (first subject enrolled: code S01).

If a subject discontinues from the investigation, the screening number will not be re-used, and the subject will not be allowed to re-enter the investigation.

Eligibilty confirmed, a randomization number will be done starting from 01 (first subject randomized: code 01).

5.5 Concomitant medications

At the screening visit (Visit 1), the Investigator will instruct the subjects on the list of permitted and non-permitted concomitant medications.

All concomitant medications taken for any reason (including those taken in the last week prior to entry in the investigation) must be recorded in the appropriate section of the CRF.

5.5.1 Permitted concomitant medications

With the exception of those products listed among non-permitted medications, participants will be allowed to use any concomitant medication (necessary for the treatment of pre-existing concomitant pathologies or for intercurrent diseases), that do not interfere with the investigation evaluation parameters.

5.5.2 Non-permitted concomitant medications and treatments; lifestyle

Chemical (drugs, medical devices, homeopathics, cosmetics, peeling etc.) and/or physical (for example laser or massage) topical treatments at the the injections site are not admitted from visit 1 to final visit. Subjects will be warned to avoid the prolonged exposure to strong sunlight and to tanning lamps in the same time lapse.

5.6 Treatment compliance

Treatment with the investigational devices will be performed at the investigational site under direct control of the treating Investigator, who will ensure correctness of the procedures.

5.7 Investigational medical device storage and accountability

After receipt of the investigational medical device supplies, the Investigator, his/her deputy or the Pharmacist will conduct an inventory and subsequently fill-in and sign the investigational medical devices Delivery Form. The Investigator, his/her deputy or the Pharmacist, will keep investigational medical devices inventory and accountability records.

The required storage conditions will be rigorously followed: protect from damage, freezing and sunlight; store at a temperature between + 4° C and 27°.

The Investigator will keep the investigational medical device in a pharmacy or a locked and secure storage facility, accessible only to those individuals authorised by the Investigator himself.

At the conclusion of the investigation, a final investigational medical devices inventory will be performed and the used and unused investigational medical device will be sent to the Sponsor or locally destroyed at the investigational study site following the completion of an appropriate form, which will be signed by the Investigator or his/her deputy or by the Pharmacist. If any supplies are missing, this must be indicated together with an explanation for the discrepancy.

5.8 Overdosage

Cases of overdosage with the investigational or the reference medical devices are not known. Moreover, in this investigation no investigational device will be left to the subjects hands and hence any risk of overdose is excluded.

6. INVESTIGATIONAL PLAN

The investigational plan will include 4 visits in total at the investigational site: visit 1 (screening and treatment); follow-up Visits 2 (after 2 weeks), Visit 3 (after 12 weeks), Visit 4 (after 24 weeks).

It is recommended that, throughout the entire investigational period, the visits on site will be performed in the morning at approximately the same time of the day for each subject. A 2 day or 10-day flexibility with respect to the scheduled date of the visit is allowed for the planned day of visit 2 and visit 3 and 4, respectively.

The investigational plan and scheduled examinations and procedures are summarised in the following schedule.

Investigation schedule

	Screening (and treatment) visit	intermediate follow –up visits		Final visit* End of the study
Visit	**1**	**2**	**3**	**4**
Day	*1*	*14*	*84*	*168*
Week		*2*	*12*	*24*
Written informed consent	X			
Demographic data	X			
Medical history	X			
Physical examination	X			
Prior and concomitant treatments[1]	X	X	X	X
Vital signs[2]	X	X	X	X
Urine pregnancy test[3]	X			
Inclusion/exclusion criteria	X			
Randomization	X			
Treatment	X			
Pain assessment	X			
GAIS		X	X	X
WSRS	X		X	X
Digital photo	X	X	X	X
Global investigator assessment				X
Global subject assessment				X
Adverse events[4]	X	X	X	X
Investigational device accountability	X			
Investigational device reconciliation				X

*Or Early termination visit in case of investigation discontinuation
[1]All concomitant medications taken by the subject (including those taken in the prior week) will have to be recorded in the medical records and in the CRF
[2] Vital signs will include measurement of blood pressure and heart rate at each visit; height and weight at screening only
[3] An urine pregnancy test will be performed in female subjects of childbearing potential (i.e., not permanently sterilised - post hysterectomy or tubal ligation status – or not postmenopausal from at least one year)
[4] Adverse events will be recorded from the obtainment of the Informed Consent form up to the end of the investigation

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6.1 Investigation schedule, visits plan and procedures

Visit 1 (Day 1): Screening visit/treatment

Potential participants will be informed orally and in writing about the scope of the investigation, the relevant procedures, the nature of the risks related to the investigation, and they will be asked to sign and date the Written Informed Consent form.

After the correct obtaining of the Informed Consent form, the following assessments and procedures will be performed:

- Demographic data (age, gender, race) will be recorded;
- General medical history will be recorded;
- A general physical examination will be performed, including the measurement of height and weight. Any abnormality identified at the screening visit (Visit 1) should be recorded in the subject's medical records and in the CRF;
- All concomitant medications taken by the subject (including those taken in the prior one week) will be recorded in the subject's medical records and in the appropriate section of the CRF;
- Vital signs (blood pressure and heart rate) will be measured and recorded;
- An urine pregnancy test will be performed in female subjects of childbearing potential (i.e., not permanently sterilised - post hysterectomy or tubal ligation status – or not postmenopausal from at least one year);
- The digital photo will be done;
- The WSRS will be done;
- Eligible subjects will be included in the investigation and treatments will be done. HAL will be injected on the one side of the face, HA on the other side –by the Treating Investigator . Treatment procedure:

    1. Check the randomization list for the type of product (HAL or HA) to be injected in the **RIGHT** side of the face;
    2. Take the selected product box;
    3. Write the subject number and the date of admnistration on the label;
    4. Open the box and pick-up the siringe;
    5. Detach the flag label and stick it on the appropriate space present in the CRF (label not available in consequence of whatever reason, a withness will write the product code –HA or HAL- in the space, dating and signing it) ;
    6. Disinfect the skin thoroughly with iodopovidone or chlorhexidine disinfectant.;
    7. Screw the needle firmly onto the luer-lock connection of the syringe;
    8. Press gently on the plunger in order to expel any residual air from the device;
    9. If the needle is obstructed, do not increase pressure on the plunger but change the needle;
    10. Perform the injection;
    11. Record in the CRF the volume injected;
    12. Replace the used siringe in the box (without needle);
    13. Store in a safe place for future check.

Repeat the procedure for the LEFT side of the face.

Warnings: Do not use product after the expiry date. Do not use the product if the primary package is not intact or damaged. Do not use the product if it does not appear to be in normal condition. The siringes are disposable and CANNOT BE RESTERILISED; once the package has been opened, the material must be used immediately. Do not mix the medical devices with other substances. Do not place in contact the devices with quaternary ammonium salts as benzalkonium chloride. Do not inject any type of drug into the gel.

- Pain assessment. After implantation, participants will remain in a medical room for at least 60 minutes to be assessed for possible adverse events and for the pain. Pain will be assessed by the Blind Evaluator immediately (within 1 min) after the last injection and later after 15-30-45-60 min. by means of a 100-mm Visual Analogic Scale (VAS) (see paragraph 7), separately for each side.
- Adverse events will be monitored throughout the duration of the study (from obtainment of Informed consent to end of the study) and recorded in the subject's medical records and in the appropriate section of the CRF;
- An appointment will be taken for the next visit, scheduled after 2 weeks (± 2 days).

Visit 2 (week 2 ± 2 days): follow-up visit

The following assessments and procedures will be performed during Visit 2:

- All concomitant medications being taken by the subject will be checked and, in case of changes from the previous visit, will be recorded in the subject's medical records and in the appropriate section of the CRF;
- Vital signs (blood pressure and heart rate) will be measured and recorded;
- The occurrence of adverse events from the previous visit will be checked and (if any) and recorded in the subject's medical records and in the appropriate section of the CRF;
- The GAIS scale will be admnistered;
- The digital photo will be done;
- An appointment will be taken for the next visit, scheduled after 12 weeks from Visit 1.

Visit 3 (week 12 ± 10 days): follow-up visit

The following assessments and procedures will be performed during Visit 3:

- All concomitant medications being taken by the subject will be checked and, in case of changes from the previous visit, will be recorded in the subject's medical records and in the appropriate section of the CRF;
- Vital signs (blood pressure and heart rate) will be measured and recorded;
- The occurrence of adverse events from the previous visit will be checked and (if any) and recorded in the subject's medical records and in the appropriate section of the CRF;
- The GAIS scale will be admnistered;
- The WSRS will be done;
- The digital photo will be done;
- An appointment will be taken for the next visit, scheduled after 24 weeks from Visit 1.

Visit 4 (week 24 ± 10 days): final visit

The following assessments and procedures will be performed during Visit 4:

- All concomitant medications being taken by the subject will be checked and, in case of changes from the previous visit, will be recorded in the subject's medical records and in the appropriate section of the CRF;
- Vital signs (blood pressure and heart rate) will be measured and recorded;
- The occurrence of adverse events from the previous visit will be checked and (if any) and recorded in the subject's medical records and in the appropriate section of the CRF;
- The GAIS scale will be admnistered;
- The WSRS scale will be done
- The digital photo will be done;
- The general satisfaction assessment concerning the results of treatment will be done both the Blind investigator and by subject .

Early termination visit

In case of premature withdrawal from the investigation during the follow-up period for whatever reason, all efforts should be made to perform an 'Early termination Visit, which will include all available assessments as described above for Visit 4 (Final visit). The Investigator will duly record the reason for premature withdrawal in the subject's medical records and in the appropriate section of the CRF.

Visit 4, or the 'Early termination Visit', will represent the conclusion of subject's participation in the investigation.

6.2 Subject withdrawals

Subjects have the right to withdraw from the investigation at any time for any reason including personal reasons (consent withdrawal).

The Investigator also has the right to withdraw any subject from the investigation if he/she deems this appropriate and in the best interest of the subjects.

The following necessitate the discontinuation of a subject from the investigation:

- Protocol violation: at least one of the conditions that represent any of the exclusion criteria occurred at any time during the investigation;
- Lack of efficacy of the product: the appearance of the face will worsen during the follow-up and an alternative treatment is required;
- Voluntary subject withdrawal for any reason (consent withdrawal);
- If an adverse event (including a concomitant illness) develops, which is considered by the Investigator as incompatible with the continuation of the investigation;
- If the administration of a drug which is not permitted is necessary;
- Failure to comply with the requirements of the protocol;
- The Investigator considers the investigation discontinuation as appropriate, in the best interest for the subject;

- Subject dies during the investigation: the reason and the date of death will have to be recorded in the medical records and in the CRF, together with the Investigator's opinion on the correlation between the cause of death and the investigational medical device.

In case of withdrawal from the investigation, the reason and the date of discontinuation must be recorded in the medical records and in the CRF.

It is understood by all concerned that an excessive rate of withdrawals can render the investigation un-interpretable, therefore unnecessary withdrawals of subjects should be avoided. However, should a subject decide to withdraw, all efforts will be made to complete and report the observations as throughly as possible. A complete final evaluation at the time of the withdrawal (investigation end-point) should be performed in the 'Early termination Visit', and a clear, univocal explanation of the reason why the subject is withdrawn from the investigation should be reported.

Subjects prematurely withdrawn from the investigation during the follow-up period will not be replaced. They will undergo a final examination according to the procedure described for the Final Visit.

6.3 Early termination of the investigation

Both the Sponsor and the Investigator reserve the right to terminate the investigation at any time.

The Sponsor has the right to terminate the entire investigation at any time, for any reason, including but not limited to the following:

- Uprising of unexpected, significant, or unacceptable risk to subjects;
- The information on the investigational medical device leads to doubt as to the benefit/risk ratio;
- Subject enrolment is unsatisfactory and the subject recruitment lags behind the prospected timetable by more than 50%;
- The Investigator has received from the Sponsor all investigational medical device, means and information necessary to perform the clinical investigation but has not included any subject after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Sub-investigators, delegated staff with any provision of the clinical investigation protocol, and breach of the applicable laws. In any case the Sponsor will notify the Investigator of its decision by written notice.

The Investigator may terminate the participation in the investigation if the investigational site for any reason becomes unable to perform or complete the clinical investigation.

Should the early termination of the investigation be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all parties involved. The Sponsor should submit a written notification to the competent authority concerned and the independent ethic committee (IEC), providing the justification of premature ending or of the temporary halt.

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7. ASSESSMENT OF PERFORMANCE

The following performance parameters will be evaluated in the investigation:

Primary endpoint

The primary performance endpoint of this investigation will be the pain severity experienced by subjects during and immediately after injections (recording times: within 1 min and 15-30-45-60 minutes after the last injection).

Secondary endpoint

The secondary performance endpoint of this investigation will be to assess and compare the efficacy of HAL and of HA injection.

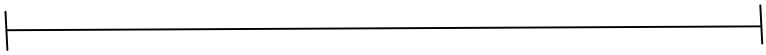
Methods of assessment

Pain severity

Pain severity associated with injection will be measured within 1 min and 15-30-45-60 minutes after the injection, separately for each site (right/left), using a 100-mm Visual Analogue Scale (VAS).

The VAS is a measurement instrument that tries to measure the amount of pain that a subject feels, that ranges across a continuum from none to an extreme amount of pain.

Operationally a VAS is usually a horizontal line (sample below), 100 mm in length, anchored by word descriptors at each end, where the left extreme mean "No pain = 0" while the right extreme means "Worst Pain Imaginable = 100".



0 — No pain

100 — Worst Pain Imaginable

Subjects will mark on the line the point that they feel representing their perceived pain.

The VAS score is the distance (in millimetres) from the left end of the line to the point where the subject's mark crossed the line. The measurement will be conducted by the same person at each visit.

Notice: the mark on the line shoud be a vertical stroke [|] *not a cross* [x].

Ten VAS forms will be provided for each subject (two forms –left and right side- for each of the five recording times), attached but not included in the CRF.

Clinical efficacy: subjective evaluation

The aesthetic results of the treatment will be evaluated by the subject, separately for each site (right/left), 2, 12 and 24 weeks after treatment. Evaluation will be done by means of the Global Aesthetic Improvement Scale (GAIS), based on five scores referred to the pre-treatment state:

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GAIS

score	definition
very much improved	excellent corrective results
much improved	marked improvement of the appearance, but not optimal
improved	improvemente of the appearance, better compared with the initial condition, but a touch-up is advised
no change	the appearance substantially remains unchanged in respect of the original condition
worse	the appearance worsened compared with the initial condition

Six GAIS forms will be provided for each subject, attached but not included in the CRF.

Clinical efficacy: objective evaluation

The aesthetic results of the treatment will be evaluated by the blind investigator, separately for each site (right/left), by means of the Wrinkle Severity Rating Scale (WSRS)[43], based on five scores, done before the treatment and a the weeks 12 and 24:

grade	*wrinkle*	*description*
1	absent	no visible nasolabial fold; continuous skin line
2	mild	shallow but visible nasolabial fold with a slight indentation; minor facial feature; implant is expected to produce a slight improvement in appearance
3	moderate	moderately deep nasolabial fold; clear facial feature visible at normal appearance but not when stretched; excellent correction is expected from injectable implant
4	severe	very long and deep nasolabial fold; prominent facial feature; <2 mm visible fold when stretched; significant improvement is expected from injectable implant
5	extreme	extremely deep and long nasolabial fold, detrimental to facial appearance; 2–4 mm visible V-shaped fold when stretched; unlikely to have satisfactory correction with injectable implant alone

The WSRS score will be entered directly in the CRF by the blinded evaluator.

At the final visit both the blind investigator and the subject will express a global satisfaction assessment (GSA) on corrective procedure (for each side of the face):

Global satisfaction assessment (GSA) scale

unsatisfying	satisfying	very satisfying
⓪	①	②

[43] Day DJ, Littler CM, Swift RW et al . *The Wrinkle Severity Rating Scale. A validation study*. Am J Clin Dermatol 2004; 5 (1):49-52

Clinical efficacy: objective recording

Immediately before treatment, after treatment (within 1 hour) and at all follow-up visits (V2-V3-V4) a digital picture of the face will be taken.

The photo will be taken from a frontal point of view according to the standard procedures of the study site (sitting position of the subject; soft environmental daylight; neutral uniform background; digital camera; distance subjects camera 1,2-2.0 m; focal lenght adjusted to 70-90 mm [35 mm format equivalent]; neutral white balance; automatic ISO exposure).

As soon as possible the digital file will be copied in a PC: for each photo almost the date of the shot and the subject number will must available. A separate backup of the files is advisable.

The digital files shoul be password-protect; the access will be permitted only to the Principal Investigator and to selected Co-Investigator(s).

Files must be recorded, stored, handled and protected according to the ICH and (UE) 2016/679 rules (privacy law)

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8. ASSESSMENT OF SAFETY

The safety endpoints of this investigation will be:

- Incidence of local and systemic adverse events;
- Changes from baseline in vital signs (blood pressure and heart rate).

Methods of assessment

Adverse events

Definitions, coding, methods of collection of adverse events and medical device incidents are described in details in Section 9.

Vital signs

Vital signs will be recorded at each investigation visit.

Systolic and diastolic blood pressure will be measured in sitting position after at least 5 minutes rest. Heart rate will be measured for one minute just prior to the sitting blood pressure measurement.

9. ADVERSE EVENTS

9.1 Definitions

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

An **Adverse Device Effect (ADE)** is defined as an AE related to the use of the medical device and includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the medical device. It also includes any AE resulting from user error or from intentional misuse of the medical device.

NOTE

in this study local pain/burning at the site of injection occurred during the admnistration and /or during the 3 hours following the procedure

WILL BE NOT JUDGET AS AE/ADE

Device deficiencies (DDs) are defined as any inadequacy of a medical device with respect to its identity, quality, durability, reliability safety or performance, including malfunctions, use errors, and inadequate labelling. A malfunction is defined as failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol. All device deficiencies will be documented during the clinical investigation and reported to the Sponsor on the appropriate form. A device deficiency that did not lead to an adverse event but could have led to a medical occurrence if suitable action had not been taken, if intervention had not been made, or if circumstances had been less fortunate, must be reported in the same way as an adverse event.

A **Serious adverse event (SAE)** is defined as an AE that:

a) Leads to death

b) Leads to serious deterioration in the health of the subject that results in

1) A life-threatening illness or injury, or

2) A permanent impairment of a body structure or a body function, or

3) In-subject or prolonged hospitalisation, or

4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

c) Leads to foetal distress, foetal death or a congenital abnormality or birth defect**.**

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

A **Serious adverse device effect (SADE)** is defined as any ADE that results in any of the consequences characteristic of a serious adverse event (SAE).

An **Unanticipated serious adverse device effect (USADE)** is defined as a SADE which by its nature, incidence, severity or outcome is not identified in the current version of the risk analysis report .

An **Anticipated serious adverse device effect (ASADE)** is an effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report.

According to MEDDEV 2.12-1, Rev. 8, a **medical device incident** is defined as 'any malfunction or deterioration in the characteristics and/or clinical performance of a device, as well as any

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inadequacy in the labelling or the instructions for use, which, directly or indirectly, might lead to or might have led to the death of a subject, or USER or of other persons or to a serious deterioration in their state of health'. A medical device incident that would require reporting includes:

a) Serious public health threat: Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action (MEDDEV 2.12-1 rev.8).

b) Death or UNANTICIPATED serious deterioration in state of health of a subject that results in:

   1) A life-threatening illness or injury, or

   2) A permanent impairment of a body structure or a body function, or

   3) In-subject or prolonged hospitalization, or

   4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

c) Other events: events that have an established link between the device and the event

9.2 Procedures for Reporting and Recording Adverse Events

It is responsibility of the Investigator to collect all adverse events (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings (e.g., how have you felt since I saw you last? Is there anything new that you wish to discuss?). Overall the Investigator shall record every adverse event and observed device deficiency, together with an assessment.

All Adverse Events/devices deficiency occurring during the clinical investigation must be documented in the subject's medical records and in the Adverse Event forms on the CRF, irrespectively of their classification.

9.3 Procedures for Reporting and Recording of Serious Adverse Events

Reporting of Serious Adverse Events

The Investigator must report all SAEs/SADEs, DDs and device incidents that could have led to a serious adverse device effect to the Sponsor Safety Officer not later than within 24 hours after the knowledge of the event. The information must be sent by fax by filling in the SAE forms or DD or device incidents form.

Day 0 is the day that the Sponsor receives a notification report from an Investigator. Any SAE/SADE/device incident is to be tracked and assessed by the Sponsor. The Sponsor will report any SAE/SADE/device incident to the relevant IEC as required by local requirements of the committee and to the Competent Authority. Any SAE/SADE/device incident is to be tracked and assessed by the Sponsor. Any SAE/SADE/device incident that might have led to a SAE if suitable action had not been taken or intervention had not been made or if circumstances had been less fortunate will be reported to the Competent Authority.

The contact for reporting is:

Dr Maria Protopapa

mobile phone: +39 3456099476

mail: m.protopapa@matexlab.com

Reporting of Serious Adverse Events to National Competent Authority

The Sponsor commits to report the following events to the National Competent Authority:

a) Any SAE;

b) Any DD or device incident that might have led to a SAE if suitable action had not been taken or intervention had not been made or if circumstances had been less fortunate (near incident);

c) New findings/updates in relation an already reported event.

The time-line for reporting reportable events is as follows:

a) Investigator to Sponsor:

- **not later than within 3 calendar days** after the occurrence of the event

b) Sponsor to National Competent Authority

- Serious public health threat: immediately (without any delay that could not be justified) but not later than 2 calendar days after awareness by the Manifacturer of this threat;
- Death or unanticipated serious deteration in state of health: immediately (without any delay that could not be justified) after the Manufacturer established a link between the device and the event but not later than 10 elapsed calendar days following the date of awareness of the event;
- Others: immediately (without any delay that could not be justified) after the Manufacturer established a link between the device and the event but not later than 30 elapsed calendar days following the date of awareness of the event;

9.4 Follow-up of adverse events

Complete and accurate data on all AEs experienced for the duration of the reporting period will be reported on an ongoing basis in the AE forms of the CRF.

It is important that each AE report include a description of the event, its expectedness, whether it is considered serious, its duration (onset and resolution dates), its intensity, its relationship to the medical device, any other potential causality factors, any action taken and its outcome.

Note: After completion of the investigation the Sponsor will continue to have an obligation to report serious and treatment-related AEs affecting the investigation subjects.

9.5 Follow-up of SAEs/SADEs/device incidents

- Reporting of SAEs/SADEs/device incidences from the investigator site begins from signing of informed consent and ends at the last investigation visit/last follow-up contact.
- All new SAEs/SADEs/device incidences occurring beyond this time frame and coming to the attention of the investigator must be recorded only if they are considered (in the opinion of the investigator) causally-related to the investigational device. Thus, only SAEs/SADEs/device incidences related to the investigational device will be followed after Visit 4, until resolution, stabilization or subject loss at follow-up.
- Reports of SAEs/SADEs/device incidences occurred during the investigation or after the site closure should be reported directly from the Investigator to the Sponsor Safety Contact.
- All SAEs/SADEs/device incidences should be followed-up in order to elucidate as completely and practical as possible their nature and/or causality. The follow-up information should be submitted until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, until progression has been stabilized or until the subject is lost to follow-up. Follow-up may therefore continue until after the subject has left the investigation.
- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the Sponsor Safety Contact by fax together with the SAE form, retaining a copy on site with the CRF.

- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the Sponsor Safety Contact as soon as available, retaining a copy on site with the CRF.

9.6 Pregnancy

- In case of accidental pregnancy, the subject will be immediately withdrawn from the investigation;
- If the pregnancy meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the Investigator must follow the procedure for reporting SAEs (see Section 9.3).

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10. DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data management and statistical analysis will be performed under the responsibility of the Sponsor.

10.1 Data management

10.1.1 Case report form (CRF)

The data generated in this investigation will be recorded at the investigational site by the appointed investigation personnel on an investigation-specific CRF.

A paper CRF will be designed to record all the protocol-required information to be reported to the sponsor. The main purpose of the CRF is to obtain data required by the clinical investigation protocol in a complete, accurate, legible, and timely manner.

All subjects' data, recorded in the CRF by the Investigator and/or his/her designee, will have to find source in the source documents (e.g., subject's medical records).

The CRF should be filled-in during or immediately after the conclusion of each visit, preferably within 24 hours but no later than five working days after the visit.

No blank sections or unanswered questions should appear in the CRF: in the case that the requested information cannot be provided, the statement "NAV" (not available) or "ND" (not detected) should apply specifying the reason or "NA" (not applicable) if not pertinent; in the section "notes/observations the statement "none" or "NOR" (nothing of relevance) or a cross line should apply when there is no need to provide further information.

The completion of the CRFs will be done using an indelible writing possibly in black colour (use a ball pen, not a fountain pen). Possible changes or additions to data already reported in the CRF should be performed using an indelible writing, possibly in black colour, dated and initialled by the person who performs changes. The reason of change/addition should be explained. In the case of correction, the original data should not be modified but ~~crossed~~ in order that the original version remains legible and verifiable. In no circumstances erasures or masks of the original data with masking fluids should appear.

The forms of the CRFs will be produced in a self-copying paper in thrice copy, one white (original, to be withdrawn by the sponsor) and two coloured copies (one to be sent to the statistician and another to be stored in the site documentation).

In the event that the CRF section dedicated to the recording of adverse events is not sufficient for the completion of recordings, a photocopy of the blank CRF can be used: in this case the original copy will be withdrawn by the monitor and 2 photocopy will be attached and punched to the corresponding CRF.

In exceptional, motivated and documented cases, the use of paper photocopied CRFs will be allowed, which will be managed as indicated in the paragraph above.

The Investigator or designee is responsible for ensuring that the data collected in the course of this investigation is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in pseudo-anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the CRFs and any other associated documents forwarded to the Sponsor or its designated organization contain no mention of any subject names or identifier.

Data reported on the CRF are confidential and have to be consistent with the source documents. The Investigator must ensure the accuracy, the completeness and the consistency of the data entered in the CRF.

The names of personnel authorized to handling the CRFs are to be given to the assigned investigation monitor before investigation initiation.

The CRFs will be archived by the investigator, as part of the essential clinical investigation documents, in a locked storage facility of the investigational study site. The data registered on the CRFs of all included subjects will be stored in a suitable database properly designed under the responsibility of th Sponsor.

Double data entry will be performed manually by the Data Entry Operators in the database. Data validation checks will be performed electronically/manually for internal consistency and completeness.

Queries generated from data entry and validation checks are issued by the Data Cleaning Operator or Data Manager according to the plan of controls previously prepared and will be referred to the Investigator.

After queries and quality checks and once the investigation database is considered cleaned, a data review meeting will be held before database lock in order to assign the subjects to each of the analysis sets according to the specified definitions.

Afterwards the database can be locked the planned statistical analysis will be performed.

10.2 Statistical analysis

All statistical analyses will be performed using Stata version 16.1. The software used to perform the statistical analysis, as well as the data management activities, is fully validated.

The following describes the statistical analysis as it is foreseen at the time of planning the investigation. A detailed statistical analysis plan (SAP) will be issued before database lock. The contents of the SAP will include the investigation's objectives, type of primary analysis, clear specification of all primary and secondary endpoints, full and detailed descriptions of the statistical methods for data analysis and will address special issues such as definition of major protocol violators, definition of subjects and data included in or excluded from each analysis, and exploratory analyses.

The plan will be reviewed and may be updated before the start of the statistical analysis, which will start only at the end of data management activities and after the description and discussion of protocol deviations by the clinical team during a data review meeting. During the meeting subjects will be confirmed in the respective analysis populations. Subjects' exclusion from each of the analysis populations will be documented and justified in a Data Review Report.

All data obtained in this investigation and documented in the CRFs will be listed and summarized with statistics or frequency tables as appropriate.

Statistical testing will be two-sided. All p-values will be rounded to the first two significant (different from zero) decimal digits, or to one significant digit if lower than 0.001. Statistical significance will be declared if the p-value will be less than 0.05. Two-sided 95% confidence intervals (CI) for outcome variables will be calculated, unless otherwise specified.

For quantitative safety and performance variables, analysis within treatments sequence will also be presented.

10.2.1 Sample size

A sample size of 52 subjects achieves 81% power to detect a mean of paired differences of 1.0 with an estimated standard deviation of differences of 2.5 and with a significance level (alpha) of 0.05 using a two-sided paired t-test.

A maximum number of 55 subjects may be recruited to account for a rate of non-evaluable subjects of about 5%

10.2.2 Populations for analysis

The following populations are defined for this investigation:

- Enrolled population: all subjects who sign the informed consent and are enrolled in the investigation after evaluation of all inclusion and exclusion criteria;
- Intention-to-treat (ITT) population: all subjects who received almost one of the investigational devices;
- Modified ITT (mITT) population: all subjects of the ITT population who have at least one valid post-treatment record per treatment;
- Per-Protocol (PP) population: all subjects of the mITT population who also meet all inclusion/exclusion criteria and who do not have any major protocol deviation (e.g. use of forbidden concomitant medications, inadequate or poor compliance to investigation procedures, etc.).
- Safety population: all subjects of the ITT population who receive at least one application of the investigational medical devices;

The analysis of safety endpoints will be performed in the safety population. The analysis of performance endpoints will be conducted in the mITT population and will be repeated in the PP population. The results obtained in the PP population will be seen as confirmative of those observed in the mITT population.

10.2.3 Missing data

Not applicable. No procedures for replacement of missing values will be used.

10.2.4 Coding Dictionaries

Adverse events (AEs), past and concomitant diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All verbatim terms will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the most recent MedDRA thesaurus version.

Previous and concomitant medications will be coded using the WHO-DRL Dictionary version 2015 or higher and classified according to 3rd level ATC level subgroup and generic name.

10.2.5 Statistical methods

Descriptive Statistics:

Descriptive statistics will be provided in summary tables by treatment group according to the type of variable.

Continuous variables will be summarized by number of observations, mean and standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts of subjects and percentages.

All data collected will be presented in the listings.

Subject accountability:

Disposition of subjects, subject status and subjects excluded from different analysis sets will be summarized.

Baseline characteristics:

Demographic and baseline characteristics will be summarized by means of descriptive statistics. No formal statistical tests will be performed to verify the homogeneity of the sequence groups at baseline visit (intra-subjects study).

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Performance endpoints

Primary performance endpoint will be the mean pain score experienced by the subject in the first hour after each treatment. The pain measurement will be obtained from the VAS scores. Based on these VAS scores, the area under the curve from treatment until 1 hour after will be calculated and this area under the curve will be divided by time. This resulted in a mean VAS score that will be compared between treatment with a paired t-test.

For secondary endpoint a two-sided Wilcoxon signed-rank test will be done.

Safety endpoints

AEs which occurred before and those which started after the application of the investigational device (treatment-emergent AEs, TEAEs) will be presented separately.

All AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) after medical coding using the most recent MedDRA thesaurus version. The primary SOC and the PT will be used for the analysis of the frequency distribution in the two groups.

The number of TEAEs (i.e. AEs started after the start of treatment), treatment-emergent SAEs, TEAEs related to the medical device under investigation, treatment-emergent SAEs related to the medical device, and the number and proportion (with exact 95% CI) of subjects with at least one TEAE, treatment-emergent SAE, TEAE related to the medical device and treatment-emergent SAEs related to the medical device will be presented by treatment group.

The incidence of TEAEs in the two treatment groups will be compared by means of McNemar test.

Risk ratios and odds ratios with 95% CIs, Fisher's exact test and logistic regression will be considered to compare proportions between treatment groups.

The results of changes from baseline in vital signs (blood pressure and heart rate) will be presented as descriptive statistics.

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11. ACCESS TO DATA AND INVESTIGATION MONITORING

The investigation will be carried out in accordance with the most recent international GCP guidelines (CPMP/ICH/135/1995) (whenever applicable), EU Directive and guidance and the local legislation on the conduct of clinical trials.

The Sponsor has the responsibility of monitoring this investigation.

In order to perform his role effectively, the Clinical Monitor must be given access to raw source data which supports data on the CRFs for the investigation, i.e. appointment books, original laboratory data, etc. The Investigator accepts herewith to allow adequate access to the facilities and to these documents and to ensure that his/her staff dedicates sufficient time to the Clinical Monitor, so that he/she can carry out his/her duties.

The objectives of monitoring, i.e. a regular and continuous verification of the investigation progress, are to check whether:

- Rights and healthcare of subjects are safeguarded, in conformity with rules, ethics and medical deontology;
- Investigation data are collected with completeness, precision and accuracy;
- The investigation is conducted according to the experimental protocol, to the rules of Good Clinical Practice (GCP) and to laws in force.

The Investigator will be visited by the monitor prior to investigation start, regularly during the conduction and at the end of the investigation. The monitor will inspect the investigation documentation stored in the Investigator study file (ISF), the CRFs, the source data (all data documented in addition to CRFs), the investigational device conservation and storage, keeping an adequate confidentiality.

Before each previously agreed monitoring visit, the Investigator will record or ask to record in the CRFs all available data. The Investigator or a co-investigator will be available for at least a part of the monitoring visit for verifications or clarifications.

It is possible that the investigation, during its conduction or even after the end, is inspected by Quality Assurance institutions (internal or external to Sponsor) and by Regulatory Authorities; in such case the Investigator must cooperate for the audit procedures, by allowing the inspection of spaces and instruments used in the investigation, the meeting with personnel involved in the investigation, the verification of investigation documents and the access to source data. Therefore, the Investigator agrees to allow the auditors/inspectors to have direct access to his/her investigation records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor of this clinical investigation is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical investigation protocol as regards ethics, clinical investigation protocol compliance, and integrity and validity of the data recorded in the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor in maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical investigation.

At regular intervals during the clinical investigation, the site will be contacted, through monitoring visits, e-mails, letters or telephone calls, by a representative of the monitoring team to review investigation progress, Investigator and subject compliance with clinical investigation protocol requirements and any emergent problems. These monitoring visits will include but are not limited to review subject informed consent, subject recruitment and follow-up, AE and SAE documentation and reporting, investigational medical device administration, investigational medical device accountability, concomitant therapy use and quality of safety and performance data.

The Investigator is responsible for ensuring that the clinical investigation will be conducted according to investigation protocol, GCP and ISO 14155 guideline.

The Investigator is responsible for ensuring that the clinical data required by the investigation protocol are carefully reported in the CRFs. The data entered in the CRF (in English language) must also be present in the source documents of the subject at the investigational site according to investigation protocol, GCP and ISO 14155 guideline.

All investigation documentation and results may be reviewed by the Quality Assurance Units of the Sponsor and/or Regulatory Authorities. The Investigator accepts herewith to give access to the facilities and to the raw source data upon request. The Investigator must also permit investigation-related monitoring, audits, Ethics Committee review or regulatory inspections.

Audits may be conducted at any time during or after the investigation to ensure the validity and integrity of the investigation data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Competent Authorities, must be permitted to access all investigation documents and other materials at the site, including the Investigator Site File, the completed CRFs, all device and device accountability records, and the original medical records or files for each subject.

13. ETHICAL AND REGULATORY ISSUES

13.1 Declaration of Helsinki

The investigation will be conducted in accordance with the Declaration of Helsinki (1964) and its amendments (protocol Appendix I).

13.2 Regulatory requirements

Application of this investigation to the National Regulatory Authority will be made according to specific national regulations and based on the ISO 14155 guideline.

A copy of the approval will be archived in the investigation master file at the Sponsor and in the local investigation file of the Investigator.

Furthermore, the investigation will be submitted to the reference Hospital/University Ethical Committee of the investigational site for approval. Financial agreement will be reached with Hospital/University Administration before initiation of the investigation.

13.3 Ethical Committee approval

Prior to commencement of the investigation, this clinical investigation protocol will be submitted together with its associated documents to the local Independent Ethics Committee (IEC) of the investigational site for the approval, together with the Information Sheet for informed consent and any other document required by the IEC. An approval document from the IEC must be received before starting the investigation and will filed in the Trial Master File.

The IEC will be asked to document the date of the meeting at which the favourable opinion or approval was given and the members and voting members present. Written evidence of favourable opinion or approval that clearly identifies the investigation, the clinical investigation protocol version and the Subject Information and informed consent form (ICF) version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical investigation protocol will also be submitted to the concerned IEC, before implementation of substantial changes (see Section 13.5). Relevant safety information will be submitted to the IEC during the course of the investigation in accordance with national regulations and requirements.

The Sponsor personnel responsible for the investigation will ensure that the investigational products are not dispatched to the site before formal authorization to conduct the investigation has been released and a copy of the authorization has been obtained.

Selection of the subjects will not start before the approval of the IEC has been obtained and the investigation notified to or authorized by the Competent Authority.

13.4 Competent Authority approval

The clinical investigation protocol and any applicable documentation (e.g., information sheet and informed consent form) will be submitted or notified to the Competent Authorities in accordance with local and national regulations.

13.5 Protocol amendment(s)

Neither the Investigator nor the Sponsor will modify or alter this protocol without first obtaining the agreement of the other part. A new approval from the IEC must be obtained before implementation of any substantial amendment, except when it is necessary to eliminate apparent immediate hazard to the subject.

All agreed substantial protocol amendments must be clearly recorded, signed and dated by the Sponsor and the Principal Investigator.

Any non-substantial amendment has to be signed by the responsible Sponsor. The original document will be filed in the investigation Master File. In trials conducted in the European Union (EU), there is no need to notify non-substantial/minor amendments to IEC or Competent Authorities, but all minor amendments should be recorded and kept available for any request for inspections at the investigational site or the Sponsor premises and should be contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment.

13.6 Written informed consent

While asking for informed consent, the Investigator will inform the subject that participation in the investigation is voluntary and that refusal will not lead to loss of any benefit or prejudice the relationship with the physician in any way. Furthermore, a statement will be made to the effect that withdrawal from the investigation is possible at any moment without having to give a specific reason.

Before enrolment into the investigation, each subject will receive a full explanation of the nature and purpose of the investigation from the Investigator, together with a description of benefits and risks associated with participation; insurance coverage will also be mentioned and related procedures in the event of injury will be explained.

A clear Information Sheet covering all important aspects in writing will be given to the subject who will read it and has the opportunity to ask any questions. The subject will be given adequate time for consideration before he/she is requested to sign and date the consent form in duplicate. One original copy of the signed and dated ICF will be kept by the Investigator in the investigation file. The subject will receive the second original for future reference.

The subjects will must specifically consent the digital shot of the face. In the informed consent form will be clearly stated that the use of the pictures outside the study purposes will be allowed only if the subject is not recognizable.

In this study the witnessed consent is not admitted.

14. DATA ARCHIVING AND CONFIDENTIALITY

14.1 Conservation of essential documents

Both the Sponsor and the Investigator should retain essential documents concerning the clinical investigation according to ISO 14155 guideline.

14.2 Subject identification and confidentiality

A unique number will be assigned to each subject immediately after informed consent has been obtained. This number will serve as the subject's identifier in the investigation as well as in the clinical investigation database. All subject data collected in the investigation will be stored under the appropriate subject's screening and treatment number. Only the Investigator will be able to link investigation data to an individual subject via an identification list kept at the sites. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Results from the medical examinations will be recorded in the subject's CRF. All the information obtained during the conduct of the investigation with regard to the subject's state of health will be regarded as confidential and agreement must be obtained from the subject prior to the disclosure of his/her personal identity to a third party different from authorised personnel of the Sponsor and/or Regulatory Authorities.

It is also understood that information from the clinical investigation will be used by the Sponsor in connection with a pharmaceutical development and therefore may be disclosed as required to other Clinical Investigators and to Government Authorities.

The Investigator accepts herewith to treat any unpublished information supplied by the Sponsor as confidential and ensures that confidentiality is kept also by all staff involved in this project. In this respect, no data will be used for presentations at scientific meetings and/or publication in scientific journals without prior agreement with the Sponsor.

14.2 Source data and subject files

14.2.1 Subject registry

Subjects' registry: since the elements that identify the subjects will be recorded in the CRFs in coded forms (screening and randomisation number - if applicable), the Investigator must keep an updated registry (stored with the other investigation documents) of subjects included in the investigation, where for each subject the following is to be reported: date of entry in the investigation, full name and family name, date of birth, screening and randomisation number (if applicable) and eventually address and phone number.

Please note: all the subjects that signed the informed consent must be recorded in the subjects' registry, regardless they have been randomised or not.

14.2.2 Investigator study file

The Investigator must keep an ISF ((Investigator Study File, i.e. medical file, original medical records) on paper or electronically for all subjects included in the investigation. It must be possible to identify each subject by using this subject's file. This file will contain at least the following demographic and medical information for the subject listed below and should be as complete as possible:

- Dated and signed copy of protocol and amendments (if any);
- Blank copy of the CRF;
- Copy of the curriculum/a vitae of principal Investigator and of all other personnel involved in the Investigation;
- Documentation of investigational devices receipt;
- Documentation of investigational devices returning;
- Investigational devices accountability;
- Copy of the correspondence with the Sponsor.;
- Copy of the favourable opinion of the Ethic Committee and its composition;
- Copy of the health authority approval;
- Copy of the CRFs;
- Registry of all subjects included in the investigation;
- Source documentation (see Section 14.2.3);
- Copy of the clinical investigation report.

14.2.3 Source data

The following items (at a minimum) will have to be collected as source data in the subject's file:

- Investigation code;
- Subject's full name, date of birth, sex, weight and height;
- Medical history and concomitant diseases;
- Prior and concomitant therapies (including changes during the investigation);
- Physical examination and vital signs;
- Eligibility of subject according to protocol criteria;
- Concomitant medications;
- Date of inclusion and subject identification numbers (screening number and treatment number);
- Date of subject's written informed consent;
- Date of start and end of investigational device administration;
- Date of the visits;
- AEs and SAEs occurring during the investigation;
- Date that the subject left the investigation including any reason for early withdrawal from the investigation.

Specific items required as source documents will be reviewed with the Investigator during the initiation visit.

All documents containing source data must be filed, including subjects' diary (if applicable).

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator and kept in a safe place at the site.

14.3 Investigator study file and archiving

Upon initiation of the investigation, the principal Investigator will be provided with an ISF dossier containing all necessary investigation documents, which will be completed throughout the investigation and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits, and for inspection by Competent Authorities during and after the investigation, and must be safely archived for at least 10 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the investigation. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site for the longest possible time permitted by the applicable regulations. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

15. INSURANCE

The Sponsor has undersigned an insurance policy covering subjects who enter the investigation. References are included in the Information Sheet for the subject.

The Sponsor will also indemnify the Investigator and hold him/her harmless for claims for damages occurred during the investigation in excess of those covered by his/her own professional liability insurance providing that the investigational medical device was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and the investigation protocol.

This indemnification does not apply to claims for damages arising out of any act of omission in his/her part or on the part of those under his/her supervision that shall or may amount to negligence in law. The Investigator must notify the Sponsor immediately upon notice of any claims or lawsuits.

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16. RESPONSIBILITIES

The responsibilities of the Investigators are those considered in the GCP and ISO 14155.

By signing this protocol, the Investigator states that he/she has been adequately informed regarding all aspects of the clinical investigation. He/she accepts to follow all the specified procedures as described in the protocol and to comply with all the requirements therein.

The Investigator is responsible for the conduct of the investigation and will ensure that the investigation is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki (Appendix 1) and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the investigation.

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17. FINAL REPORT AND PUBLICATION OF RESULTS

17.1 Clinical investigation report

A clinical investigation report (CIR) will be prepared according to ICH topic E3 guidelines. A final CIR will be prepared once the results of the final analysis will be made available.

The report will include a thorough description of the relevant methods, a discussion of the results, and a list of all the measurements.

A draft of the CIR will be submitted to the Investigator for comments. The Investigator's agreement and signature will be obtained and two original signed copies will be produced. One signed original copy of the CIR will remain with the Sponsor and the other original copy will be archived in the ISF. At the end of the investigation the Sponsor should provide the Ethics Committee and Competent Authorities with a synopsis of the CIR.

17.2 Publication of results

The data collected during the investigation will be the property of the Sponsor. The Sponsor is entitled to publish and/or present any results of this investigation at scientific meetings, and to submit these clinical investigation data to national and international Regulatory Authorities.

The Investigator accepts herewith to treat any unpublished information supplied by the Sponsor as confidential and ensures that confidentiality is kept also by all staff involved in this project.

Any publication in scientific journals and/or presentations at scientific meetings concerning the data deriving from the present investigation will be the result of a bilateral agreement (between the Investigator and the Sponsor). The Sponsor has the right to review any manuscript about the investigation. The publication will neither disclose the identity of subjects nor any patent information, fully respecting the data protection laws in force.

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18. REFERENCES

References are reported throughout the text.

APPENDIX I

DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the subject's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on subjects or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their subjects in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the subjects who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious subjects, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the subject which aspects of their care are related to the research. The refusal of a subject to participate in a study or the subject's decision to withdraw from the study must never adversely affect the subject-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the subjects who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual subject, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the subject or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.