Clinical Investigation Plan

A Post Market Clinical Follow Up (PMCF) Study to Assess the Safety and Efficacy of MaiLi Volume and MaiLi Extreme in the Treatment of Temporal Hollowing, Mid-Face Volume Deficit, Jawline Ptosis, and Chin Retrusion

Protocol Number: CS-21-03

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Version Number: V.1.0

24 January 2022

GENERAL INFORMATION

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DOCUMENT HISTORY

Version	Date	Description of change	Rationale

CONFIDENTIALITY STATEMENT

This document contains confidential information of “Sinclair Pharmaceuticals Ltd”. This document must not be disclosed to anyone other than the study staff and members of the Institutional Ethics Committee and Competent Authorities. The information in this document cannot be used for any purpose other than the conduct or evaluation of the clinical investigation without the prior written consent of “Sinclair Pharmaceuticals Ltd”.

APPROVAL OF THE PROTOCOL

Protocol Number Code: CS-21-03

Protocol Title: A Post Market Clinical Follow Up (PMCF) Study to Assess the Safety and Efficacy of MaiLi Volume and MaiLi Extreme in the Treatment of Temporal Hollowing, Mid-Face Volume Deficit, Jawline Ptosis and Chin Retrusion

Version: V.1.0/ 24 January 2021

Name	Company	Function	Date	Signature
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HimaBindu Nemalikanti	Inductive Quotient (In alliance with Aesculape CRO)	Data Management and statistics		

INVESTIGATOR'S AGREEMENT

Protocol Title: A Post Market Clinical Follow Up (PMCF) Study to Assess the Safety and Efficacy of MaiLi Volume and MaiLi Extreme in the Treatment of Temporal Hollowing, Mid-Face Volume Deficit, Jawline Ptosis and Chin Retrusion

Protocol Number Code: CS-21-03

Protocol Version/ Date: Version 1.0/ 24 January 2022

Sponsor Name: Sinclair Pharmaceuticals Ltd

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations, ISO 14155:2020 and Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

Principal Investigator's institution (if applicable):_____

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ABBREVIATIONS

3D	Three-dimensional
2D	Two-dimensional
ADE	Adverse Drug Event
AE(s)	Adverse Events
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ASADE	Anticipated Serious Adverse Device Effect
BDDE	1,4-butanediol diglycidyl ether
CHX	Chlorhexidine digluconate
CaHA	Calcium hydroxylapatite
CI	Confidence Interval
CIP	Clinical Investigational Plan
COVID	Coronavirus Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CSP	Clinical Study Protocol
CTR	Common Treatment Site Responses
CV	Curriculum Vitae
EC	Ethics Committee
ECM	Extracellular Matrix
eCRF	Electronic Case Report Forms
EoS	End of Study
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA(s)	Hyaluronic Acid(s)
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFU	Instruction for Use
ISF	investigator site file
ISO	International Organization for Standardization
ISR	Injection Site Reaction
PCL	Polycaprolactone
PI	Principal Investigator

PLLA	Polylactic acid
PMCF	Post-Market Clinical Follow-up
PMMA	polymethyl methacrylate
QA	Quality Assurance
QC	Quality Control
RA	Regulatory Authorities
SADE	Serious Adverse Drug Event
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
UV	Ultraviolet

PROTOCOL SYNOPSIS

Title of clinical trial	A Post Market Clinical Follow Up (PMCF) Study to Assess the Safety and Efficacy of MaiLi Volume and MaiLi Extreme in the Treatment of Temporal Hollowing, Mid Face Volume Deficit, Jawline Ptosis and Chin Retrusion
Protocol Code Number	CS-21-03
Protocol Short Name	MaiLi Belgium
Trial Phase	PMCF
Sponsor	Sinclair Pharmaceuticals Ltd Eden House, Lakeside, Chester Business Park, Chester, CH4 9QT, United Kingdom
Medical Condition or Disease Under Investigation	Temporal Hollowing, Mid Face Volume Deficit, Jawline Ptosis and Chin Retrusion
Purpose of the Study	To generate a clinical data set to demonstrate the efficacy and safety of: • MaiLi Volume as a treatment for mid-face volume deficit and temporal hollowing • MaiLi Extreme as a treatment for mid-face volume deficit, jawline ptosis and chin retrusion
Study Period **Date of First Enrolment** **Date of Last Completed Subject**	28 months (including 4 months enrolment and 24 months study duration) April 2022 August 2024
Primary Objectives	Evaluate the proportion of subjects with an improvement (score of 3 and above) at 6 months in the Global Aesthetic Improvement Scale (GAIS) with assessments of: • MaiLi Volume as a treatment for mid-face volume deficit and temporal hollowing. • MaiLi Extreme as a treatment for mid-face volume deficit, jawline ptosis and chin retrusion. as determined by an on-site live independent evaluator. Evaluate safety through the collection of all adverse events, inclusive of Serious Adverse Events (SAE), unanticipated problems, and Unanticipated Adverse Device Effects (UADE), experienced in the post-treatment follow-up period.

Secondary Objectives	Evaluate: • The proportion of subjects with an improvement (score of 3 and above) in Global Aesthetic Improvement Scale (GAIS) assessments of the i) mid-face and ii) jawline and iii) chin area and iv) temple at 3, 12, 18 and 24 months by an on-site live independent evaluator. • The proportion of subjects with an improvement (score of 3 and above) in Global Aesthetic Improvement Scale (GAIS) assessments of the i) mid-face and ii) jawline iii) chin area and iv) temple at 3, 6, 12, 18 and 24 months by the subject. • The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the mid-face volume deficit scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator. or The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the scale for the assessment of jawline sagging at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator. or The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the chin retrusion assessment scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator. or The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the temporal hollowing assessment scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator. • Subject and investigator treatment satisfaction will be assessed by questionnaire.

Exploratory Objective	Aesthetic treatment of deep depressions at the level of the face (temporal hollowing) and facial volume and contour restoration in the treatment of mid face volume deficit, jawline ptosis and chin retrusion.
Trial Design	The study is a 24-month, open-label, prospective, post-market clinical follow- up trial (PMCF), with two treatment groups. One group will receive the MaiLi Volume, another group will receive the MaiLi Extreme. The study will be conducted in 4 European study sites, located in Belgium and Germany. The study consists of 5 visits to assess efficacy at month 3, month 6, month 12, month 18, and month 24. And consists of 6 visits to assess safety at week 2, month 3, month 6, month 12, month 18, and month 24. The trial requires 140 subjects that complete the study visits. Taking into account a drop-out rate of 20%, 168 subjects will have to be recruited (42 per site; a minimum of 36 per site respectively). Eligible subjects include female or male subjects between the ages of 25 and 65 years of age inclusively across a range of Fitzpatrick skin types. In the MaiLi Volume treatment arm, 30 subjects will be assigned for treatment of mid-face volume deficit and 36 subjects of temple hollowing. In the MaiLi Extreme treatment arm, 30 subjects will be assigned of treatment of mid-face volume deficit, 36 subjects of jawline ptosis, and 36 subjects of chin retrusion. However if subjects meet the inclusion criteria, they have the option to receive injections in multiple treatment areas and generate data for more than one treatment indication.
Sample Size	168 subjects recruited (42 per site; a minimum of 36 per site respectively), over 4 investigational study sites, to meet a sample size of 140 subjects completing the study.
Summary of Eligibility Criteria	Subjects who meet all inclusion- and no exclusion criteria are eligible for participation in the clinical study. Eligible subjects include males and females aged 25-65 years inclusively across a range of Fitzpatrick skin types, defined as (the completed study size requirements for each treatment group are provide in brackets):

	• mild to significant facial volume deficit (mid-face area) (n=60 (50), MaiLi Volume 30 (25) subjects and MaiLi Extreme 30 (25) subjects) or • mild to moderate jawline ptosis (n=36 (30), MaiLi Extreme) or • minimal to severe chin retrusion (n=36 (30), MaiLi Extreme) or • minimal to severe temporal hollowing (n=36 (30), MaiLi Volume) Subjects can be treated in multiple areas if they meet the required inclusion criteria, but cannot be treated with both MaiLi Volume and Extreme.
Inclusion Criteria	Subjects meeting all of the following criteria are eligible for participation in this clinical study: 1. Subjects must be generally healthy and 25-65 years of age at Screening Visit 2. Subjects who have: mild to significant volume deficit in the mid-face (score of 2-4 on the designated photographic assessment scale (see section 5)) or mild to moderate jawline ptosis (score of 1-2 on the designated photographic assessment scale (see section 5)) or minimal to severe chin retrusion (score of 1-3 on the designated photographic assessment scale (see section 5)) or

	minimal to severe temporal hollowing (score if 2-4 on the designated photographic assessment scale (see section 5)) 3. Subjects who are willing to provide written informed consent, including approval for facial photographs to be taken. 4. Subjects willing to commit to having no further facial aesthetic treatments (see Table 2), that could affect the appearance of the facial treatment area, for the duration of the study period, including follow-up. 5. Subjects must be willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions and be likely to complete the study as planned. 6. Female of childbearing potential should use a medically accepted contraceptive regimen since at least 12 weeks prior to study entry and during all the study.
Exclusion Criteria	Subjects meeting any of the following criteria will be excluded from the study: 1. Subjects who, in the twelve months prior to their enrolment assessment had undergone: a. cosmetic facial plastic surgery (other than rhinoplasty), b. tissue grafting (e.g., fat injections), c. tissue lifting implants (e.g., threads, barbs) or other implants, d. augmentation with any permanent or semi-permanent filler (e.g., silicone, PMMA, PLLA) or temporary filler (e.g., Ha, CaHA, PCL) e. neuromodulator injections, f. mesotherapy, g. resurfacing in the mid-face (e.g., laser, radio frequency, dermabrasion, or chemical peel) in the region of the face to be treated. 2. Subjects who have received other facial aesthetic procedures, that affects the appearance of the facial treatment (see Table 2 in Protocol), at any time during the study period.

3. Subjects currently enrolled in other clinical trials.
4. Subjects with facial hair as this could interfere with study evaluations.
5. Subject who had been deprived of their freedom by administrative or legal decision or who is under guardianship.
6. Subject is an employee of the aesthetic surgery department on the investigational site, the CRO or study sponsor.
7. Pregnant or nursing woman or planning a pregnancy during the study.
8. Subjects taking thrombolytics or anticoagulants.
9. Subjects with bleeding disorders.
10. Subjects with known hypersensitivities to hyaluronic acid, lidocaine, amide local anaesthetics or other components of the treatment.
11. Subjects with a history of severe allergy or anaphylactic shock.
12. Subjects with active (or a history of) autoimmune disease.
13. Subjects with porphyria.
14. Subjects with cutaneous disorders and areas affected by inflammation and/or infectious skin problems (e.g., acne, herpes) at or near the treatment site.
15. Subjects with a tendency to form keloids, hypertrophic scars or any other healing disorders.
16. Subject with known history of precancerous lesions/skin malignancies.
17. Subjects must avoid receiving COVID-19 vaccination for the 14 days before and following injection.

Investigational Test Product and Dosage	In this study there are two test products (of 1mL): 1. MaiLi Volume (cross-linked hyaluronic acid (21mg/ml) + lidocaine hydrochloride monohydrate (3mg/ml) + phosphate buffer (q.s. 1ml)) 2. MaiLi Extreme (cross-linked hyaluronic acid (24mg/ml) + lidocaine hydrochloride monohydrate (3mg/ml) + phosphate buffer (q.s. 1ml)) At the Screening Visit, 66 subjects will be assigned to the MaiLi Volume treatment group and 102 subjects to the MaiLi Extreme treatment group. The injection will be administrated slowly into the subcutaneous fat tissue or into the supraperiostic zone in the appropriate area of the face by a well-trained physician. The injection volume varies depending on the correction required. Lidocaine is a component of the gel, incorporated to reduce pain resulting from injection during the treatment. The Instruction for Use (IFU) includes the dosing, the use of the needle or cannula, the procedure of administration, its storage conditions, and the waste disposal.
Route of Administration	Injection into the subcutaneous fat tissue or into the supraperiostic zone
Maximum Study Duration of a Participant	24 months
Procedures: Approach, Screening, Consent and Enrolment	Potentially eligible individuals will be approached by authorized physicians and/or local research teams during a (routine) appointment or advertisement. Written consent will be obtained in compliance with ICH-GCP, ISO 14155:2020, the local regulatory and the legal requirements from all potential subjects, once they have been given sufficient time to consider their participation in the study. Consent will include permission to retain contact details at the clinical site, which will enable the Sponsor, via the investigator, to inform the study subjects about a potential product recall or possible participation in future intervention/research studies. After informed consent has been obtained, the subjects will be screened based on the inclusion/exclusion criteria. If the criteria are met, the subject will be assigned in the appropriate treatment arm (i.e. MaiLi Volume or MaiLi Extreme) and enrolled in the study.

Procedures: Treatment Period	The subject will receive the corresponding treatment (i.e. MaiLi Volume or MaiLi Extreme) by a slow injection into the subcutaneous fat tissue or into the supraperiostic zone in the appropriate area of the face. The administration of the treatment will be done only by an authorized physician in accordance with local legislation. All instructions are clarified in the 'Instruction for Use' card. In addition, a video training will be used to explain the different procedures of the injection technique for each treatment area. These treatment instructions are important to standardize the application of the dermal filler as much as possible.
Procedures: Follow-up Period	There are 6 follow-up visits to assess safety and efficacy at week 2 (only safety), month 3, month 6, month 12, month 18, and month 24. At these follow-up visits, the effect of the treatment will be assessed.
Criteria for Withdrawal of Participants	All subjects are free to withdraw their participation in this study at any time, for any reason and without penalty or loss of benefits to which the subject was otherwise entitled. The Case Report Form (CRF) has to be completed up to the time of withdrawal. The following withdrawal-related data has to be recorded in the CRF: 1. The date of last follow-up visit or withdrawal 2. Reason for withdrawal 3. Possible relation to the study treatment

1. BACKGROUND AND RATIONALE

The facial morphology from infancy to old age is a complex, three-dimensional (3D) interplay of multiple structural tissue layers, and our understanding of this process is in a constant state of evolution and refinement[1]. At this time, facial aging research is defining the basic changes that occur in specific tissues, but it is how these changes affect what is observed in the aging face that remains to be defined. Cumulative changes over time in all structural tissue layers of the face lead to a change in the morphology of the entire face in terms of shape, proportions, and topography. Those changes in facial topography with aging sharpen the once smooth transition between anatomic units.

The skin of the face has consistent attachment points to the underlying structures through the facial retaining ligaments, and as the volume of the face deflates, these attachment points will define most of the shadows that develop with age. In youth, the 3D-surface contours of the face predominantly reflect light. Volume changes over time result in broken reflections with intervening shadows. This concept is critical to our understanding because seemingly subtle changes in light and shadow over time can have an enormous impact on our perception of a face in an almost indiscernible way. Moreover, the integration of volume replacement into the surgical and non-surgical therapeutic algorithm as a treatment for volume loss during aging is probably the most important recent development in the field of facial rejuvenation.

Hyaluronic acid

The key molecule involved in skin moisture is hyaluronan or hyaluronic acid (HA), a glycosaminoglycan (GAG) with a unique capacity to bind and retain water molecules[2]. HA is the most prominent component of the skin extracellular matrix (ECM). During the past decades, the constituents of the skin have been well characterized. In the beginning, most of the studies focused on the cells that comprise the skin layers, such as the epidermis, the dermis, and the underlying subcutis. Recently, it is appreciated that ECM molecules that lie between cells, in addition to providing a constructive framework, exert major effects on cellular function.
During facial aging, the most dramatic histochemical change observed is the marked disappearance of epidermal HA, while dermal HA is still present[2]. Epidermal loss of the essential molecule for binding and retaining water molecules results in loss of skin moisture. In the dermis, the major age-related change is the increasing avidity of HA with tissue structures with the concomitant loss of HA extractability. This parallels the progressive cross-linking of collagen and the steady loss of collagen with age. All the above age-related phenomena contribute to the apparent dehydration, atrophy, and loss of elasticity that characterize aged skin.

Dermal Fillers

The correction of lines and wrinkles and the restoration of facial shape alterations are key approaches to fight the appearance of aging and enhance facial appearance[3]. Therefore, in recent years, purified fractions of HA in the form of chemically stabilized injectable gels have become the standard for the non-surgical correction of facial wrinkles, receiving high subject satisfaction scores. Dermal fillers containing native HA polymer chains alone have little therapeutic utility due to the rapid degradation that occurs within the tissue. In order to obtain acceptable durability in the body, it is essential to perform a chemical process called “cross-linking”, which aims to improve *in vivo* resistance to degradation. The ideal filler must be

biocompatible, non-allergenic, non-migratory, and must provide long-lasting and reversible effects. Nowadays, product development is focused on improving the aesthetic outcome in terms of softness, a "natural" look and feel of the product *in situ*, in addition to the longevity of results.

HA-based gels are a well-established class of dermal filler that are approved for use in the treatment of a variety of facial features and conditions, primarily associated with the aging process[4]. The primary function of HA fillers relies on the HA gel having appropriate rheological characteristics (e.g. elasticity, viscosity) such that, following administration, the implanted gel provides an additional volume that effectively pushes out, for example, the wrinkle or nasolabial fold, thereby modifying the external facial appearance as desired[5]. The rheological characteristics of the implanted HA gels must also be appropriate to resist permanent deformation and remain in place following normal facial movements.

The Signs and Symptoms of Mid-face Volume Deficit, Jawline Ptosis, Chin Retrusion, and Temple Hollowing

Mid-face Volume Deficit: The midface is an important factor in facial aesthetics because perceptions of facial attractiveness are largely founded on the synergy of the eyes, nose, lips, and cheekbones (central facial triangle)[6]. As individuals age, the bony skeleton and soft tissues of the face lose volume, drop and shrink to produce a wider orbital aperture and less anterior projection[7]. This results in drooping eyes and tear trough deformity, lateral eyebrow ptosis, malar descent, a heavy jawline, and hypertonic contractions of the depressor muscles. For aesthetic purposes, this area should be considered from a 3D rather than a 2D perspective, and restoration of a youthful 3D facial topography should be regarded as the primary goal in facial rejuvenation.

Jawline ptosis: A well-contoured jawline is desirable in men and women, giving a perception of beauty and youth[8]. Jawline ptosis describes the descent of the soft tissues of the pre-symphyseal soft tissues below the inferior border of the mandible[9]. It cannot be addressed by standard rhytidectomies, and certain deformities may become more noticeable if other misdirected procedures are performed, for example, a submental lipectomy in the presence of dynamic ptosis. The nonsurgical rejuvenation and beautification of the lower third of the face are becoming more frequent[8]. The aesthetic goal of the rejuvenation approach is to redefine the mandibular angle and line. In young subjects, beautification can be achieved through correction of constitutional deficit or enhancement of the contour of the face, improving the facial shape.

Chin retrusion: For both men and women, good chin projection and a youthful jawline are considered the standards of beauty and can influence an individual's psychosocial well-being[10]. The shape and projection of the chin contribute to a "well-balanced and harmonious" face. Although congenital elements are the predominant factor in chin aesthetics, aging can result in bony resorption and produce sagging as well as laxity and droop in the chin area. In addition, aging can result in bulges and depressions in the pre-jowl sulci.

Temple hollowing: Temple hollowing with associated upper facial thinning is a common feature of the aging face[11]. Narrowing of the upper facial dimensions is a recognized aesthetic issue in

subjects with human immunodeficiency virus (HIV)–related and antiretroviral therapy-related lipoatrophy. The temple is also a standard site of inclusion during Coleman autolog fat transfer for rejuvenation.

Hyaluronic acids (HAs) have been extensively investigated in the areas to be treated in the present Maili Volume and Maili Extreme study namely midface, temple, chin and jawline. As examples, some of the most recently published studies among the numerous related ones are mentioned hereafter to document the safety/efficacy of HAs in those indications.
Generally, the HAs used in the facial volume deficit conditions (i.e. mid-face volume deficit, jawline ptosis, chin retrusion, and temple hollowing) have particular rheological properties with a high G' value. These HAs are injected at the subdermal or supraperiosteal planes and Global Aesthetic Improvement Scale (GAIS) is one of the main criteria used for evaluation. Moreover, they are long lasting their effects often measured up to 18 months - 2 years.
Two recent VYCROSS HAs can illustrate the targeted effects. In midface deficit the reference is Juvederm Voluma the first HA to obtain an FDA approval in this indication and object of several studies[12-13] . In addition, this HA was also recently investigated for correction of chin augmentation[14].
For the chin, Juvederm Volux, another recently developed HA, was Food and Drug Administration (FDA) approved in this indication. A recent study evidenced its effect on chin and jaw restoration, which are often tested together[15].
The temples are also an important element of facial rejuvenation and HAs are largely used for volumization of this area. The effect of NASHA HA Restylane, which is another category of HA, has been evaluated[16].
This information serves as a support for the interest of further investigation of new HAs for use in midface, chin , jaw and temple.

MaiLi
The MaiLi product family is a line of four sterile, transparent, and resorbable cross-linked hyaluronic acid gels of bio-fermentation. The devices are intended to modify the anatomy and/or to alleviate a physiological process at the level of the face. Especially, the line has reconstructive purposes in treatment of facial changes associated with the aging process (i.e. mid-face volume deficit, jawline ptosis, chin retrusion, or temple hollowing) and other underlying conditions. The product family is represented by devices sharing the same mode of action and general intended use and based on the same established manufacturing technology.

The MaiLi range is indicated for intradermal, subcutaneous, and supraperiosteal application depending upon the product used and the indication targeted and submucosal implantation in the lips.

There are four products within the MaiLi family: Precise, Define, Volume and Extreme. All four products are HA fillers; cross-linked HA is suspended in a solution of phosphate buffer and lidocaine hydrochloride monohydrate with an overall concentration of HA ranging between 15 and 24mg/ml. The constituent HA is of bio-fermentation. All of the MaiLi products are formulated with sodium hyaluronate gel which has been cross-linked with 1,4-butanediol diglycidyl ether (BDDE).

The MaiLi range of products has demonstrated an excellent efficacy and safety profile in a clinical trial. All adverse device effects reported during the study were expected for injectable gels of hyaluronic acid and the vast majority of them lasted less than ten days. No Serious Adverse Event (SAE) occurred during the study. An independent evaluator and subjects reported significant improvements when treatment areas using the Global Aesthetic Improvement Scale (GAIS) were globally improved aesthetically one month, six months and twelve months after treatment: a twelve months post-treatment, with 81% of treated subjects showing improved, very improved, or exceptionally improved results in that period, with no top-up treatment performed[17].

MaiLi Volume
MaiLi Volume is an injectable gel intended for the treatment of deep skin depressions and for augmenting the volume of facial tissues. It is also used to correct structural defects such as asymmetry, volume loss, lipoatrophy and contour deformities in the facial area. MaiLi Volume is intended to be administrated via injection into the subcutaneous fat tissue or into the supraperiostic zone by an authorized health professional. Lidocaine is a component within the gel, included to reduce pain resulting from injection during the treatment.

MaiLi Extreme
MaiLi Extreme is an injectable gel intended to restore volume of the face. It is also used to correct structural defects such as asymmetry, volume loss, lipoatrophy and contour deformities in the facial area. MaiLi is intended to be administrated via injection into the subcutaneous fat tissue or into the supraperiostic zone by an authorized health professional. Lidocaine is a component within the gel, included to reduce pain resulting from injection during the treatment.

Description of the investigational devices

Reference	MaiLi Volume®	MaiLi Extreme®
Classification	Class III medical device	Class III medical device
Intended use	• Facial reconstruction of structural defects from congenital or medical origin: volume lost by HIV-associated lipoatrophy	
	• Aesthetic treatment of deep skin depressions at the level of the face and augmentation of the volume of facial tissues.	• Aesthetic treatment of facial volume restoration.
Composition	• Cross-linked hyaluronic acid: 21 mg/mL • Lidocaine hydrochloride monohydrate: 3 mg/mL • Phosphate buffer: q.s. 1 mL	• Cross-linked hyaluronic acid: 24 mg/mL • Lidocaine hydrochloride monohydrate: 3 mg/mL • Phosphate buffer: q.s. 1 mL
Galenic form	Injectable gel in 1-mL pre-filled syringe	

Route and mode of administration/use	Injection into the subcutaneous fat tissue or into the supraperiostic zone, up to 2mL per area
Packaging	Each box contains four graduated pre-filled syringes of MaiLi Volume® / MaiLi Extreme® an instruction leaflet, a set of traceability labels and four single use sterile 27G ½ needles. For each syringe, one label is to give to the subject, the other one is to be added to the subject record.
Preservation and storage	At room temperature (between 2°C and 25°C), away from the light and from the frost.

Legal Manufacturer details
MaiLi Volume and MaiLi Exteme are manufactured by:
KYLANE LABORATOIRES SA
Chemin Pré-Fleuri 1-3
CH-1228 Plan-Les-Ouates
Switzerland

Legal EU Representative details
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2. HYPOTHESIS AND OBJECTIVES

To generate a coherent clinical data set to demonstrate the efficacy and safety of:

- MaiLi Volume as a treatment for the mid-face volume deficit and temporal hollowing
- MaiLi Extreme as a treatment for mid-face volume deficit, jawline ptosis, and chin retrusion

2.1. Primary Objective

Evaluate the proportion of subjects with an improvement (score of 3 and above) at 6 months in the Global Aesthetic Improvement Scale (GAIS) with assessments of:

- MaiLi Volume as a treatment for mid-face volume deficit and temporal hollowing.
- MaiLi Extreme as a treatment for mid-face volume deficit, jawline ptosis and chin retrusion.

as determined by an on-site live independent evaluator.

Evaluate safety through the collection of all adverse events, inclusive of Serious Adverse Events (SAE), unanticipated problems, and Unanticipated Adverse Device Effects (UADE), experienced in the post-treatment follow-up period.

2.2. Secondary Objectives

Evaluate:

- The proportion of subjects with an improvement (score of 3 and above) in Global Aesthetic Improvement Scale (GAIS) assessments of the i) mid-face and ii) jawline and iii) chin area and iv) temple at 3, 12, 18 and 24 months by an on-site live independent evaluator.
- The proportion of subjects with an improvement (score of 3 and above) in Global Aesthetic Improvement Scale (GAIS) assessments of the i) mid-face and ii) jawline iii) chin area and iv) temple at 3, 6, 12, 18 and 24 months by the subject.
- The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the mid-face volume deficit scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.

  or

  The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the scale for the assessment of jawline sagging at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.

  or

  The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the chin retrusion assessment scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.

  or

  The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the temporal hollowing assessment scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.
- Subject and Investigator treatment satisfaction will be assessed by questionnaire.

2.3. Exploratory Objectives

Aesthetic treatment of deep depressions at the level of the face (temporal hollowing) and facial volume and contour restoration in the treatment of mid face volume deficit, jawline ptosis and chin retrusion

3. EXPECTED RISKS AND BENEFITS

The expected benefits for subjects participating in this investigation is the aesthetic improvement by augmentation of the volume of the facial tissues and improvement of the facial contour. The MaiLi Volume/Extreme products are to modify the anatomy and/or to alleviate for a physiological process at the level of the face. The injectable gels are intended for facial reconstruction of structural defects from congenital or medical origin (i.e. volume lost by human immunodeficiency virus (HIV)-associated lipoathrophy). It is also beneficial for aesthetic treatment of deep skin depressions and augmentation of the volume in facial areas such as mid-face, jawline, chin, and temples.

Before the brand name MaiLi was chosen, the products were first identified as Hyalurogel B. Hyalurogel B2 corresponds to MaiLi Volume and Hyalurogel B3 corresponds to MaiLi Extreme (Clinical Evaluation Report, Hyalurogel B, 2020 [18]). Kylane Laboratories launched a clinical pilot study (reference 17E1176, version 1.0 of 27/06/2019) with 50 subjects (among which 30 subjects received MaiLi Volume or MaiLi Extreme). The purpose was to assess the efficacy and safety of all the products within the MaiLi range, including MaiLi Volume or MaiLi Extreme, and perform a comparison of MaiLi Extreme with the comparator Juvéderm VOLUMA (with lidocaine). The pilot study included two MaiLi products and additional treatment areas (e.g. lips and nasolabial folds) that are not part of the current proposed study. The pilot study was approved by the French Health Authority Agence nationale de sécurité du médicament et des produits de santé (ANSM) on 27th December 2017 (under ANSM registration number: A01694-49). The subjects were treated between 7th March 2018 until 9th March 2018 in the site of the Contract Research Organization (CRO) Dermscan (Lyon, France) by four different practitioners. This study was completed in 2019, after 12-month of clinical follow-up and it confirmed the safety and effectiveness of the MaiLi Volume/Extreme devices. Forty-five (45) adverse device effects were reported as related to one of the MaiLi devices. The frequency of the adverse device effects is shown in Table 1. All adverse device effects reported during the pilot clinical study were usual ones for injectable gels of hyaluronic acid and most of them lasted less than 10 days. No Serious Adverse Event (SAE) occurred during the study. Injectors were satisfied to very satisfied (depending on the item and device) of the performance of the MaiLi Volume/Extreme devices during injection. Independent evaluator and subjects reported that treated sites were globally improved aesthetically one month, six months and twelve months after treatment.

Table 1: Frequency Adverse Events

Frequent AE (≥10%)	Less frequent AE (<10%)
• Hardness (induration)/firmness • Lumps/bumps	• Itching (pruritis) • Discoloration (ecchymosis) • Pain • Tenderness • Swelling (oedema) • Bruising (haematoma) • Redness (erythema) • Itching (pruritis) • Difficulty for eating • Difficulty to drink • Faint during injection • Inflammatory reaction

The compliance of the risk analysis and the Instruction for Use (IFU) of MaiLi Volume/Extreme devices (MaiLi Europe IFU-0002[19]) to the State-of-the-Art has been checked. The risks identified by Kylane Laboratories have all been mitigated to an acceptable risk level. For these risks, the benefit/risk ration is considered as acceptable for the use of MaiLi Volume/Extreme to the intended purpose "to modify the anatomy of the face area and/or to alleviate for a physiological process" and to specific intended uses of each device of the range, as long as users are appropriately warned of known limitations and risks associated with these devices.

Furthermore, the benefits of MaiLi Volume/Extreme outweigh the risks, as determined by the robustness of the effectiveness results, the lack of long-term sequelae, and the high subject satisfaction. No new risks have been identified by screening the international and national public databases, and do not need to be taken into consideration in the risk analyses of MaiLi Volume/Extreme products. The risks of short term adverse events outcomes seen after injection and rare adverse events are sufficiently well understood for subjects to make informed decisions about devices use. Moreover, the Instruction for Uses (IFUs) correctly describe the indications of the MaiLi Volume/Extreme devices as supported by sufficient clinical data.

If the subject has ever suffered from herpes infection, the risk of herpes reactivation following dermal filler injection has been reported to about 1.5%[20].

Side effects of MaiLi Volume/Extreme (MaiLi Europe IFU-0002 [19])

Events which are naturally resolve within one week in most cases include:

- Injection-related events and/or inflammatory reactions such as (bleeding, skin redness (erythema), bruising (haematoma), swelling (oedema), and infection which may be associated with local pain or itching (pruritis) occurring after injection)
- Hardness (induration)/lump /granuloma at injection site
- Sensitivity at the injection site
- Skin coloration or discoloration (ecchymosis) at the injection site

Undesirable immediate/ delayed onset effects (non-exhaustive list):

- Immediate or delayed hypersensitivity to hyaluronic acid and/or to lidocaine.
- Nodule, abscesses or granuloma.
- Vascular compromise may occur due to inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable soft tissue filler. This may manifest as blanching, discoloration, necrosis or ulceration at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolization. Isolated rare cases of ischemic events affecting the eye leading to visual loss, and the brain resulting in cerebral infarction, following facial aesthetic treatments have been reported. These rare cases of vascular events are mostly reported in glabella, in and around the nose, in forehead and in periorbital area.
- Infection or reactivation of a previous infection.
- Displacement of the gel.

4. STUDY POPULATION

4.1. List the number and nature of subjects to be enrolled.

A total of 168 subjects (42 per site; a minimum of 36 per site respectively), to meet a completed study size requirement of 140, will be recruited across four sites in Europe. The completed study size requirements for each treatment group are provided in brackets. Male or female subjects between the ages of 25 and 65 years of age inclusively across a range of Fitzpatrick skin types having:

- mild to significant facial volume deficit (mid-face area) (n=60 (50), MaiLi Volume 30 (25) subjects and MaiLi Extreme 30 (25) subjects)

or

- mild to moderate jawline ptosis (n=36 (30), MaiLi Extreme)

or

- minimal to severe chin retrusion (n=36 (30), MaiLi Extreme)

or

- minimal to severe temporal hollowing (n=36 (30), MaiLi Volume)

Subjects can be treated in multiple areas if they meet the required inclusion criteria, but cannot be treated with both MaiLi Volume and Extreme. The lead area the subject will be treated, need to be decided by the investigator for recruitment purposes. For example, if a subject meets the inclusion criteria for treatment for temple hollowing and would like to receive treatment in this area in addition to the mid-face, then the use of MaiLi Volume would allow treatment in both areas. If the lead treatment area is judged by the investigator to be volumization of the mid-face, then for the purposes of recruitment, the subject will be assigned to the mid-face group, even though they are treated in both areas.

4.2. Criteria for Recruitment and Recruitment Process

Potential subjects who visit the clinic for aesthetic procedures will be explained about the study by the investigator for recruitment and informed consent will be taken from the subjects before the study procedures.

4.3. Inclusion Criteria

1. Subjects must be generally healthy and 25-65 years of age at Screening Visit
2. Subjects who have:

   mild to significant volume deficit in the mid-face (score of 2-4 on the designated photographic assessment scale (see section 5))

   or

   mild to moderate jawline ptosis (score of 1-2 on the designated photographic assessment scale (see section 5))

   or

   minimal to severe chin retrusion (score of 1-3 on the designated photographic assessment scale (see section 5))

   or

   minimal to severe temporal hollowing (score if 2-4 on the designated photographic assessment scale (see section 5))
3. Subjects who are willing to provide written informed consent, including approval for facial photographs to be taken.
4. Subjects willing to commit to having no further facial aesthetic treatments (see Table 2) for the duration of the study period, including follow-up.
5. Subjects must be willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions and be likely to complete the study as planned.

6. Female of childbearing potential should use a medically accepted contraceptive regimen since at least 12 weeks prior to study entry and during all the study

4.4. Exclusion Criteria

1 Subjects who, in the twelve months prior to their enrolment assessment had undergone:

a. cosmetic facial plastic surgery (other than rhinoplasty),
b. tissue grafting (e.g., fat injections),
c. tissue lifting implants (e.g., threads, barbs) or other implants,
d. augmentation with any permanent or semi-permanent filler (e.g., silicone, PMMA, PLLA) or temporary filler (e.g., Ha, CaHA, PCL)
e. neuromodulator injections,
f. mesotherapy,
g. resurfacing in the mid-face (e.g., laser, radio frequency, dermabrasion, or chemical peel)

in the region of the face to be treated.

2 Subjects who have received any other facial aesthetic procedures (as described at exclusion criteria 1) at any time during the study period (see Table 2).

Table 2: MaiLi Volume and Extreme – Non-allowable treatments

Subject treatment area	No further aesthetic treatments are allowed in the region of:	Reason
Mid-face	Nasolabial folds	Adjacent to treatment area
	Nose	Effect on facial appearance is too significant
	Tear troughs	Area assessed within mid-face scale
	Prejowl sulcus	Area assessed within mid-face scale
	Nasojugal folds	Area assessed within mid-face scale
Jawline/Jowls	Nose	Effect on facial appearance is too significant
	Pre-jowl sulcus	Adjacent to treatment area
	Marionette lines	Adjacent to treatment area
Chin	Nose	Effect on facial appearance is too significant
	Platysma	Adjacent to treatment area
	Pre-jowl sulcus	Adjacent to treatment area
	Lips	Lips are reference points for chin scoring scale
Temples	Nose	Effect on facial appearance is too significant
	Periorbital lines	Adjacent to the treatment area
	Forehead	Adjacent to the treatment area

3 Subjects currently enrolled in other clinical trials.

4 Subjects with facial hair as this could interfere with study evaluations.

5 Subject who had been deprived of their freedom by administrative or legal decision or who is under guardianship.

6 Subject is an employee of the aesthetic surgery department of the investigational site, the CRO or study sponsor.

7 Pregnant or nursing woman or planning a pregnancy during the study.

8 Subjects taking thrombolytics or anticoagulants.

9 Subjects with bleeding disorders.

10 Subjects with known hypersensitivities to hyaluronic acid, lidocaine. amide local anaesthetics or other components of the treatment.

11 Subjects with a history of severe allergy or anaphylactic shock.

12 Subjects with active (or a history of) autoimmune disease.

13 Subjects with porphyria.

14 Subjects with cutaneous disorders and areas affected by inflammation and/or infectious skin problems (e.g., acne, herpes) at or near the treatment site

15 Subjects with a tendency to form keloids, hypertrophic scars or any other healing disorders

16 Subjects with known history of precancerous lesions/skin malignancies.

17 Subjects must avoid receiving COVID-19 vaccination for the 14 days before and following injection.

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

The study is a 24-month, open-label, prospective, post-market clinical follow-up trial, conducted in compliance with ISO 14155:2020, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) principles. The trial will be approved by the ethical committee of the participating sites and complied with local regulatory authority requirements. Following the guidelines of the European Standard for Aesthetic medicine services-non-surgical medical treatments, which lists the allowed aesthetic procedures, premises, and training requirements to conduct aesthetic procedures for doctors.

Potential subjects who visit the clinic for aesthetic procedures will be explained about the study by the investigators for recruitment and informed consent will be taken from the subjects before the study procedures.

Potential subjects will first be registered at the clinic. The investigator will explain the study to the subjects, including details of the treatment procedure and the associated benefits and risks. The subjects will be given time to read the consent form and clarify any questions they have about the study with the investigator. The subject should be informed of the product's indications, contraindications, precautions, warnings, expected results, and potential adverse events and questioned on her/his medical history. In addition, the subject must be given the option to indicate whether he/she would like to remain unidentifiable in the photographs (through the use of a black box) and whether the photographs may be used for publication and promotion of the medical devices.

If the subject is agreeable to take part in the study, appropriate informed consent will be taken in the clinic followed by physical examination and taking of medical history to ensure that the subject is eligible for the study. Moreover, if the subject is a childbearing woman, the subject will have to take a pregnancy test. A repeat pregnancy test must be done if the subject misses periods of menstrual cycle or becomes irregular. No additional visits or test are needed for screening of the subject. Recruited subjects will be given a subject identification for the study. A separate file that links the subject identification to the subject's identifiable information will be stored in a secure place that is only accessible to the study's team members.

There is a possibility that the screening and enrolment of the subject(s) happens separately from the administration of the treatment. In that case, a screening visit will take place where the subject will be screened and, if he/she meets the criteria, enrolled. Thereafter, a separate treatment visit will take place where the subject will receive the treatment according to the procedure described below.

The investigator will do a screening assessment of the subject using the photographic assessment scales (explained in Tables 2-6) to determine if the subject is eligible for the study. For the photographic assessment scales (see Tables 3-6), references are included that refer to publications containing photographs associated with the graduation of severity of specific condition.

The investigator will take photographs of all subjects at the screening visit for use in the

Global Aesthetic Improvement Score (GAIS) assessment.

These photographic assessment scales are validated reference scales with photographs that classify the severity of respectively, mid-face volume deficit, jawline ptosis, chin retrusion, and temple hollowing. Therefore, it enables a valid and reproducible assessment of facial volume deficit.

The written description of the different grades and severity of the validated reference scales are shown below:

Table 3: Global Aesthetic Improvement Scale (GAIS)

Grade	Severity	Definition
1	Worse	The appearance is worse than the original condition
2	No change	The appearance is essentially the same as the original condition
3	Improved	Improvement in appearance from the initial condition but re-treatment is indicated
4	Much improved	Marked improvement in appearance but not completely optimal
5	Very much improved	Excellent corrective results

Table 4: Assessment Scale for Mid-face volume deficit (see appendix 1[21])

Grade	Severity	Definition
0	None	• Moon face; • Fullness (convexity) in the zygomaticomalar region, anteromedial cheek, and/or submalar region
1	Minimal	Flattening in the zygomaticomalar region, anteromedial cheek, and/or submalar region
2	Mild	• Mild concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region; • Mild tear troughs and/or nasolabial folds
3	Moderate	• Moderate concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region; • Moderate tear troughs and/or nasolabial folds; • Mild nasojugal folds and/or pre-jowl sulcus; • Mild prominence of bony landmarks; • Mild visibility of musculature
4	Significant	• Significant concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region; • Significant tear troughs and/or nasolabial folds; • Moderate nasojugal folds and/or prejowl sulcus; • Moderate prominence of bony landmarks; • Moderate visibility of musculature
5	Severe	• Wasting; • Severe concavity in the zygomaticomalar region,

		anteromedial cheek, and/or submalar region; • Severe tear troughs and/or nasolabial folds; • Significant nasojugal folds and/or prejowl sulcus; • Significant prominence of bony landmarks; • Significant visibility of underlying musculature

Table 5: Assessment Scale for ptosis of Jawline (see appendix 2[22])

Grade	Severity	Definition
0	None	Continuous jawline contour, no loss of jawline volume
1	Mild	Mild loss of jawline contour and continuity, mild loss of volume in post-jowl region, loss of volume in pre-jowl region may be present.
2	Moderate	Moderate loss of jawline contour and continuity, moderate loss of volume in post-jowl region, loss of volume in pre-jowl may be present.
3	Severe	Severe loss of jawline contour and continuity, severe loss of volume in post-jowl region, loss of volume in pre-jowl region may be present
4	Extreme	Extreme disruption of jawline contour, extreme post-jowl and pre-jowl volume loss

Table 6: Assessment Scale for Chin retrusion (see appendix 3[23])

Grade	Severity	Definition
0	None	No chin retrusion; chin midpoint at or in front of the lower vermilion border vertical line
1	Minimal	Minimal chin retrusion; chin midpoint is between the labiomental sulcus vertical line and lower vermilion border vertical line
2	Moderate	Moderate chin retrusion; chin midpoint is at labiomental sulcus vertical line
3	Severe	Severe chin retrusion; chin midpoint slightly behind labiomental sulcus vertical line
4	Extreme	Extreme chin retrusion; chin midpoint significantly behind labiomental sulcus vertical line

Table 7: Assessment Scale for Temporal hollowing (see appendix 4[24])

Grade	Severity	Definition
0	Convex	Rounded temple
1	Flat	Flat temple; temporal fusion line may be visible
2	Minimal	Shallow depression or concavity with minimal volume loss; temporal fusion line may be visible
3	Moderate	Moderate depression or concavity with moderate volume loss; moderate prominence of the temporal fusion line

4	Severe	Deeply recessed, sunken appearance, marked prominence of temporal fusion line and zygomatic arch

Subjects and investigator will also be given a questionnaire (see appendix 5) to assess the appearance of their mid-face volume deficit, jawline ptosis, chin retrusion, or temple hollowing before the treatment.

The investigator will then proceed to thoroughly disinfect the treatment area with an appropriate antiseptic solution (e.g. chlorhexidine digluconate (CHX) solution). The investigator will ensure:

- The correct product (MaiLi Volume or MaiLi Extreme);
- The correct subject (double identifiers i.e. full name, date of birth and/or medical identification (ID) number) and
- Correct indication (into the subcutaneous layer and supraperiostic zone of the mid-face)

before the procedure.

The investigator will assemble the MaiLi Volume or MaiLi Extreme syringe and the appropriate needle (27G ½). Depending on the treatment site, the depth of injection, and gel quantity to be injected, the investigator will decide the injection technique to be used for the treatment. The investigator will begin to slowly inject MaiLi Volume or MaiLi Extreme on the subcutaneous fat tissue or into the supraperiosteal zone of the subject's facial treatment area. It is recommended to use the technique of linear threading injection, multipoint injection, or a combination of both techniques. Then, the treated area will be massaged by the investigator to ensure the uniform distribution of the gel.

Investigator will be given a questionnaire (see appendix 6) to assess their satisfaction of using the MaiLi Volume or Extreme product during the treatment procedure.

The content of the syringe is sterile until opening. The external surface of the syringe is not sterile and should not be used in a controlled environment such as an operation room. If needed, the surface of the syringe must be cleaned up in respect of the aseptic techniques in place.

Once the treatment is done, a safety assessment will be conducted and the investigator will do another photographic assessment of the subject. The investigator will complete the electronic case report form (eCRF) of the subject before giving instructions for the next follow-up appointment. The subject will be given a diary card to bring home and record any adverse reactions they experience. The subject will then bring back the diary card on their first follow-up appointment 2 weeks after the treatment. The diary card will be reviewed and documented down by the investigator.
For the subsequent follow-up visits (i.e. 3 months, 6 months, 12 months, 18 months, and 24 months after the treatment), the subject will be given a questionnaire to assess their overall satisfaction with the results of their treatment (see appendix 5).

During the study, two independent evaluators will be involved:

- An on site live independent evaluator (I) (one for each site (4)) will be responsible for

conducting the live Global Aesthetic Improvement Scale (GAIS) assessment during the subject's scheduled visits at 3, 6, 12, 18, and 24 months (see appendix 7). This assessment will be done in comparison to the face of the subject (at the time of the visit) and the 'full face' photograph taken at the baseline visit.

- A blinded independent evaluator (II) (one per country (2)) will be responsible for the remote assessment of the photographs using the different aesthetic grading scales (namely: Allergan Mid-Face Volume Deficit Scale, Merz Aesthetics scale for Jawline, Allergan Chin Retrusion Scale, and/or Allergan Temple Hollowing Scale). This evaluator will do the assessment of the photographs of all performed visits at month 6 (to generate the data for the interim 6 months report) and 24 (for the final report) of the follow-up period.

Photographs will be taken at each visit, and assessed by a blinded independent evaluator at 6 months and 24 months.

All data collected for the study will be kept in a secure place and is only accessible to the study's team members.

MaiLi Volume or MaiLi Extreme may be administered only by an authorized physician in accordance with local legislation. These devices are designed to be injected into the subcutaneous fat tissue or the supraperiostic zone by a physician who has been specifically trained in injection techniques for dermal filler procedures. The physician's technical competence is crucial to the success of the treatment. All injections carry a risk of infection, aseptic techniques and standard practices should be employed to avoid contamination and infection. Deep knowledge of the anatomy of the area to be treated is essential and shall be used to perform similar interventions (i.e. cross-linked hyaluronic acid injection in the face area) in order to avoid perforation or compression of vessels, nerves, and other more fragile structures. Use of the supplied needle is recommended. The design, diameter, and length have been validated for optimum use with the injection. The usage of another needle could not ensure the correct fitting to the syringe and/or the correct delivery of the product

If the subject has an herpes zoster episode in the treatment area at the time of study visit, the subject can miss the visit (or attend for a safety assessment without an efficacy assessment/photographs) and attend the next study visit when the herpes has resolved.

In some cases of (serious) adverse events ((S)AE) related to the study product in one or more treatment areas, hyaluronidase might need to be injected into the treated facial area(s) to degrade the study product and contribute to manage the adverse event. Hyaluronidase has to be available on site. After, The (S)AE must be reported in accordance with the (S)AE guidelines. Hyaluronidase must be immediately available at each study site for rapid use if needed. The study investigator must be familiar with the guidelines for the appropriate use of hyaluronidase effectively for the effective management of the adverse event if required. A guidance document on the use of hyaluronidase in aesthetic practice is provided in appendix 8. After, The (S)AE must be reported in accordance with the (S)AE guidelines.

In case the subject is unsatisfied with the treatment, he/she will fill in a complaint form. This filled form will be sent to the Vigilance team for further assessment (for further information, see section 6.2.4.3.)

CONTRAINDICATIONS/WARNINGS:

- Do not inject subjects having known risk of hypersensitivity to hyaluronic acid or lidocaine or amide local anaesthetics.
- Do not inject subject having history of severe allergy or anaphylactic shock.
- Do not inject subjects suffering from autoimmune disease.
- Do not inject subjects suffering from porphyria.
- Do not inject subjects having cutaneous disorders, inflammation or infection (herpes, acne, etc.) at the treatment site or nearby.
- Do not inject subjects for whom the medical history shows a sensitivity that could lead to a reaction to the treatment.
- Do not use in subjects with bleeding disorders or in subjects who are undergoing treatment with thrombolytics or anticoagulants.
- Do not inject subjects with a tendency to form keloids, hypertrophic scars or any other healing disorders.
- Warn subjects who have a medical history of herpes zoster of the potential risk of reactivation before deciding to participate in the study.
- Do not use during pregnancy or breast-feeding.
- Do not use for children.
- Do not inject into blood vessels (intra-vascular) or directly near blood vessels (for avoiding vessels compression). An unintended intravascular administration can cause high blood concentration and acute central nervous system and cardiovascular toxic symptoms.
- Do not inject in area other than the face (e.g. hands, body).
- Do not inject MaiLi Volume/Extreme in the periorbital area (eyelids, palpebromalar groove, crow's feet) and glabellar region.
- The injection of MaiLi Volume/Extreme into the subcutaneous fat tissue or into the supraperiostic zone is reserved to specialists specifically trained in these injection techniques.
- Do not inject intramuscularly. There is no available clinical data about injection of MaiLi Volume/Extreme into an area which has already been treated with another brand of resorbing product. It is therefore recommended not to inject in areas in which another brand of resorbing
- product is not still fully resorbed.
- Do not inject jointly with another brand of resorbing product in the same area.
- Do not inject jointly with a permanent product.
- Do not mix with other products.
- Do not re-sterilise the product (the syringe and/or the needle).
- Do not inject more than 20 mL per year per subject.
- Do not inject more than 2 mL per treatment area during each session.
- Do not overcorrect.
- Do not use after expiry date or if the packaging is damaged or the syringe opened.
- Do not re-use (risk of contamination). The product is intended for single use only.

- Do not use a syringe for several subjects (risk of cross-contamination).
- Do not used simultaneously with chemical peels, dermabrasion, laser treatment or radiofrequency treatment.
- Treatment with MaiLi Volume or MaiLi Extreme in combination with drugs and other devices has not been clinically evaluated.
- The investigator should exercise special caution when treating areas in close proximity to vulnerable structures such as vessels and nerves.
- Warn the subject to avoid exposure to the sun, UV rays, and temperatures below 0 °C, sauna, or hammam sessions during the two weeks following the injection procedure.
- Warn the subject not to use cosmetic products (e.g. makeup, skincare products) during the twelve hours following the injection treatment.
- Warn the subject to avoid applying intense pressure or massaging the treatment site for a few days following the injection.
- Warn the subject who are on medication that affects platelet functions (aspirin or non-inflammatory drugs) of the potential increased risks of haematomas and bleeding during the injection.
- The investigator should consider that the product contains lidocaine, at a concentration identical to that in the majority of HA products containing lidocaine. For normal healthy adults, the maximum total dose of lidocaine should not exceed 200 mg per session. When using concurrently (case of topical administration), the total administered dose of lidocaine should be considered. The concomitant use of other local anaesthetic agents should also be considered since the systemic toxic effects may be additive. Care should be taken for subjects with congenital methaemoglobinemia and subjects who are receiving concomitant treatment with methaemoglobin-inducing agents. In the case of athletes, the presence of lidocaine may produce a positive result in anti-doping tests.

5.1. Study Assessments of Efficacy and Safety

Table 8: Schedule of assessment & study timepoints

	Baseline visit	2 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Informed consent	X						
Inclusion/Exclusion criteria	X						
Medical history	X						
Physical examination	X						
Pregnancy test	X						
Prior/Concomitant medications/Treatments	X						
Facial photography (full face, 45° angle left and right, 90° angle left and right)	X		X	X	X	X	X
Photographic assessment[1] by blinded independent evaluator (II)				X			X
Global Aesthetic Improvement Scale (GAIS)[2] by the subject			X	X	X	X	X
Global Aesthetic Improvement Scale (GAIS) by on-site live independent evaluator (I)			X	X	X	X	X
Subject self-assessment for overall satisfaction	X		X	X	X	X	X
Investigator self-assessment for injection satisfaction	X						
Subject diary	X	X	X	X	X	X	X
Administer study treatment[3]	X						
Safety assessment: Identify and Record AEs		X	X	X	X	X	X

[1] The volume deficit is assessed using different aesthetic grading scales corresponding to the area of the face: the Mid-Face Volume Deficit Scale (see Table 4) is a 6 point photon numeral rating for classifying the severity mid-face volume deficit; the Jawline scale (see Table 5) is a 5 point photon numeral rating scale for classifying the severity of jawline ptosis; the Chin Retrusion Scale (see Table 6) is a 5 point photon numeral rating scale for classifying the severity of chin retrusion; the Temple Hollowing Scale (see Table 7) is a 5 point photon numeral rating scale for classifying the severity of temple hollowing.
[2] The Global Aesthetic Improvement Scale (GAIS) is a 5-point scale rating global aesthetic improvement in appearance, compared to pretreatment, The rating categories are classified as very much improved (1), much improved (2), slightly improved (3), no change (4), or worsened (5).
[3] The administration of the study treatment, handover of the subject diary, and subject self-assessment for overall satisfaction could be done on a different date than the baseline/screening.

5.1.1. Day 1 – Baseline visit (incl. treatment administration)

During the screening/baseline visit, the following actions will be taken:

- Signing the Informed consent form.
- When signing the Informed Consent Form (ICF), the subject will be given the option to apply a black box over the eyes on the photographs that will be taken (if the independent evaluator will not be hindered to evaluate the treatment area(s) such as cheekbones and mid-face). In addition, the subject will be given the option to give consent to the use of the photos for the promotion of the study products.
- Screening according the inclusion and exclusion criteria.
- Analysing medical history.
- Physical examination: measuring the vital parameters (e.g. blood pressure, weight and height).
- Analysing prior or concomitant medications and/or treatments.
- A urine pregnancy test will be performed on potential childbearing women.
- Photographing the face at different angles (i.e., full face, 45°, and 90°).
- Subject will be given a questionnaire to indicate their overall satisfaction with the appearance of the area(s) of the face that will be treated (see appendix 5).
- Investigator will fill in the injection satisfaction questionnaire (see appendix 6).
- Treating the subject. The study doctor will inject one of the dermal fillers (MaiLi Volume or MaiLi Extreme) into the specific area(s) of the face. Which dermal filler you receive will depend on the area(s) of the face to be treated.
- Subject will be given a blank diary for the next period (Day 1 – Week 2).

5.1.2. Week 2 – Safety Assessment Visit

- A safety assessment is performed including the recording of any adverse events.
- Subject will return the completed subject diary (Day 1 – Week 2) and will be given a blank diary for the next period (Week 2 till Month 24).

5.1.3. Month 3 till Month 24 Visits

In the period from month 3 to month 24 of the study, the following actions will be carried out:

On month 3, 12 and 18:

- Photographing the face at different angles (i.e., full face, 45°, 90°). A black box will be placed over the eyes in the photograph if the subject has ticked this option when signing the Informed consent form.
- Subject will be given a questionnaire to indicate their overall satisfaction with the appearance of the treated area(s) of the face (see appendix 5).
- If the subject has completely filled in the subject diary or has lost it, he/she will receive another blank diary (Week 2 to Month 24).
- Subject and independent evaluator (I) will do a live assessment using the GAIS scale and the 'full face' photograph taken at the baseline visit (see appendix 7).
- A safety assessment is performed including the recording of any adverse events.

On month 6 and month 24:

- The same actions taken at the above timepoints.
- An assessment of the photographs will be made of any improvement in the face using appropriate assessment scale for the treated area(s), by a blinded independent evaluator (II) (here: blinding means that the evaluator does not know at what time in the study period the photograph were taken).

5.1.5. End of Study (EoS)/ Premature Discontinuation Visit

- The subjects will come to the Investigator's office.
- They will bring back their completed subject diary.
- Collection of the eventual adverse events and concomitant treatments.

5.1.6. Unscheduled/ Rescue treatment Visit

Subjects should receive prompt medical attention. Evaluation by an appropriate medical practitioner specialist could be necessary in case of an intravascular injection that should occur. In case of adverse device effect affecting subject well-being, the investigator is authorized to prescribe to the subject a rescue treatment. The adverse event (AE) will be recorded in the subject's electronic Case Report Form (eCRF) and source document, including details on rescue medication.

6 SAFETY MEASUREMENTS

6.1. Definitions

6.1.1. Investigational Medical Device

An investigational medical device that is being assessed in a clinical investigation. This definition includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials, and/or design changes. In this protocol, the terms "investigational medical device" and "investigational device" are used interchangeably.

6.1.2. Adverse event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated

- Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.
- Note 2 to entry: This definition includes events related to the procedures involved.
- Notes 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

6.1.3. Adverse device effect (ADE)

An ADE is defined as an adverse event related to the use of an investigational medical device.

- Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
- Note 3 to entry: This includes comparator if the comparator is a medical device.

6.1.4. Serious adverse event (SAE)

A SAE that led to any of the following:

- Death
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - Life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function including chronic diseases, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a function,
- Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment.

NOTE 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

6.1.5. Serious ADE (SADE)

A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event

6.1.6. Unanticipated serious adverse device effect (USADE)

An USADE is defined as:

- Any serious adverse effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

6.1.7. Anticipated serious adverse device effect (ASADE)

An ASADE is defined as:

- An effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.

6.1.8. Common treatment site responses (CTRs)

CTRs are common clinical presentations and/or side effects that a study subject may experience following treatment. Subjects will self-report CTRs, as defined a priori in the protocol, on diary cards provided to them. The treating investigator will review and initial the diary and determine if any entries should be reported as
AEs. A CTR that is more severe than what is generally expected and/or is not resolving should also be evaluated by the investigator as a possible AE, SAE, ADE, SADE, and/or UADE.

6.1.9. Device deficiency

A device deficiency is defined as any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

- Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
- Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.

6.1.10. Malfunction

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 CIP, or IB.

6.2. Reportable events

Only Serious Adverse Events (SAEs) where a causal relationship between the serious adverse event and the preceding investigational procedure has been established are considered reportable events.

6.2.1. Causality assessment

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan (CIP) or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential

risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The above considerations apply also to the serious adverse events occurring in the comparison group.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

1. Not related: Relationship to the device, comparator or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis9, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

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

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting not be delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

6.2.2. Reporting timelines to Competent Authorities by sponsor

For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

Any other reportable event or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

6.2.3. Report to whom

Reportable events must be reported all at the same time to all national competent authorities where the clinical investigation is authorized to start or has commenced.

6.3 Procedures for reporting specific events

6.3.1 Adverse event (AE) and adverse device effect (ADE)

Subjects will be carefully monitored during the clinical investigation for possible AEs and ADEs. The period of observation for AEs and ADEs extends from signing of the Informed Consent Form (ICF) until the subject's last visit. Any medical occurrence between the time the ICF is signed and the first treatment with the investigational medical device is classified as an AE or ADE and must be documented in the subject's file and in the eCRF. New AEs or ADEs reported to the investigator during the observational period (i.e., after the start of treatment with the investigational medical device) must also be documented, treated, and followed.

Any AE, ADE, and/or device deficiency observed during study conduct will be fully investigated, documented, and followed until the event is either resolved, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up.

The investigator will assess and record any AE or ADE in detail in the subject's file (medical record) and in the eCRF AE report form. The information will be passed on to the sponsor/CRO where the assessment of AE would be done.

All details should be reported by the investigator to Sinclair Vigilance team (quality@sinclairpharma.com) and **AESCULAPE CRO Clinical Safety Management (safety@aesculape.com).**

6.3.1.1. Determining severity/intensity

The investigator is required to grade the severity/intensity of each AE. The clinical severity/intensity of an AE will be classified as follows:

- Mild: Signs and symptoms that can be tolerated easily. Symptoms can be ignored and disappear when the subject is distracted.
- Moderate: Signs and symptoms that cause discomfort and interfere with normal functioning but are tolerable. They cannot be ignored and do not disappear when the subject is distracted.
- Severe: Signs and symptoms that affect usual daily activities and incapacitate the subject, thereby interrupting his/her daily activities.

The definitions above are difficult to apply for some data (e.g. clinically relevant laboratory values that are documented and evaluated on the eCRF AE report form). In such situations, the investigator should exercise medical and scientific judgment.

6.3.1.2. Determining outcome

The reportable outcomes and/or sequelae of an AE may include the following:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

NOTE: If a subject experiences more than one AE, only the AE leading to death will be attributed with a “fatal” outcome.

6.3.2 Serious adverse event (SAE) and serious adverse device effect (SADE)

The investigator must report all SAEs/SADEs, irrespective of severity, that occur during the observational period within 72 hours to quality@sinclairpharma.com and safety@aesculape.com whether they are considered related or not related to the investigational device.

The following information should be provided:

- Status (new reportable event, update, unchanged)
- Investigator/investigational site name/country
- Subject ID/age/gender

- Event description
- Event classification (seriousness)
- Date of onset
- Investigational device name/date of implantation
- Investigational device location
- Causality or relationship of investigational device
- Action/treatment/outcome

When the sponsor first receives notice of the SAE/SADE, the sponsor will conduct an assessment of the SAE/SADE and, if applicable, report the results of such evaluation to regulatory agencies, IECs/IRBs, and investigators.

Follow-up SAE/SADE reports should be sent without delay to the sponsor or designee as an SAE form (marked as a "follow-up" report). The SAE/SADE must be followed until the SAE/SADE is resolved/recovered or a plausible explanation is available.

In the case of a reportable death, the investigator shall make every effort to obtain a copy of the autopsy report and/or death certificate. The investigator will be required to review any post-mortem findings, including histopathology, and provide a synopsis of all pertinent findings by updating the SAE form.

SAEs/SADEs occurring after the end of the observational period will need to be reported if the investigator considers the event to be related to the investigational medical device. These reports generally will not be entered into the investigation database. Following the database lock for the study, all ongoing SAEs/SADEs will be followed until resolution or stabilization under the responsibility of the investigator per his/her standard of care.

Note that in case of pregnancy, an SAE will be completed and sent within 72 hours to Sinclair Vigilance team (quality@sinclairpharma.com) and Aesculape CRO Clinical Safety Management (safety@aesculape.com).

6.3.3 Technical device complaints

For device deficiencies or device malfunctions, the investigator will attempt to evaluate if the deficiency or malfunction might have led to an AE if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate. Complaints are defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, or performance of a medical device.

- A Device Technical Complaint form must be completed and submitted by the investigative site, irrespective of the seriousness of the case.
- A Device Technical Complaint form must be completed and submitted by the investigative site, irrespective of whether the complaint led to an AE.
- If a technical complaint is associated with an SAE, the investigative site must also

complete and submit an SAE form (see Section 6.2.4.2) in addition to the Device Technical Complaint form. SAE forms for device clinical trials should be sent to the sponsor for processing (as defined in Section 6.2.5).

Any technical complaints should be reported to the sponsor. The investigator will complete the Device Technical Complaint form and send it within 72 hours to Sinclair Vigilance team (quality@sinclairpharma.com) and Aesculape CRO for processing (kyara.wullaert@aesculape.com).

If further sample analysis is requested, medical devices will need to be returned to the manufacturer:

Kylane Laboratories SA:
Chemin Pré-Fleuri 1-3, CH-1228 Plan-Les-Ouates, Switzerland

6.4 Safety Monitoring Plan

Subject's wellbeing and safety will be continuously taken into consideration during the trial period. If there is any contraindication observed during the interim of the study procedure that requires the discontinuation of the procedure, a decision should be made by the principal investigator (PI) and co- investigators to discontinue the subject from the study.

7 DATA ANALYSIS

7.1. Data Quality Assurance

7.1.1. Standardization procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, centralized evaluations, and validation methods).

This study will be monitored regularly by a qualified monitor from the sponsor or its designee according to Good Clinical Practice (GCP) guidelines, ISO 14155:2020 and the respective Standard Operating Procedures (SOPs).

7.1.2. Data management

The investigator will prepare and maintain complete and accurate electronic Case Report Forms (eCRFs), recording all observations and data pertinent to the study for each subject. Data reported on eCRFs should be derived from source documents and must be consistent with the sources from which it derive. Investigators will sign and date the eCRFs as appropriate to verify the accuracy of the reported data. It is the responsibility of the investigator to ensure that all data are submitted to the sponsor in a timely manner.

7.1.3. Data review and clarification procedures

All data required by this clinical study protocol are to be entered into a validated database. Individual subject data are to be recorded in eCRFs within five days of each study visit.

By signing and dating the eCRFs, the investigator is confirming that all data entered were reviewed accurate and correct.

If corrections in the subject diary or questionnaires are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date and initial the correction. The investigator should not make any changes to these documents

Essential documents should be retained per applicable regulations and as instructed by the study sponsor. Essential documents at the investigational site include, but are not limited to:

- Subject files
- Subject identification code list
- A copy of the study protocol and any amendments
- Investigator’s copies of the eCRFs and any associated subject-related source data
- Signed Informed Consent Forms (ICFs)

- Copies of all direct correspondence with the Independent Ethics. Committee/Institutional Review Board (IEC/IRB) and with the regulatory authority(ies), and with the sponsor
- Copies of any photographs
- Copies of investigational device disposition records

Study documents may not be destroyed by study-site personnel prior to the end of the required retention period as specified by local regulations. The principal investigator (PI) or the institution must inform the sponsor in due time if the PI leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

7.1.4. Study auditing

To ensure compliance with applicable standards and regulations, the sponsor, or sponsor's designee, IEC/IRB, or regulatory authorities may conduct a quality assurance assessment or audit of site records at any time during or after completion of the study. In the event of an audit, investigators must grant access to all relevant documents (including source documents, electronic records, and other applicable study documentation) and always provide support for auditing activities.

7.2. Data Entry and Storage

All data shall be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs shall be completed as soon as possible during (based on source documents) or after the subject's visit. The subject's identity must always remain confidential (i.e. the name and address of the subjects must not be registered in the eCRFs or in the study database). The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the investigator will indicate this in the eCRF. The investigator shall electronically sign off on the study data. By signing, the investigator takes responsibility for the accuracy, completeness, and legibility of the data reported to the Sponsor in the eCRF.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

The study population will include all subjects who are enrolled, and the entire study population will be included in statistical analysis.

Average Efficacy=85%
Lower bound of 95% Confidence Interval (CI) =65%
Clinical Margin=-20%
Alpha=5%
Power= 80% (Beta =0.20)

Considering 20% dropout rate, a total of 168 subjects (42 per site; a minimum of 36 per site respectively), to meet a completed study size requirement of 140, will be recruited.

- Mild to significant facial volume deficit (mid-face area) (n=60 (50), MaiLi Volume 30 (25) subjects and MaiLi Extreme 30 (25) subjects)
- Mild to moderate jawline ptosis (n=36 (30), MaiLi Extreme)
- Minimal to severe chin retrusion (n=36 (30), MaiLi Extreme)
- Minimal to severe temporal hollowing (n=36 (30), MaiLi Volume)

8.2. Statistical and Analytical Plans

Primary objective
Evaluate the proportion of subjects with an improvement (score of 3 and above) at 6 months in the Global Aesthetic Improvement Scale (GAIS) with assessments of:

- MaiLi Volume as a treatment for mid-face volume deficit and temporal hollowing.
- MaiLi Extreme as a treatment for mid-face volume deficit, jawline ptosis and chin retrusion.

as determined by an on-site live independent evaluator.

Evaluate safety through the collection of all adverse events, inclusive of Serious Adverse Events (SAE), unanticipated problems, and Unanticipated Adverse Device Effects (UADE), experienced in the post-treatment follow-up period.

Secondary objective

Evaluate:

- The proportion of subjects with an improvement (score of 3 and above) in Global Aesthetic Improvement Scale (GAIS) assessments of the i) mid-face and ii) jawline and iii) chin area and iv) temple at 3, 12, 18 and 24 months by an on-site live independent evaluator.
- The proportion of subjects with an improvement (score of 3 and above) in Global Aesthetic Improvement Scale (GAIS) assessments of the i) mid-face and ii) jawline iii) chin area and iv) temple at 3, 6, 12, 18 and 24 months by the subject.
- The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the mid-face volume deficit scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.

or

The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the scale for the assessment of jawline sagging at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.

or

The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the chin retrusion assessment scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.

or

The proportion of subjects exhibiting an improvement of ≥ 1 point from baseline on the temporal hollowing assessment scale at 3, 6, 12, 18 and 24 months as rated by a blinded independent evaluator.

- Subject and Investigator treatment satisfaction will be assessed by questionnaire.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/institution will permit direct access to source data/documents for study related monitoring, audits, Ethical Committee (EC) review, and regulatory inspections. Subjects providing informed consent agree to allow Sponsor or designee access and copying rights to pertinent information in their medical records concerning their participation in this study. The investigator will obtain, as part of the informed consent, permission for study monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Quality control

On-site monitoring of the study will be arranged by or on behalf of the Sponsor according to Good Clinical Practice (GCP) guidelines and ISO 14155:2020 to verify that the rights and well-being of the subjects are protected, the reported data is accurate, complete, verifiable from source documents, and that the conduct of the study complies with the approved clinical investigational plan (CIP), subsequent amendment(s), ISO 14155:2020, GCP and the applicable regulatory requirements.

Any CIP deviation shall be reported, verified, discussed, and collected by the monitor and appropriate actions will be taken. The principal investigator (PI) is responsible for promptly reporting any deviations from the CIP that affects the rights, safety, or well-being of the subject or the scientific integrity of the study, including those which occur under emergency circumstances, to the sponsor as well as the Independent Ethics (IEC) if required by national regulations. Deviations will be reviewed to determine the need to amend the CIP, implement corrective actions or to terminate the study. Handling of CIP deviations will be performed as described in the monitoring manual.

10.2. Quality assurance

The study site may be subject to quality assurance audit by or on behalf of the sponsor as well as inspection by appropriate Regulatory Authorities (RA). It is important that the principal investigator (PI) and other relevant study site personnel are available during the monitoring visits, possible audits, and inspections, and that sufficient time is devoted to the monitoring process.

Each participating member of the study site team shall provide a curriculum vitae (CV) or equivalent that demonstrates their qualifications to conduct the study. The CV shall give name, role, and place of work, and shall show the training, appointments and, for the PI, any other information that will confirm the suitability of the PI to be responsible for the study.

It is the responsibility of the PI to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed. All Investigators and other responsible persons shall be listed together with their function in the study on the signature and delegation log.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice (GCP), ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice, and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Ethical Committee (EC), prior to enrolment of any subject into the study.

The principal investigator is responsible for informing the EC of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

Written informed consent must be obtained from every subject or his/her legal representative prior to the initiation of any screening or study specific procedures. The investigator will follow a standard process for obtaining consent that complies with all applicable regulatory requirements. If applicable, a certified translation of the informed consent form (ICF) into the relevant local language will be provided. The original and any amended, signed and dated ICF must be retained at the study site; and a copy must be given to the subject.

It is not anticipated that members of a vulnerable population will participate in this study. If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the Independent Ethics Committee/Institutional Review Board (IEC/IRB) and use of the amended form (including for ongoing subjects).

During the study, the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study. In the case of Adverse Events (AEs), the subject should inform the investigator, who then will make a judgment whether continuing in the study serves the subject's best interest. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

Each ICF will include contact information (with phone number) the subject should use to communicate any medical concerns 24 hours a day.

11.2. Confidentiality of Data and Subject Records

Subject anonymity is to be maintained during the study. Subjects will be identified by an assigned number on all study documentation. Documents that identify the subject must be maintained in strict confidence by the investigator to the extent permitted by applicable laws and regulations,

unless their disclosure is necessary to allow auditing/inspection by regulatory authorities, the sponsor, or the sponsor's designee.

Subject medical information obtained during the study is confidential. At a subject's request, the subject's medical information may be provided to the subject's personal physician or other appropriate medical personnel. Disclosure of subject medical information to third parties other than those noted above is not permitted.

12. PUBLICATIONS

The study protocol, study data, and information related to the study or the sponsor's products, or research programs are to be kept confidential and may not be disclosed without the consent of the sponsor. The investigators have the responsibility to provide complete study data, records, and reports for inspection by the appropriate regulatory authorities, the sponsor, or the Independent Ethics. Committee/Institutional Review Board (IEC/IRB), as appropriate.

The investigator agrees that the results of this study may be used for submission to national or international registration and supervising authorities. The sponsor may disclose the information obtained during the study to regulatory authorities or other personnel as required. If necessary, the sponsor may disclose the names, contact information, and qualifications of all Investigators as well as their roles in the study. Upon completion of the study, publication or disclosure of the study results will be at the discretion and approval of the sponsor.

13. RETENTION OF STUDY DOCUMENTS

Upon closure of the study, the investigator must maintain all study-site records in a safe and secure location. The investigator is responsible for the integrity, retention, and security of all study-related records. The investigator must ensure that any reproductions of the original records are legible and provide a true and accurate copy of the original. Accurate, complete, and current records must be stored in such a way as to permit easy and timely retrieval for the sponsor or any applicable regulatory authorities.

The sponsor will inform the investigator of the time for retaining these records to comply with all applicable regulatory requirements, with the minimum retention time being the longest of those times dictated by institutional requirements, local laws or regulations, or the sponsor's standard procedures. The investigator must notify the sponsor in the event of any changes to archival arrangements due to withdrawal of the investigator's responsibility for keeping study records to ensure that suitable arrangements for the retention of study records are made.

14. FUNDING AND INSURANCE

The sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of the insurance will be kept in the study files.

PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of Institutional Review Board (IRB)-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

REFERENCES

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APPENDICES

Appendix 1

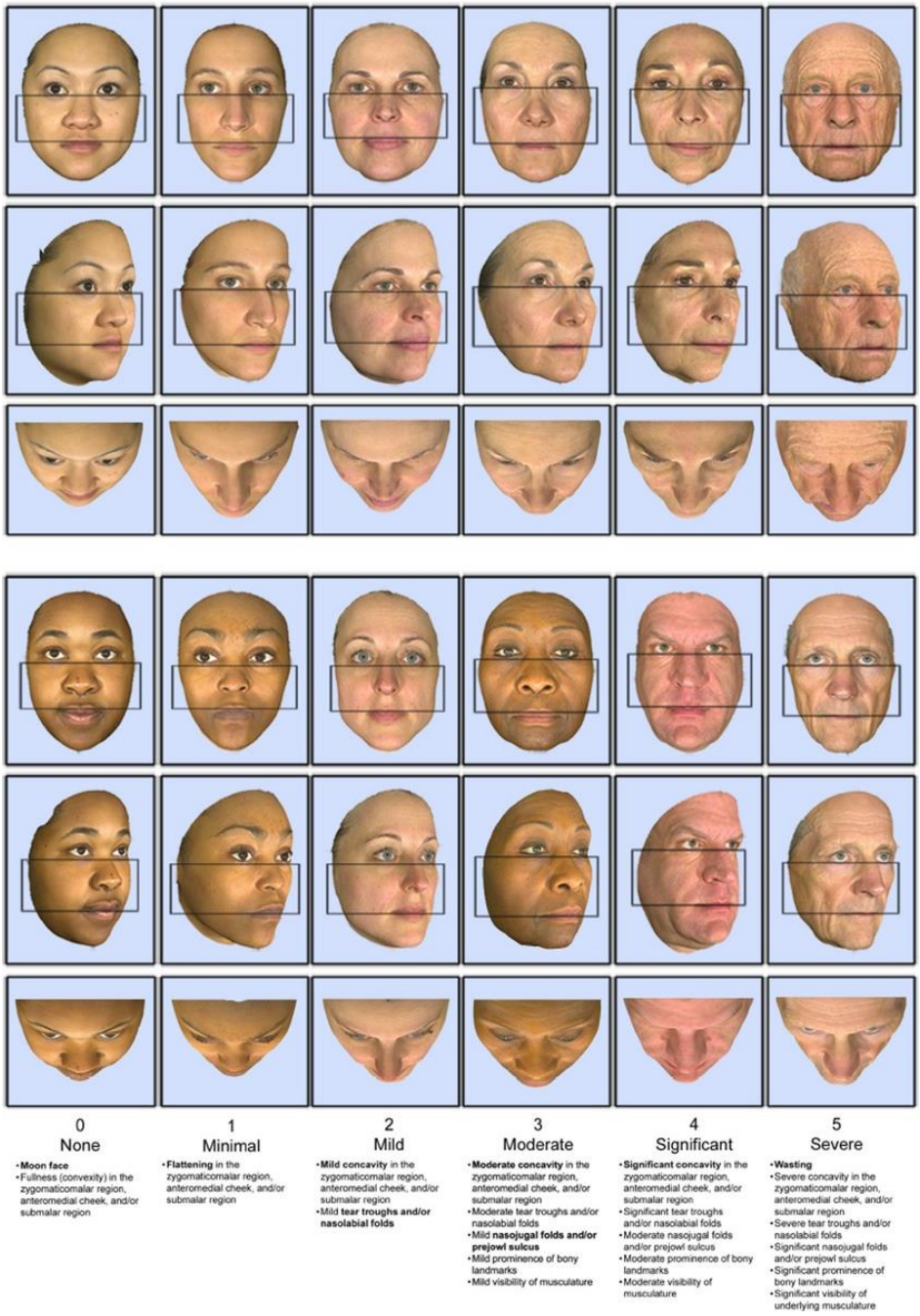


Figure 1 "The Photometric Midface Volume Deficit Scale"[21]. This scale uses a six-point photo-numeric instrument to evaluate the overall degree of the midface volume deficit, with grades ranging from 0 (none) to 6 (severe).

Appendix 2

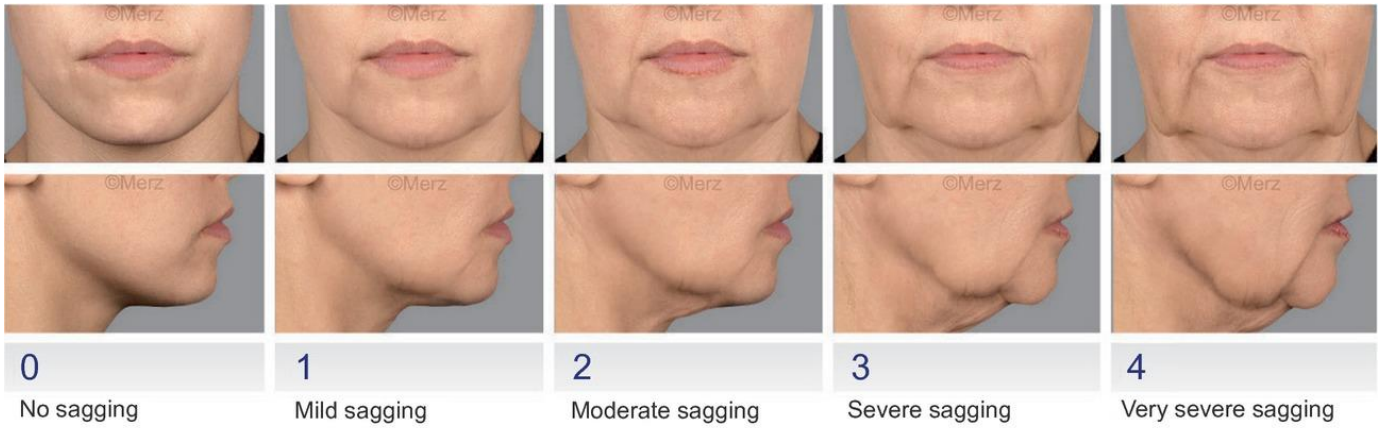


Figure 2 "The Aesthetics scale for Jawline"[22]. This five-point scale assigns a grade from no sagging (0) to very severe sagging (4) that describes the degree of volume deficit within the jawline area.

Appendix 3

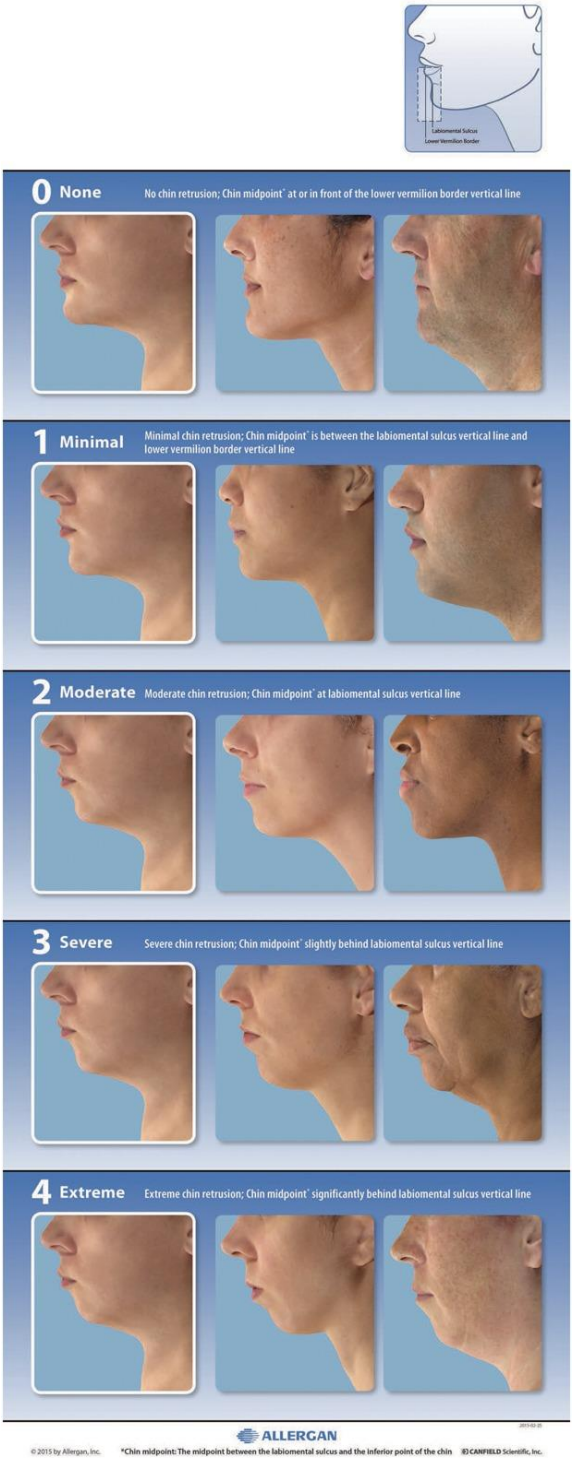


Figure 3 "The Chin Retrusion Scale"[23]. This five-point scale assigns a grade from none (0) to extreme (4) that describes the degree of the chin's placement posterior to the normal position.

Appendix 4

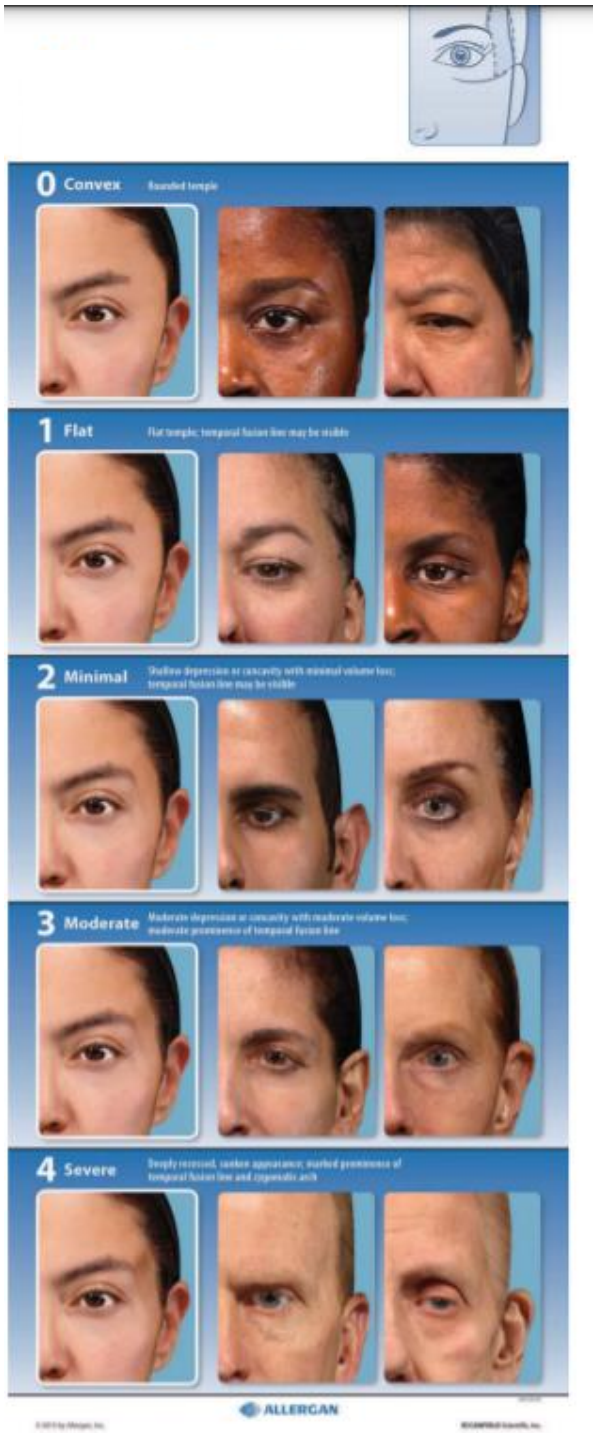


Figure 4 "Allergan Temple Hollowing Scale"[24]. This five-point scale assigns a grade from convex (0) to severe (4) that describes the degree of volume deficit within the temple area.

Appendix 5

BASELINE VISIT

(Tick in the table which applies to you. If you leave this open, we assume the table is not applicable to you.)

Mid-Face	Totally agree	Agree	Somewhat agree	Somewhat disagree	Disagree	Totally disagree
Q1C I am satisfied with the overall appearance of my cheeks	☐	☐	☐	☐	☐	☐
Q2C I am satisfied with the outline/contour of my cheeks	☐	☐	☐	☐	☐	☐

Temples	Totally agree	Agree	Somewhat agree	Somewh at disagree	Disagree	Totally disagree
Q1T I am satisfied with the appearance of my temples	☐	☐	☐	☐	☐	☐
Q2T. I am satisfied with the smoothness of my temples	☐	☐	☐	☐	☐	☐

Jawline	Totally agree	Agree	Somewhat agree	Somewh at disagree	Disagree	Totally disagree
Q1J I am satisfied with the appearance of my jawline	☐	☐	☐	☐	☐	☐
Q2J I am satisfied with the smoothness of my jawline	☐	☐	☐	☐	☐	☐
Q3J I am satisfied with the outline/contour of my jawline	☐	☐	☐	☐	☐	☐

Chin	Totally agree	Agree	Somewhat agree	Somewh at disagree	Disagree	Totally disagree
Q1C I am satisfied with the appearance of my chin	☐	☐	☐	☐	☐	☐
Q2C I am satisfied with the outline/contour of my chin	☐	☐	☐	☐	☐	☐

VISIT at MONTH 3 till MONTH 24

(Tick in the table which applies to you. If you leave this open, we assume the table is not applicable to you.)

Mid-Face	Totally agree	Agree	Somewhat agree	Somewhat disagree	Disagree	Totally disagree
Q1C I am satisfied with the overall appearance of my cheeks	☐	☐	☐	☐	☐	☐
Q2C I am satisfied with the outline/contour of my cheeks	☐	☐	☐	☐	☐	☐
Q3C I feel more attractive after my mid-face/cheek treatment	☐	☐	☐	☐	☐	☐
Q4C I look younger after my mid-face/cheek treatment	☐	☐	☐	☐	☐	☐
Q5C The treatment of my cheeks looks natural	☐	☐	☐	☐	☐	☐

Temples	Totally agree	Agree	Somewhat agree	Somewhat disagree	Disagree	Totally disagree
Q1T I am satisfied with the appearance of my temples	☐	☐	☐	☐	☐	☐
Q2T I am satisfied with the smoothness of my temples	☐	☐	☐	☐	☐	☐
Q3T The depth of my temple hollowing has been reduced	☐	☐	☐	☐	☐	☐
Q4T The hollowing of my temples appear less visible	☐	☐	☐	☐	☐	☐
Q5T I feel more attractive after the treatment of my temples	☐	☐	☐	☐	☐	☐
Q6T I look younger after treatment of my temples	☐	☐	☐	☐	☐	☐
Q7T The treatment of my temples looks natural	☐	☐	☐	☐	☐	☐

Jawline	Totally agree	Agree	Somewhat agree	Somewhat disagree	Disagree	Totally disagree
Q1J I am satisfied with the appearance of my jawline	☐	☐	☐	☐	☐	☐
Q2J I am satisfied with the smoothness of my jawline	☐	☐	☐	☐	☐	☐
Q3J I am satisfied with the outline/contour of my jawline	☐	☐	☐	☐	☐	☐
Q4J The sagging of my jawline has been reduced	☐	☐	☐	☐	☐	☐
Q5J I feel more attractive after the treatment of my jawline	☐	☐	☐	☐	☐	☐
Q6J I look younger after treatment of my jawline	☐	☐	☐	☐	☐	☐
Q7J The treatment of my jawline looks natural	☐	☐	☐	☐	☐	☐

Chin	Totally agree	Agree	Somewhat agree	Somewhat disagree	Disagree	Totally disagree
Q1C I am satisfied with the appearance of my chin	☐	☐	☐	☐	☐	☐
Q2C I am satisfied with the outline/contour of my chin	☐	☐	☐	☐	☐	☐
Q3C The retrusion of my chin has been reduced	☐	☐	☐	☐	☐	☐
Q4C I feel more attractive after the treatment of my chin	☐	☐	☐	☐	☐	☐
Q5C I look younger after treatment of my chin	☐	☐	☐	☐	☐	☐
Q6C The treatment of my chin looks natural	☐	☐	☐	☐	☐	☐

Table 9 "Subject's Overall Satisfaction Questionnaire": These two questionnaires will be completed by the subject during the course of the study to measure the overall satisfaction of the subject during the study duration. Only the table that applies to the subject will be filled in.

Appendix 6

	Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied
Ease of injection	☐	☐	☐	☐	☐
Mouldability	☐	☐	☐	☐	☐
Ease of product positioning	☐	☐	☐	☐	☐
Immediate result	☐	☐	☐	☐	☐
Result after massage	☐	☐	☐	☐	☐

Table 10 "Investigator's Satisfaction Questionnaire": This questionnaire will be completed by the investigator shortly after administration of the study treatment. The purpose of this questionnaire is to obtain feedback on the satisfaction of using the MaiLi Volume or Extreme product during the treatment procedure.

Appendix 7

Rating		Description	
1	Worse	The appearance is worse than the original condition	☐
2	No change	The appearance is essentially the same as the original condition	☐
3	Improved	Improvement in appearance from the initial condition but re-treatment is indicated	☐
4	Much improved	Marked improvement in appearance but not completely optimal	☐
5	Very much improved	Excellent corrective results	☐

Table 11 "Global Aesthetic Improvement Scale (GAIS) Questionnaire": This questionnaire will be completed by the on-site level independent evaluator at the time of the subjects' scheduled visits (i.e. month 3, 6, 12, 18, and 24). The assessment scale will be done using the full face picture (taken at the baseline/screening visit (incl. treatment administration)) and the face of the subject at the time of the visit. This questionnaire is designed to measure the level of improvement in facial volume restoration and recontouring .

Appendix 8

JCAD AESTHETIC COMPLICATIONS GUIDELINES

Welcome to the JCAD Aesthetic Complications Guidelines by The Aesthetic Complications Expert (ACE) Group. The ACE Group developed a series of evidence-based, peer-reviewed guidelines that cover complications that can occur in nonsurgical aesthetic practices. The objective of this series is to help dermatologists and other physicians performing aesthetic procedures identify and manage these potential complications. Each guideline was produced after a vast literature review by leading experts in the United Kingdom. We hope these guidelines help raise treatment standards within the medical community and ensure early diagnosis and appropriate management of complications, ultimately improving outcomes for our patients.

This month's guideline:

The Use of Hyaluronidase in Aesthetic Practice (v2.4)

by Martyn King, MD; Cormac Convery, MD; and Emma Davies, RN, NIP

J Clin Aesthet Dermatol 2018;11(6):E61–E68

BACKGROUND

Hyaluronic acid (HA)-based dermal fillers are the most commonly used fillers in the aesthetics market.[1] A glycosaminoglycan and a chief component of the extracellular matrix, HA is mainly responsible for maintaining hydration in the dermis. HA is a linear polysaccharide chain with the alternating monosaccharides d-glucuronic acid and N-acetyl-d-glucosamine.[2]

Hyaluronidases are enzymes (endoglycosidases) that can depolymerise HA, leading to its degradation[3] by hydrolyzing the disaccharides at hexosaminidic β-1through β-4 linkages.[4] Hyaluronidase is licensed in the United Kingdom for enhancing permeation of subcutaneous or intramuscular injections, local anaesthetics, and subcutaneous infusions, and to promote resorption of excess fluids and blood.[5] There is considerable evidence for the off-label use of hyaluronidase for managing vascular compromise due to inadvertent intravascular injection or external compression,[6] over-correction, asymmetry, and lumps and nodules[7] caused by the injection of HA filler.

There are several sources of hyaluronidase, and they are generally divided into three subgroups: mammalian (obtained from the testes); hookworm or leech; and microbes.[8] Recombinant human hyaluronidase (Hylenex®, Halozyme Therapeutics, San Diego, California) has a purity 100 times higher than some of the bovine preparations.[9] There is no long-term data for this product yet, but it has been speculated to have a lower incidence of allergic reactions.

Hyaluronidase has immediate effect and a half-life of two minutes with duration of action of 24 to 48 hours.[10,11] Though it has a short half-life, its effectiveness lasts longer. This might be due to the low number units required to have a clinically significant effect; thus, even when the hyaluronidase has mostly degraded, its action continues. Additionally, the initial action of hyaluronidase might break cross-links in the HA dermal filler so that it behaves like native

HA in the skin, which has a half-life of 24 to 48 hours.[12]

OFF-LABEL USE OF HYALURONIDASE

Although hyaluronidase is not licensed for the use in correcting problems with dermal filler injections and off-label promotion is not allowed by Article 87 of Directive 2001/83/EC, the use of hyaluronidase is allowed provided the patient's best interest and autonomy are a respected part of informed consent (as indicated by the 2009 guidelines from the United Kingdom's Medicines and Healthcare Products Regulatory Agency [MHRA]).

INDICATIONS FOR THE USE OF HYALURONIDASE IN AESTHETIC PRACTICE

Vascular occlusion. The incidence of impending necrosis following dermal filler treatment has been estimated at 0.001 percent (1 in 100,000 cases).[7] Vascular compromise due to HA filler injection should be treated immediately (refer to the ACE Group guidance on impending necrosis[13]). Normal skin should be non-discolored and warm, with a capillary refill time of 1 to 2 seconds, whereas arterial compromise will have a slow capillary refill time and dusky or blue-grey-black appearance, and venous insufficiency will have a fast capillary time and bluish discoloration.[14] Signs of impending necrosis also include pain and coolness of the skin. Hyaluronidase should be administered as soon as this complication occurs (within 4 hours).[4,15] There is strong evidence that tissue necrosis can be prevented or reduced in severity if treatment is administered within 48 hours.[6,16] However, a small animal-based study tested this theory and found that injecting hyaluronidase at 24 hours failed to afford any benefit.[17]

Blindness. Blindness due to periocular embolism of HA is instant and associated with excruciating ocular pain. The retinal circulation needs to be restored within 60 to 90 minutes if the retina is to survive. Blindness is a medical emergency and the patient should be transferred immediately to the nearest hospital eye department (Refer to the ACE Group guidance on blindness[18]). Retrobulbar injection of hyaluronidase (150–200 units in 2–4mL of diluent) into the inferolateral orbit[19] should be considered by practitioners who have appropriate experience and competence while waiting for an ambulance. Treatment of blindness is rarely successful.[19]

Tyndall effect. The Tyndall effect refers to the scattering of light that may be seen in some patients after injection of HA resulting in a bluish hue of the skin and most commonly seen in the sub ocular region. The problem can be resolved using hyaluronidase (Refer to ACE Group guidance on the Tyndall effect[20]).

Unacceptable cosmetic outcome. Overcorrection or misplacement of HA filler can be successfully treated with hyaluronidase, although this is often caused by poor injection technique or poor choice of product for a particular indication. If HA is present, then hyaluronidase is effective, and HA gel has been successfully removed 63 months post-treatment.[21]

Delayed onset nodules. Lumps or nodules that appear several months after the initial treatment might be amenable with hyaluronidase (Refer to ACE Group guidance on delayed onset nodules [22]). It is important to remember that hyaluronidase is used to help diffuse fluids intradermally and for hypodermoclysis. To prevent potential dissemination of infection in inflammed nodules, it is important to prescribe antibiotics for one week before administering hyaluronidase.

Allergic or immunogenic reaction to the HA dermal filler. When an allergic, immunogenic, or sensitivity reaction occurs and does not settle on its own within an acceptable amount of time following a short course of antihistamines or systemic corticosteroids, removal of the filler with hyaluronidase is appropriate. If the reaction is considered moderate or severe, oral corticosteroids should be taken before hyaluronidase use to manage or prevent the potential initial worsening of symptoms due to the increase in antigens as the HA is broken down.

STORAGE AND RECONSTITUTION

It is recommended that hyaluronidase be stored at cool temperatures (2–8°C, 35–46°F) to maintain the quality of the product over a long period of time. If stored at room temperature (25°C, 77°F), the stability is only guaranteed for 12 months. Once the ampoule is opened, hyaluronidase should be used immediately and any unused contents discarded (Hyalase® SPC).

Hyaluronidase may be reconstituted with either saline or water for injection (Hyalase SPC). Saline is less painful on injection and is recommended for this reason. Although unlicensed for this purpose, bacteriostatic saline is often preferred for its additional anaesthetic properties. Although local anaesthetics may be used to reconstitute the product, as the enzymatic action of hyaluronidase can be affected by pH[7], caution should be applied to the choice of diluent. There is little evidence to support the addition of local anaesthetic agents to hyaluronidase,[18] and when combined, may lead to widespread, increased systemic absorption of anaesthetic and potential complications.

The volume of diluent used will depend on the indication and surface area to be treated and a range of 1 to 10mL has been evidenced in clinical practice and published papers. Larger volumes of dilution are recommended when smaller amounts of Hyalase are required to allow more precise dosing. Smaller volumes should be used in the case of vascular occlusion or when large volumes of dissolution are required to allow a higher concentration of Hyalase in a smaller area. Once the volume of diluent has been chosen, add 1mL of diluent to the opened ampoule of Hyalase and ensure the powder is fully dissolved by drawing up and expelling the syringe a couple of times. Aspirate the 1mL of saline with the reconstituted Hyalase, adding this to the remaining diluent.

$$\text{Volume to inject (mLs)} = \frac{\text{Number of units required (units)} \times \text{Volume of diluent (mL)}}{\text{Total number of units (1500 units)}}$$

FIGURE 1. Formula

TABLE 1. Aesthetic Complications Group Emergency Kit

REGION	HYALURONIDASE (UNITS)
Nasal and perioral skin	15–30[26,27]
Periorbital	3–4.5[28]
Infraorbital	10–15[29]
Lower lid	1.5[28]

Agitate the solution to ensure the Hyalase is mixed throughout the whole volume. The reconstituted solution can now be drawn up in a syringe and injected where needed. The formula for the number of units to be injected can be found in Figure 1.

DOSAGES OF HYALURONIDASE

Hyaluronidase may degrade the body's natural HA in preference to foreign HA filler that has been injected and specifically cross-linked to prevent its natural breakdown.[14] The dosage required is dependent on several factors relating to the HA filler; whether it is particulate or non-particulate, the amount of cross-linking, and the concentration of HA.[23] Different HA fillers have differing physical properties that influence their degradation by hyaluronidase in a time- and dose-dependent manner. A study by Rao et al[24] demonstrated Restylane® (Galderma Laboratories, Lausanne, Switzerland) dissipated most and Belotero® (Merz Pharmaceuticals, Raleigh, North Carolina) least.[25] However, a more recent study has shown that Belotero was the fastest to dissolve and Juvederm Voluma® (Allergan, Dublin, Ireland) and Restylane® Lyft were the slowest, with the authors concluding that a high concentration of HA, larger particle size, and increased cross-linking increases the durability of the filler.[17]

The literature offers examples of widely divergent doses; however, it is recommended to inject as much hyaluronidase as required to obtain the desired effect rather than following an absolute dosage.[14]

Dosages for all indications except vascular occlusion. Although the amount injected should be titrated to clinical effect,[14] Table 1 offers a guide to actual dosages used in published articles.

A consensus opinion in the literature states five units of hyaluronidase is needed to break down 0.1mL of 20mg/mL HA,[10] although there is quite a range. In one instance, Woodward et al[25] recommend 30 units to dissolve 0.1mL. A further study showed no statistical difference between the use of 20 or 40 units of hyaluronidase in degrading 0.2mL (4 to 6mg of HA) of various fillers.[23]

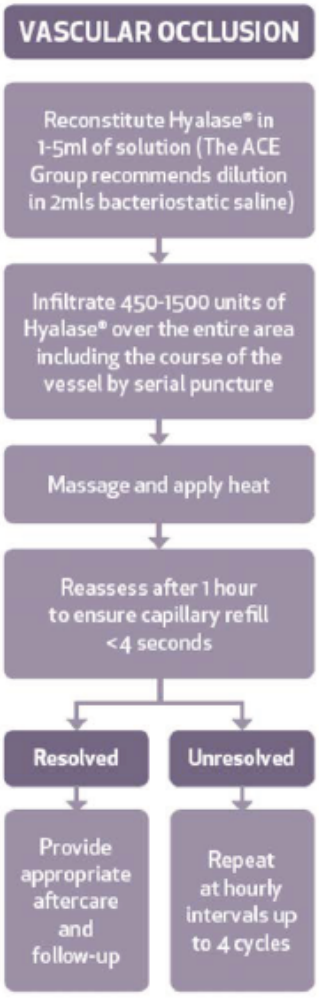
Treatment results may be assessed from 48 hours[4] and may be repeated at intervals of 48 hours or longer. The degree of further treatment will depend upon indication, risks versus benefits, side effects from treatment, and patient and practitioner satisfaction.

Dosages for vascular occlusion. In the event of a suspected vascular obstruction, a high dose pulsed protocol should be adopted.[31] Large volume of hyaluronidase (450–1500 units) should be infiltrated over the entire area including the course of the vessel.[4,14,32] Perivascular hyaluronidase will permeate vascular walls.[4,33] Massage the area to promote diffusion and mechanical breakdown. Observe and reassess capillary refill after 60 minutes; if there is still vascular compromise, repeat treatment at hourly intervals for up to four cycles.[34] The patient should be kept under observation in clinic for any adverse reactions and provided with written aftercare and advice. When anaphylaxis occurs, it is usually within minutes, but there have been cases where there has been a delayed onset. All patients should be given appropriate aftercare advice, warned about the symptoms of an allergic or anaphylactic response, and instructed to seek appropriate medical attention. Daily follow up should occur until there is satisfactory resolution.

Vascular occlusion is often immediate; however, the Aesthetic Complications Expert group have found many reported cases when the symptoms of ischaemia start several hours or even days later. This may be due to the dermal filler being intravascular but trapped at a bifurcation or branch point, only to dislodge at a later point to cause an occlusion.[33] Alternatively, if the venous return is compromised by secondary swelling following injection of hydrophilic dermal filler, this can cause increased pressure in the arterial tree and a reduction in tissue perfusion.

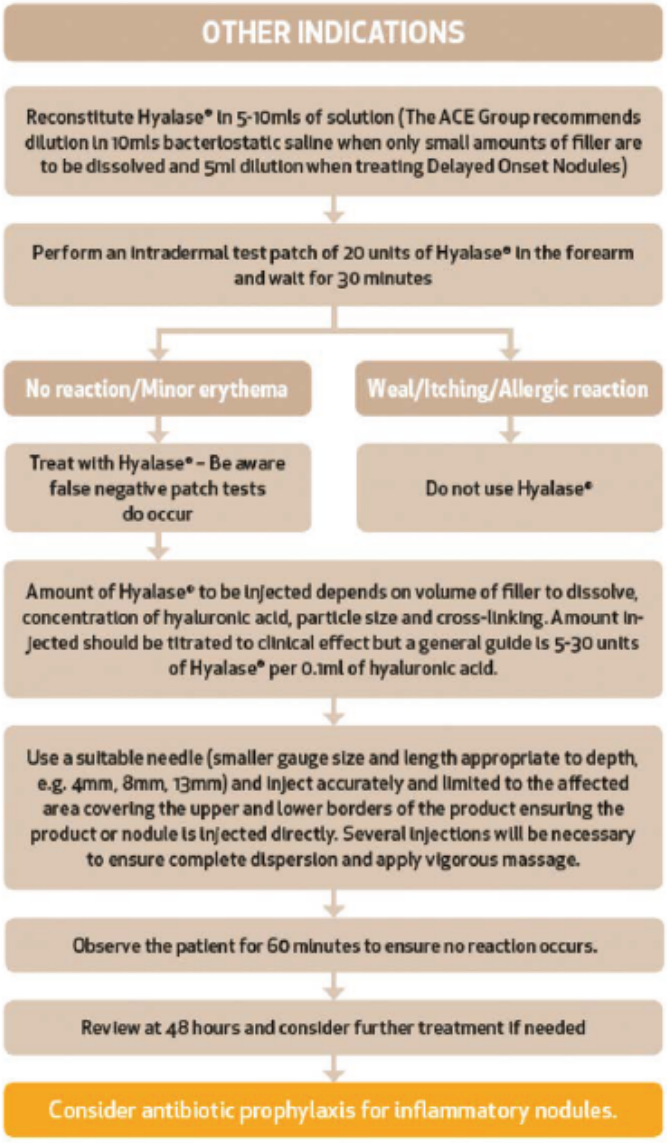
INTRADERMAL PATCH TESTING

A test patch should be performed except when the indication is for vascular compromise and a delay could result in further harm to the patient.[35] An intradermal injection of 4 to 8 units of hyaluronidase in the forearm and observing the results after 30 minutes has been advocated.[36] However, it is recommended that a higher test dose of 20 units of hyaluronidase is used, as a positive reaction at lower doses might not be recognised.[37] A positive reaction is identified by a weal and itching observed at the injection site, minor inflammation, and erythema.



DRUG INTERACTIONS

The most common interactions occur with furosemide, benzodiazepines, phenytoin, dopamine, and α-adrenergic agonists, so it is important to obtain a medical history. Although interactions are not particularly significant, it is best to avoid them if



possible. Several drugs act as antagonists to hyaluronidase, including anti-inflammatory drugs (such as ibuprofen, aspirin, diclofenac), anti-histamines, mast cell stabilisers, Vitamin C, flavonoids, and anti-oxidants.[3] Higher doses or repeated treatments may be required with concomitant use of these medicines.[32] Where possible, patients should be advised to stop taking non-prescribed medication in advance of treatment.

ADMINISTRATION

Prior to injection, the area should be inspected, palpated, and marked out if needed. The area should be cleansed and disinfected using an appropriate skin solution and the procedure should be carried out using an aseptic technique. A 27G or 30G needle with an appropriate length to treat the depth of the area should be used. Administration should be accurate and limited to the affected area. Depth may be difficult to assess on palpation; therefore injections should cover the upper and lower borders of the product that has been injected.

Nodules, and product that has been injected into the superficial dermis should be injected directly, injections should be placed immediately into and below the product.[38] [[Not sure what the previous sentence is trying to convey]] For vascular compromise, serial puncture should be used to inject hyaluronidase along the course of the vessel and cover the affected area.[4] The needle should be perpendicular to the skin and several injections are often necessary.

During and after the procedure, the treated area should be massaged vigorously to optimise the result and aid mechanical breakdown. Due to the spreading effect of hyaluronidase, treatment should not be performed in an area where botulinum toxin treatment has been performed within the last 48 hours or on an area of infected skin, unless there is a vascular occlusion and the risks outweigh the benefits.

FOLLOW-UP

Results are often seen almost immediately; although for denser, more cross-linked products, it may take 48 hours for the effects to be seen. Consent should be obtained for the practitioner to inform the patient's General Practitioner (See Appendix 1 for an example of a patient consent form). A review appointment should be offered at this point, along with further treatment if needed.

Following administration of hyaluronidase, the patient should be observed for 60 minutes to ensure no adverse reactions occur. Aftercare instructions should be given. In the event of any delayed reaction to the treatment, the patient should be seen at the earliest opportunity.

COMPLICATIONS

Bruising and swelling post-treatment are common.[15,39] The most serious complication

following the administration of hyaluronidase is an allergic reaction. Depending on the area treated, different allergic responses have been described. Local reactions are by far the most common, and according to clinical studies, occur at a rate of 0.05 to 0.69 percent.[3] However, these figures are likely to be a little lower due to under reporting. Signs include edema, erythema, pain, and itching. Urticaria and angioedema have been reported in less than 0.1 percent of cases.[40] Anaphylaxis has occurred with the use of hyaluronidase when high doses have been administered and with intravenous administration (refer to Aesthetic Complications Expert Group Anaphylaxis guidance). Type I (IgE mediated) and Type IV (mediated by T-cells) hypersensitivity reactions have occurred after hyaluronidase treatment. Following the use of hyaluronidase, the patient should be observed for 60 minutes in a clinical environment and given appropriate aftercare information (Appendix 2).

A history of allergic reaction to wasp or bee stings represents an increased risk of allergic reaction to hyaluronidase and should be considered as a relative contraindication, as the venom of stinging insects might contain hyaluronidase and this mechanism might be the source of sensitization in affected individuals.[14,41,42] Unless there is a past medical history of allergic reaction or anaphylaxis to hyaluronidase or insect bites, previous history of allergy seems unrelated for the administration of hyaluronidase and it can be safely performed.[43]

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"Guidance for using Hyaluronidase in case of Adverse Event (AE)" This article describes the various steps to be taken if hyaluronidase is to be used during an AE.