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**Study ID**: CMO-MA-FAS-0617

**Title:** Prospective, Open-Label Study, to Evaluate The Impact on Skin Quality Attributes by Juvederm® Volite Injection on Healthy Volunteers

**Protocol Date**: 21Aug2019

# PROSPECTIVE, OPEN-LABEL STUDY, TO EVALUATE THE IMPACT ON SKIN QUALITY ATTRIBUTES BY JUVEDERM® VOLITE INJECTION ON HEALTHY VOLUNTEERS

***Clinical Investigational Plan for Medical Device according to ISO standard 14155:2012 and its updates***

| | |
|---|---|
| **Clinical Investigational plan #:** | **18E2581PL – CMO-MA-FAS-0617** |
| **ANSM registration #:** | **2019-A00317-50** |
| **Device under investigation:** | **Juvederm® VOLITE** |
| **Form(s):** | **Sterile gel** |
| **Application(s):** | **Intradermal injection** |
| **CRO :** | **DERMSCAN - Pharmascan**<br>114 Boulevard du 11 Novembre 1918<br>69100 VILLEURBANNE<br>FRANCE |
| **Investigational Centre** | Dermscan Poland Sp. z o.o.<br>ul. Matuszewskiego 12<br>80-288 GDANSK<br>POLAND |
| **Principal Investigator:** | [redacted] |
| **Sponsor:** | **Allergan Pharmaceuticals International Limited**<br>Clonshaugh Industrial Estate<br>Coolock<br>Dublin 17<br>Ireland |
| **Clinical Investigation Plan date and version:** | Final version 1.0 of 21/08/2019 |

# *TABLE OF CONTENTS*

*1- GENERAL INFORMATION AND SIGNATURES ..... 5*

*1.1 Introduction ..... 5*
*1.2 Identification of the clinical investigation plan (CIP) ..... 6*
*1.3 Sponsor ..... 7*
*1.4 Principal Investigator, coordinating investigator and investigation site(s) ..... 7*
*1.5 Overall synopsis of the clinical investigation ..... 9*

*2- IDENTIFICATION AND DESCRIPTION OF THE DEVICE UNDER INVESTIGATION 14*

*2.1 Summary description of the device under investigation and its intended purpose 14*
*2.2 Details concerning the manufacturer of the device under investigation ..... 14*
*2.3 Name or number of the model/type ..... 14*
*2.4 Traceability of the device under investigation ..... 14*
*2.5 Intended purpose of the device in the proposed clinical investigation ..... 14*
*2.6 Population and indications for which the device under investigation is intended. 15*
*2.7 Description of the device under investigation ..... 15*
*2.8 Summary of the training and experience needed to use the device under investigation ..... 15*
*2.9 Description of the specific medical or surgical procedures involved in the use of the device under investigation ..... 15*

*3- JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION .....17*

*3.1 Summary of the results of the relevant pre-clinical testing/ assessment carried out to justify the use of the device under investigation in human subjects ..... 17*
*3.2 Clinical data ..... 17*

*4- RISKS AND BENEFITS OF THE DEVICE UNDER INVESTIGATION AND CLINICAL INVESTIGATION.....18*

*4.1 Anticipated clinical benefits ..... 18*
*4.2 Anticipated adverse device effects ..... 18*
*4.3 Residual risks associated with the device under investigation ..... 18*
*4.4 Risks associated with participation in the clinical investigation ..... 19*
*4.5 Potential Interactions with concomitant medical treatments ..... 19*
*4.6 Steps that will be taken to control or mitigate the risks ..... 19*
*4.7 Risk-to-benefit rationale ..... 19*

*5- OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION .....20*

*5.1 Objective ..... 20*
*5.2 hypotheses to be accepted or rejected by statistical data ..... 20*
*5.3 Claims and intended performance of the device under investigation that are to be verified ..... 20*
*5.4 Risks and anticipated adverse device effects that are to be assessed ..... 20*

*6- DESIGN OF THE CLINICAL INVESTIGATION .....20*

*6.1 General information ..... 20*
*6.2 Device under investigation ..... 23*

*6.3 Studied population ..... 24*
*6.4 Procedures ..... 27*
*6.5 Monitoring ..... 40*

*7- STATISTICAL CONSIDERATIONS ..... 41*
*7.1 Statistical design, method and analytical procedures ..... 41*
*7.2 Sample size and its statistical justification ..... 43*
*7.3 Level of significance and power of the clinical investigation ..... 43*
*7.4 Expected drop-out rates ..... 43*
*7.5 Statistical pass/fail criteria to be applied ..... 43*
*7.6 Criteria for the termination of the clinical investigation on statistical grounds ..... 43*
*7.7 Deviation(s) from the original statistical plan ..... 43*
*7.8 Treatment of missing, unused or spurious data, including drop-outs and withdrawals ..... 43*

*8- DATA MANAGEMENT ..... 43*
*8.1 Procedures used for data review, database cleaning and issuing/resolving data queries ..... 43*
*8.2 Procedures for verification, validation and securing of electronic clinical data systems, if applicable ..... 45*
*8.3 Procedures for data retention ..... 45*
*8.4 Other aspects of clinical quality assurance ..... 45*

*9- AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN ..... 45*

*10- DEVIATIONS FROM CLINICAL INVESTIGATION PLAN ..... 45*
*10.1 Procedures for evaluating subject compliance ..... 46*
*10.2 Procedures for recording, reporting and analysing CIP deviations ..... 46*
*10.3 Corrective and preventative actions and principal Investigator disqualification criteria ..... 46*

*11- DEVICE ACCOUNTABILITY ..... 46*

*12- STATEMENTS OF COMPLIANCE ..... 46*
*12.1 Regulatory aspect ..... 46*
*12.2 Ethics Committee ..... 47*
*12.3 Personal data protection ..... 47*
*12.4 Insurance ..... 47*

*13- INFORMED CONSENT PROCESS ..... 47*

*14- ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES 48*
*14.1 Definitions ..... 48*
*14.2 Process for reporting adverse events and device deficiencies ..... 51*
*14.3 Process for reporting a pregnancy ..... 52*
*14.4 List of foreseeable adverse events and anticipated adverse device effects ..... 53*
*14.5 Information regarding the Data monitoring committee (DMC) ..... 53*

*15- VULNERABLE POPULATION ..... 53*

*16- SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION ..... 53*

*16.1 Study end ..... 53*

*16.2 Suspension or premature termination of the clinical investigation ..... 53*

*17- PUBLICATION POLICY ..... 54*

*18- BIBLIOGRAPHY ..... 54*

*18.1 Ethical aspect ..... 54*

*18.2 Skin Quality and Quality of Life ..... 54*

*18.3 Justification for Design of Clinical Investigation ..... 54*

*18.4 Residual Risk Associated with Device Under Investigation ..... 55*

*18.5 Instrumental devices ..... 55*

## LIST OF FIGURES

**Figure 1- Localization of injection zone, skin quality measurement zone and biopsies** ..... 28

## LIST OF TABLES

**Table 1- Study flow-chart** ..... 22
**Table 2- Summary of performance parameters** ..... 30
**Table 3- MoistureMeter D® probes used for the study** ..... 31
**Table 4- List of ISR** ..... 39

# 1- GENERAL INFORMATION AND SIGNATURES

## 1.1 INTRODUCTION

The phenotypic changes of the skin provoked by aging are affected by both intrinsic and extrinsic factors (Sachs and Voorhees, 2011). Intrinsic factors such as age, sex, and estrogenic status induce changes in the composition and appearance of the dermis that are accompanied by a substantial reduction in the levels of glycosaminoglycans (including hyaluronic acid [HA]). This reduction, which is directly related to age and a decrease in the synthesis of glycosaminoglycans such as HA (Biecker and Schachtschabel, 2001; Okano et al, 2002), is accelerated by dermal exposure to ultraviolet (UV) radiation. Histological studies confirm that the epidermis loses a substantial amount of density, a process accompanied by atrophy, decline in several epidermal differentiation indicators, and loss of water retention capacity. This process results in tissue dehydration and interphase weakness, which compromise the organization of the dermal-epidermal junction. Extrinsic factors, such as UV radiation, wind, extreme temperatures, medication, and exposure to abrasive substances, can result in the production of free radicals, which induce catabolism of HA and can lead to substantial changes in the extracellular matrix and loss of interstitial collagen (Agren et al, 1997). This damage promotes wrinkles and loss of skin tone and elasticity.

Over time, the intrinsic and extrinsic factors together affect the structure and function of the components of skin, leading to measurable changes in its viscoelastic properties and to visible manifestations of aging. Aging or poor skin quality as well as skin conditions that result in facial symptoms such as wrinkles, fine lines, blemishes, tone or pigmentation changes, or lesions can have an effect on a person's physical and psychological well-being, and therefore may be regarded as an impaired health state (Fried 1998, Sadick 2008, Sommer 2003). The effects of skin conditions and diseases as well as poor skin quality and advancing age that alter facial appearance negatively impact one's self-perception and HRQoL (Health-related quality of life). For those not directly affected by poor facial skin quality there is a tendency to trivialize its potential impact (Schmid-Ott 2010).

Today, many injectable fillers are used to treat facial aging, correct skin defects, and enhance and pout the lips to correct structural or age-related defects such as asymmetry, contour deficiencies, and volume loss. In the past decade, many new HA-based dermal products have become available to treat/prevent the visible signs of aging, by filling wrinkles and folds. Crosslinking HA with an agent such as butane-diol-diglycidyl-ether (BDDE) improves duration of treatment effect by reducing susceptibility to degradation mechanisms. Different crosslinking technology and HA concentrations result in fillers with varying rheological properties and specific indications.

HA filler products can be placed within the superficial, mid, or deep dermis, at the dermal-subcutaneous junction, or in the superficial subcutis, depending on the nature of the correction that is necessary and the characteristics of the filler being used (Arlette and Trotter, 2008). In recent years, there has been increased demand for products that improve attributes of skin quality in addition to treating skin depressions. As such, many of these HA rejuvenation products have proven successful within their indications of amelioration of the visible signs of cutaneous aging and treatment of cutaneous depressions, with limitations linked to duration in situ as many of these products are not crosslinked.

JUVÉDERM VOLITE®, which is included in the JUVÉDERM® range of products, contains 12 mg of HA of nonanimal origin crosslinked by BDDE, 3 mg of lidocaine hydrochloride (to reduce patient's pain during treatment) and 1 mL quantity sufficient (QS) phosphate buffer pH 7.2 and is supplied in a cyclic olefin copolymer (COC) syringe. JUVÉDERM VOLITE® was designed to treat by filling superficial cutaneous depressions such as fine lines and for additional improvement of skin quality. The injection depth for JUVÉDERM VOLITE® is specified as intradermal, with the depth of injection being determined by healthcare professionals with regard to the desired correction.

Although various materials have been investigated as potential candidate soft-tissue fillers, none have produced as consistent and optimal results as HA fillers. HA is capable of providing volume to the targeted area, reducing the appearance of cutaneous depressions, and restoring the natural contour of

the region to which it is applied. Risks associated with the device have been mitigated by its formulation, and potential complications that may arise have been described in the literature and DFU. The success of HA dermal fillers for the treatment of superficial skin depressions such as fine lines and for improvement of skin hydration and elasticity restoration is reflected in the CE Mark approvals of VOLBELLA, JUVÉDERM Hydrate and JUVÉDERM VOLITE® which demonstrate that the benefit of usage outweighs the risk of potential complications.

JUVÉDERM VOLITE, a hyaluronic acid gel enhanced with lidocaine, is an injectable implant used for treatment, by filling, of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity. The unique formulation of JUVÉDERM VOLITE is intended to provide optimized durability versus fillers with similar indications, as shown by in vitro and animal testing.

To gain greater knowledge on the impact of JUVÉDERM VOLITE® on skin quality attributes such as hydration, elasticity, thickness and density, and cell/tissue responses, various skin measurement devices will be used and cutaneous biopsies will be taken on the volar forearm of healthy volunteers, who will be followed up to 3 months.

Biopsies collected in the study from injections in the volar forearm will allow to better understand the interactions of this particular hyaluronic acid-based filler with cells and tissues and to improve understanding of the clinical benefits relating to skin quality attributes assessed in previous studies. The improvement of skin quality attributes is not purely an aesthetic goal but, in fact, relates directly to patient quality of life.
Biopsy analysis is as important as the skin measurements and as it is an exploratory study, it was decided to include them all under a single objective of the study. This type of study has indeed never been done on this product. The risks associated with biopsies are minimized by the fact that it is skin biopsies of small diameter (3 mm), generally allowing proper healing. The criteria for inclusion and non-inclusion will include subjects with limited risk, particularly in terms of poor healing.
The number of biopsies was decreased to the necessary minimum. 2 biopsies per zone and per time point are needed to have enough material for the planned analysis. It was preferred to sample 2 small biopsies instead of one larger biopsy to decrease the risks of visible and anaesthetic scars. Two time points are important to better understand the kinetics of product action on tissues and cells. A 1 month time point was chosen to align with previous studies evaluating the visible effects of this product and a 3 month time point was selected to evaluate any kinetic effects of the cell and tissue interaction. A non-treated area is essential to have baseline data to compare the treatment data to. Finally, volar forearms have been chosen because this is an area less visually exposed than the usual injection sites (face, neck, neckline, hands,…) but structure, thickness and properties of skin forearms are very close to the skin of usual injection site areas.

## 1.2 IDENTIFICATION OF THE CLINICAL INVESTIGATION PLAN (CIP)

**TITLE OF THE CIP: PROSPECTIVE, OPEN-LABEL STUDY, TO EVALUATE THE IMPACT ON SKIN QUALITY ATTRIBUTES BY JUVEDERM® VOLITE INJECTION ON HEALTHY VOLUNTEERS**

**CLINICAL INVESTIGATION #: 18E2581PL**

**VERSION AND DATE OF THE CIP: FINAL V1.0 OF 21/08/2019**

**SUMMARY OF THE REVISION HISTORY (IN THE CASE OF AMENDMENTS): NA**

### 1.3 SPONSOR

| DATE | CONTACT | SIGNATURE |
|---|---|---|
| August 22, 2019 | [redacted] Exec Dir, Biological Research [redacted] | [redacted] |
| August 22, 2019 | Clinical Project Manager [redacted] | |

### 1.4 PRINCIPAL INVESTIGATOR, COORDINATING INVESTIGATOR AND INVESTIGATION SITE(S)

**CRO AND PRINCIPAL INVESTIGATOR SIGNATURES**

We agree to conduct the study in accordance with the study protocol described in this document and in compliance with GCP and applicable regulatory requirements.

| DATE | CONTACT | SIGNATURE |
|---|---|---|
| August 27 2019 | [redacted] Principal/Coordinating Investigator [redacted] | [redacted] |
| August 26, 2019 | [redacted] Project Manager [redacted] | |
| August 26, 2019 | [redacted] Biostatistician [redacted] | |

# ABBREVIATION LIST:

| | |
|---|---|
| **ADE** | Adverse Device Effect |
| **AE** | Adverse Event |
| **ASADE** | Anticipated Serious Adverse Device Effect |
| **USADE** | Unanticipated Serious Adverse Device Effect |
| **ANSM** | Agence Nationale de Sécurité Sanitaire des Produits de Santé = French Competent Authority |
| **ARS** | Agence régionale de santé (regional health agency) |
| **CIP** | Clinical Investigational Plan |
| **CNIL** | Commission Nationale Informatique et Libertés |
| **CRA** | Clinical Research Assistant |
| **CRF** | Case Report Form |
| **CRO** | Contract Research Organization |
| **CSP** | Code de la Santé Publique |
| **D** | Day |
| **DFU** | Directions For Use |
| **DMC** | Data Monitoring Committee |
| **EC** | Ethics Committee |
| **GCP** | Good Clinical Practice |
| **HA** | Hyaluronic Acid |
| **HIV** | Human Immunodeficiency Virus |
| **95% CI** | 95% confidence interval |
| **I.C.H** | International Conference on Harmonisation |
| **ISE** | Instant Skin Elasticity |
| **ISR** | Injection Site Reaction |
| **ITT** | Intent To Treat |
| **MD** | Medical device |
| **OCT** | Optical Coherence Tomography |
| **SAE** | Serious Adverse Event |
| **SADE** | Serious Adverse Device Event |
| **SOP** | Standard Operating Procedure |
| **UV** | UltraViolet |
| **TMF** | Trial Master File |

## 1.5 OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

| | |
|---|---|
| **ANSM registration #:** | **2019-A00317-50** |
| **Clinical investigation plan #:** | 18E2581PL – CMO-MA-FAS-0617 |
| **Title of the Clinical Investigation:** | **PROSPECTIVE, OPEN-LABEL STUDY, TO EVALUATE THE IMPACT ON SKIN QUALITY ATTRIBUTES BY JUVEDERM® VOLITE INJECTION ON HEALTHY VOLUNTEERS** |
| **Sponsor:** | **Allergan Pharmaceuticals International Limited**<br>Clonshaugh Industrial Estate<br>Coolock<br>Dublin 17<br>Ireland |
| **Investigation category:** | This study will be considered as an interventional research involving human beings. |
| **Objectives:** | To evaluate the impact on skin quality attributes, including physical measurements [redacted] following administration of Juvéderm® VOLITE in the volar forearms of healthy volunteers. |
| **Design:** | Prospective, single-center, open study |
| **Planned Sample Size:** | 11 subjects included for 10 subjects analyzed |
| **Number of centres:** | One center |
| **Inclusion criteria:** | 1. Healthy subject<br>2. Sex: male and female<br>3. Age: between 30 and 50 years old at the time of the written consent.<br>4. Subjects with Fitzpatrick skin type II or III.<br>5. Subject willing to receive Juvéderm® VOLITE in the forearms and agrees to complete all study required procedures, including having 6 cutaneous punch biopsies taken in the forearms and blood drawn (HIV, B and C hepatitis analysis at screening).<br>[redacted]<br>9. Written informed consent and data privacy consent obtained. |

**Exclusion criteria:**

**In terms of population:**

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

[redacted]

4. Subject participating to another research on human beings or being in an exclusion period for a previous study.
5. Intensive exposure to sunlight or UV-rays within the previous month and foreseen during the study.
6. Subject having other resorbable filling product injections, a laser treatment, an ultrasound-based treatment, radiation treatment, a dermabrasion, a surgery, a deep chemical peeling or other ablative procedure on the studied zones within the past 12 months prior to study start.
7. Subject with subcutaneous retaining structure on the studied zones (meshing, threads, gold strand).
8. Subject having received injections of permanent or semi-permanent filling products in the studied zones.

[redacted]

| | |
|---|---|
| | [redacted]<br>**Related to previous or ongoing treatment**<br>24. Subject under anti-coagulant treatment or treatment liable to interfere with the healing process or hemostasis, during the previous month and during the study.<br>25. Subject receiving or is planning to receive anti-inflammatory drugs (oral/injectable corticosteroids or NSAIDs, e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (herbal supplements with garlic or ginkgo biloba, etc) for 10 days prior to study treatment and 3 days after.<br>26. Subject under immunosuppressive therapy.<br>[redacted] |
| **Device under investigation:**<br>**Name / code:** | Juvéderm® VOLITE |
| **Galenic form:** | Sterile gel in disposable syringe |
| **Dosage:** | On Day 0 (D0) the specialist injector will treat the study area with an appropriate volume based on his/her clinical experience and according to Instructions for Use. |
| **Administration route:** | Intra-dermal injection in forearms |

**Evaluation criteria/Endpoints:**

**Performance exploratory Endpoints**

Changes in skin quality parameters, one and three months after Juvéderm® VOLITE injection in the forearms, in comparison with before treatment (D0). Evaluated skin parameters and instruments used are summarized in the table below:

| Instrument | Measurement of interest |
|---|---|
| MoistureMeter D® 0.5 mm | Hydration (epidermis + dermis) |
| MoistureMeter D® 1.5mm | Hydration (epidermis + dermis) |
| Corneometer® | Hydration (superficial layers of epidermis) |
| Cutometer® | Elasticity |
| Elastimeter® | Elasticity |
| Skin Scanner® | Skin thickness and density |
| Vivosight OCT® | Skin roughness, density and vascularity |
| Glossymeter® | Brightness |
| Spectrophotometer® | Colour |
| Mexameter® | Melanin content |

[redacted]

**Safety Endpoints**

- Injection Site Reactions (ISRs) evaluated by the investigator at each time point after injection.
- Collection of adverse events and incidents at all visits including severity, action taken, and relationship to device.

**Study Procedures:**

**Screening visit:** informed consent, medical examination, medical background and previous treatment, subject selection, blood sampling.

[redacted]

| | |
|---|---|
| **Statistical methods:** | All the variables will be described using adapted statistics according to their type (quantitative data or qualitative data).<br>Where appropriate, statistical tests will be performed, to assess the change from baseline. Skin quality parameter changes will be evaluated with a mixed ANOVA model for repeated measures. |
| **Foreseen study duration:** | Foreseen First Subject First Visit: Q3 2019<br>Foreseen Last Subject Last Visit: Q2 2020<br>Clinical investigation global duration: 10 months<br>Duration by subject: 9 months + screening period |

# 2- IDENTIFICATION AND DESCRIPTION OF THE DEVICE UNDER INVESTIGATION

## 2.1 SUMMARY DESCRIPTION OF THE DEVICE UNDER INVESTIGATION AND ITS INTENDED PURPOSE

Juvéderm® VOLITE is a class III resorbable injectable medical device with CE marking since 2016. It is a sterile pyrogen-free physiological solution of cross-linked hyaluronic acid which is not of animal origin. This injectable implant is used for the treatment, by filling, of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity. The presence of lidocaine in the product is meant to reduce the patient's pain during treatment.

## 2.2 DETAILS CONCERNING THE MANUFACTURER OF THE DEVICE UNDER INVESTIGATION

**Manufacturer:**

ALLERGAN
Route de Promery
Zone Artisanale de Pré-Mairy
74370 PRINGY-FRANCE

## 2.3 NAME OR NUMBER OF THE MODEL/TYPE

Juvéderm® VOLITE

## 2.4 TRACEABILITY OF THE DEVICE UNDER INVESTIGATION

Each device is assigned a batch number to insure its traceability from its production to its destruction. In the device packaging, 2 traceability labels mentioning the device name, batch number and expiry date are present. One of these labels should be stuck in subject medical file.

Moreover, each device will be labelled with a specific label for the investigational study.
The labelling of the devices for the clinical study will be realized by Dermscan.
Here is an example of the label which will be pasted on each device packaging (blister and box), in Polish language:

## 2.5 INTENDED PURPOSE OF THE DEVICE IN THE PROPOSED CLINICAL INVESTIGATION

Improvement of skin quality attributes.

## 2.6 POPULATION AND INDICATIONS FOR WHICH THE DEVICE UNDER INVESTIGATION IS INTENDED

In the proposed clinical study, the device under investigation is intended to be administered to healthy subjects aged between 30 and 50 years old. This age group has been chosen to have homogeneous mature skins, able to be improved by hyaluronic acid injection.

## 2.7 DESCRIPTION OF THE DEVICE UNDER INVESTIGATION

| | |
|---|---|
| **Tested device** | Juvéderm® VOLITE |
| **Formula** | Hyaluronic Acid Gel 12 mg<br>Lidocaine hydrochloride 3 mg<br>Phosphate buffer pH 7.2 q.s. 1 ml (or g) |
| **Galenic form** | Sterile pyrogen-free physiological gel of cross-linked hyaluronic acid |
| **Route/ mode of administration** | Intra-dermal injection |
| **Packaging** | The gel is presented in a graduated, pre-filled, disposable syringe of 1 ml.<br>Each box contains two 1 mL Juvéderm® VOLITE syringes, 4 single-use 32G1/2" sterile needles to be used only for injecting Juvéderm® VOLITE, an instruction leaflet and a set of labels in order to ensure traceability. |
| **Blinding procedure** | Commercial packaging will be used |
| **Storage** | At room temperature (below 25°C) |
| **Intended purpose** | ✓ Juvéderm® VOLITE is an injectable implant used for the treatment, by filling, of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity.<br>✓ The presence of lidocaine is meant to reduce the patient's pain during treatment. |

## 2.8 SUMMARY OF THE TRAINING AND EXPERIENCE NEEDED TO USE THE DEVICE UNDER INVESTIGATION

The device under investigation must only be used by authorised practitioners, trained in injecting implants, after fully familiarizing themselves with the device, its complete instruction leaflet and CIP.

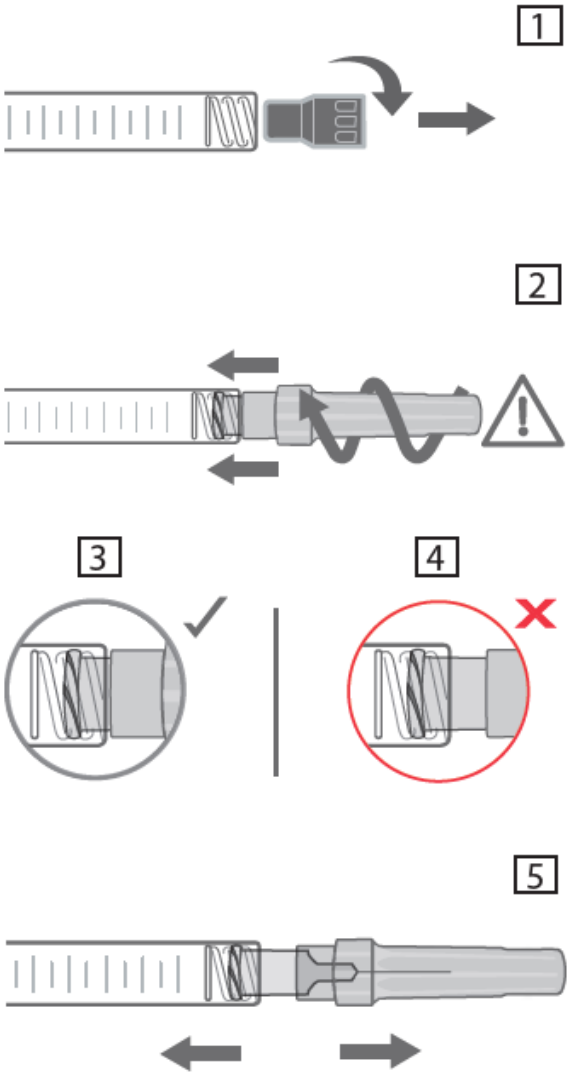
## 2.9 DESCRIPTION OF THE SPECIFIC MEDICAL OR SURGICAL PROCEDURES INVOLVED IN THE USE OF THE DEVICE UNDER INVESTIGATION

1. The area to be treated should be disinfected thoroughly prior to the injection. Hyaluronic acid is known to be incompatible with quaternary ammonium salts such as benzalkonium chloride. Juvéderm® VOLITE should therefore never be placed in contact with these substances or with medical-surgical instrumentation which has been treated with this type of substance. There is no known interaction with other local anaesthetics.

2. Remove tip cap by pulling it straight off the syringe as shown in fig. 1 below. Then firmly push the needle provided in the box (fig. 2) into the syringe, screwing it gently clockwise. Twist once more until it is fully locked and has the needle cap in the position shown in fig. 3. If the needle cap is positioned as shown in fig. 4, it is incorrectly attached.

3. Next, remove the protective cap by holding the body of the syringe in one hand, the protective cap in the other, as shown in fig. 5, and pulling the two hands in opposite directions.

4. Prior to injecting, depress the plunger rod until the product flows out of the needle. Inject slowly and apply the least amount of pressure necessary.




Recommendations:

- ✓ If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle. Failure to comply with these precautions could cause a disengagement of the needle and/or product leakage at luer-lock level.
- ✓ After needle insertion and before injection, it is recommended to withdraw slightly the plunger to aspirate and verify the needle is not intravascular.
- ✓ If immediate blanching occurs at any time during the injection, the injection should be stopped and appropriate action taken such as massaging the area until its return to a normal color.
- ✓ The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue and the injection technique. The amount injected will depend on the areas which are to be corrected based on the experience of the medical practitioner.
- ✓ Do not overcorrect as injection of an excessive volume can be at the origin of some side effects such as tissue necrosis and oedema.
- ✓ It is important to massage the area treated after the injection in order to ensure that the material has been uniformly distributed.

# 3- JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

## 3.1 SUMMARY OF THE RESULTS OF THE RELEVANT PRE-CLINICAL TESTING/ ASSESSMENT CARRIED OUT TO JUSTIFY THE USE OF THE DEVICE UNDER INVESTIGATION IN HUMAN SUBJECTS

The device is already on the market and has the CE marking since 2016.

## 3.2 CLINICAL DATA

The safety of JUVÉDERM VOLITE XC is supported by preclinical biocompatibility data, which show that it is nontoxic, noncytotoxic, nongenotoxic, nonirritant, nonsensitizing, noncarcinogenic, and nonpyrogenic.

A prospective, single-arm European postapproval study (V12 001) was conducted at a single center (6 injecting physicians from 6 countries) to assess the safety and effectiveness of JUVÉDERM VOLITE without lidocaine in treating fine lines and skin roughness in the face and neck. Treatment was administered on both sides of the face (cheek and forehead) and neck (if desired) for fine lines and the improvement of skin roughness. For 131 treated subjects, a total of 261 cheeks, 120 foreheads, and 96 necks were treated. Touch-up treatments were provided for 31 subjects (23.7%) and 46 cheeks (17.6%), and repeat treatments at 9 months were provided for 62 subjects (47.3%) and 124 cheeks (47.5%). Among treated cheeks with scores of moderate or severe at baseline on the Allergan Fine Lines Scale (AFLS), the AFLS responder rate was 89.4% at Month 1, 66.7% at Month 4, 40.5% at Month 6, 15.6% at Month 9, and 94.3% at 1 month after repeat treatment. The responder rate on the Allergan Cheek Smoothness Scale (ACSS; (formerly known as the Allergan Skin Roughness Scale) was 96.2% at Month 1, 76.3% at Month 4, 34.9% at Month 6, 15.8% at Month 9, and 87.1% at 1 month after repeat treatment. A statistically significant improvement ($p < 0.001$) in subject satisfaction with skin based on the FACE Q Satisfaction with Skin questionnaire was observed at all timepoints. The V12 001 study served as the basis for the present study's injection volumes and treatment characteristics (see Section 6.2) as well as a study follow-up duration of 3 months based on the product's responder rate and observed clinical duration.

Existing studies have primarily evaluated the physical and visual changes (e.g. reduction of wrinkles, changes in hydration, etc.) following HA filler treatment (see European post-approval study V12 001 above). Additional effects due to the physical interaction of cells and tissue with the implanted filler are not well understood, except through a limited number of animal studies (Wang et al., 2007; Paliwal et al., 2014; Mochizuki et al., 2018; Fan et al., 2019) and clinical studies evaluating primarily changes in collagen production (Turlier et al., 2013; Wanick et al., 2016). Changes to gene and protein expression of extracellular matrix proteins and cytokines/growth factors beyond collagen can have a significant impact on clinical outcomes beyond just evaluating the ability to correct wrinkles but have not been evaluated clinically. Further understanding of these effects requires biopsies and can lead to improved understanding of the clinical benefits for patients, especially related to improvements in skin quality.

# 4- RISKS AND BENEFITS OF THE DEVICE UNDER INVESTIGATION AND CLINICAL INVESTIGATION

## 4.1 ANTICIPATED CLINICAL BENEFITS

Volite is indicated for treatment, by filling, of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity. This study is designed to further evaluate improvements to skin quality attributes that may have an impact on potential clinical benefits for patients receiving Volite to address skin quality and early signs of aging. No direct clinical benefit is expected for healthy subjects participating in the study, as the product injection will only be done on a small zone of volar forearms. However, locally, an improvement of skin quality, such as moisturization or elasticity may be observed. This study will help to add further understanding of the benefits of treatment for patients.

## 4.2 ANTICIPATED ADVERSE DEVICE EFFECTS

As described in the product leaflet:

Potential side effects associated with implantation of this product, may occur immediately or may be delayed. These include, but are not limited to:

| Potential immediate side effects | Potential delayed side effects |
|---|---|
| Inflammatory reactions (redness, oedema, erythema, etc.) which may be associated with itching and/or pain on pressure and/or paresthesia, occurring after the injection. These reactions may last for a week | In rare cases, abcesses or granuloma after hyaluronic acid injection have been reported. |
| Haematomas. | Delayed hypersensitivity after hyaluronic acid and/or lidocaine injections have also been reported. |
| Induration or nodules at the injection site. | |
| Staining or discoloration of the injection site might be observed, especially when HA dermal filler is injected too superficially and/or in thin skin (Tyndall effect). | |
| Immediate hypersensitivity after hyaluronic acid and/or lidocaine injections have also been reported. | |

## 4.3 RESIDUAL RISKS ASSOCIATED WITH THE DEVICE UNDER INVESTIGATION

As with any skin injection, risks can be posed by the injection procedure itself, the anesthetic agent, and injection of JUVÉDERM VOLITE XC injectable gel. Risks related to the injection procedure include redness, itching, pain, tenderness, swelling, bruising, and lumps and bumps, which are common to dermal filler injection procedures in general and typically resolve within 1 month (De Boulle et al., 2015; Signorini et al., 2016; Heydenrych et al., 2018). The use of a small gauge needle to deliver JUVÉDERM VOLITE XC used in this study is intended to minimize tissue trauma. In rare instances, adverse events (e.g. abcesses, nodules, swelling) may occur weeks to months following implantation. Materiovigilance data of the last three years (since the product launch) show a 0.004% rate of inflammatory nodules reported after injection of Juvederm® VOLITE, without any case of confirmed granuloma by biopsy. The ability to reverse (dissolve) hyaluronic acid fillers and defined consensus treatment algorithms minimize the long-term impact of these events (Alam et al., 2008, De Boulle et al., 2015; Signorini et al., 2016; Heydenrych et al., 2018). The inclusion of 0.3% lidocaine in the formulation is meant to reduce pain during the injection, and this needs to be taken into account when administering concomitant additional anesthetics as well as in relation to subjects' medical history (ie, allergy to lidocaine). Risks associated

with the anesthetic agent include allergic reactions that may manifest as an anaphylactic reaction, skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient loss of skin color.

### 4.4 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

Blood sampling:
Subjects may experience a brief uncomfortable pricking sensation from the introduction of a needle into their forearm vein and hematoma at the puncture point. There is also a small risk of fainting during the sampling and a risk of infection or nervous lesion (motor or sensitive disability).

[redacted]

Scarring:
The subject may experience visible scarring as a consequence of the biopsies. The subject will have to not expose the biopsies zones to the sun or UV light, in order to minimize the chance of scarring, during at least three months.

### 4.5 POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

As described in the product leaflet:

- Juvéderm® VOLITE should not be used simultaneously with laser treatment, deep chemical peels or dermabrasion. For surface peels, it is recommended not to inject the product if the inflammatory reaction generated is significant.
- It is recommended not to inject into a site which has been treated with a permanent implant.
- No clinical data is available regarding the efficiency and tolerance of Juvéderm® VOLITE injections in patients having a history of, or currently suffering from, autoimmune disease or autoimmune deficiency or being under immunosuppressive therapy.
- Patients on anti-coagulation medication or using substances that can prolong bleeding (warfarin, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, or other substances known to increase coagulation time such as herbal supplements with garlic or ginkgo biloba, etc.) must be warned of the potential increased risks of bleeding and haematomas during injection.

These treatments are part of exclusion criteria of the study. Such subjects will not be included.

### 4.6 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

The risks are mitigated by using qualified clinical injectors who have training and experience in intradermal procedures, implants, and biopsies and have access to modern medical facilities to conduct those procedures. Only one site will participate in this study. In addition, risks are mitigated by including only those subjects that meet the study entry criteria. Consequently, careful definitions of specific eligibility criteria, study procedures and instructions for use, appropriate selection, qualification and training of the investigator, and subject follow-up procedures have been designed as to further contribute to reduce risks as far as possible for the subject and residual risk acceptance.

### 4.7 RISK-TO-BENEFIT RATIONALE

Based on pre-clinical and clinical data already obtained on the product before its commercialization, as well a materiovigilance feedback, no specific risk is expected after intra-dermal injection of Juvéderm® VOLITE in forearms by a qualified and trained injector.

No specific benefit is anticipated for healthy subjects participating in the study.

# 5- OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

## 5.1 OBJECTIVE

To evaluate the impact on skin quality attributes, including physical measurements [redacted], following administration of Juvéderm® VOLITE in the volar forearms of healthy volunteers.

## 5.2 HYPOTHESES TO BE ACCEPTED OR REJECTED BY STATISTICAL DATA

Not applicable. Exploratory study.

## 5.3 CLAIMS AND INTENDED PERFORMANCE OF THE DEVICE UNDER INVESTIGATION THAT ARE TO BE VERIFIED

Improvement of skin quality attributes such as hydration and elasticity and good tolerance.

## 5.4 RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS THAT ARE TO BE ASSESSED

The anticipated adverse device effects that are to be assessed are the one described in § 4.2.

# 6- DESIGN OF THE CLINICAL INVESTIGATION

## 6.1 GENERAL INFORMATION

### 6.1.1 Study design

The study will be:

- prospective,
- open-label, single arm
- intra-individual,
- single centre,
- on healthy subjects

### 6.1.2 Foreseen study dates

Foreseen First Subject First Visit: Q3 2019
Foreseen Last Subject Last Visit: Q2 2020
Global duration of the study: 10 months
Global duration by subject: 9 months + screening period

### 6.1.3 Sample size

11 subjects will be included to expect at least 10 subjects analyzed.

### 6.1.4 Description of the measures to be taken to minimize or avoid bias

A repositioning mask of the injection zone will be made for the injected area and measurement zones in order to find back the exact same area at each time point.

### 6.1.5 Primary and secondary endpoints

6.1.5.1 Performance/Exploratory Endpoints

Changes in skin quality parameters, as listed in the table below, one and three months after Juvéderm® VOLITE injection in the forearms, in comparison with before treatment (D0). Evaluated skin parameters and instruments used are summarized in the table below:

| Instrument | Measurement of interest |
|---|---|
| MoistureMeter D® 0.5 mm | Hydration (epidermis + dermis) |
| MoistureMeter D® 1.5mm | Hydration (epidermis + dermis) |
| Corneometer® | Hydration (superficial layers of epidermis) |
| Cutometer® | Elasticity |
| Elastimeter® | Elasticity |
| Skin Scanner® | Skin thickness and density |
| Vivosight OCT® | Skin roughness, density and vascularity |
| Glossymeter® | Brightness |
| Spectrophotometer® | Colour |
| Mexameter® | Melanin content |

[redacted]

6.1.5.2 Safety Endpoints

- Injection Site Reactions (ISRs) evaluated by the investigator at each time point after injection.
- Collection of adverse events and incidents at all visits including severity, action taken, and relationship to device.

### 6.1.6 Flow chart

**Table 1- Study flow-chart**

[redacted]

### 6.1.7 Equipment to be used for assessing, recording and analysing variables and arrangements for monitoring maintenance and calibration

[redacted]

## 6.2 DEVICE UNDER INVESTIGATION

### 6.2.1 Description of the exposure to the device

Juvéderm® VOLITE will be injected on D0, on a zone of 8 cm x 4 cm (32 $cm^2$) of the volar left forearm.

6.2.1.1 Dosage

The study area will be treated by the specialist injector per the DFU (approximately 0.01 mL intradermal microboluses, spread 0.5 - 1 cm apart, over a 4 x 8 cm area) into the left forearm. A maximum of 1 ml will be injected on the zone treated.

6.2.1.2 Instructions for use

Juvéderm® VOLITE will be injected as per the current European DFU (Directions For Use).
The 32G$^{1/2"}$ needles present with the product will be used for the injection.
Superficial intra dermal injections of micro aliquots (or microbolus) without papular formation will be performed.
A massage is necessary post injection and a basic cream for the massage can be used.

### 6.2.2 Justification of the choice of comparator(s)

Not applicable, non-comparative study.

### 6.2.3 Other medical device or medication to be used during the clinical investigation

[redacted]

### 6.2.4 Concomitant treatments

6.2.4.1 Collection of concomitant treatments

Any concomitant medication at selection of the subject into the study must be reported on the source document and in the study Case Report Form (CRF) at the initial visit and will be taken into consideration by the Investigator deeming study eligibility.
Any modification on these medications during the study must be reported on the source document and in the study CRF.
Use of any concomitant medication will be recorded in the CRF with the following information:

- Indication for use of the treatment;
- Name of the drug, and unit strength;
- Dose administered;
- Route of administration;
- Duration of treatment (start and stop date).

6.2.4.2 Rescue treatment(s)

In case of adverse reaction affecting subject well-being, the investigator is authorized to prescribe to the subject a rescue treatment/medication.
The adverse event will be recorded in the subject's CRF and source document, including details on rescue medication.

## 6.3 STUDIED POPULATION

### 6.3.1 Inclusion criteria for subject selection

1. Healthy subject
2. Sex: male and female
3. Age: between 30 and 50 years old at the time of the written consent.
4. Subjects with Fitzpatrick skin type II or III.
5. Subject willing to receive Juvéderm® VOLITE in the forearms and agrees to complete all study required procedures, including having 6 cutaneous punch biopsies taken in the forearms and blood drawn (HIV, B and C hepatitis analysis at screening).

[redacted]

9. Written informed consent and data privacy consent obtained.

### 6.3.2 Exclusion criteria for subject selection

**In terms of population:**

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

[redacted]

4. Subject participating to another research on human beings or being in an exclusion period for a previous study.
5. Intensive exposure to sunlight or UV-rays within the previous month and foreseen during the study.
6. Subject having other resorbable filling product injections, a laser treatment, an ultrasound-based treatment, radiation treatment, a dermabrasion, a surgery, a deep chemical peeling or other ablative procedure on the studied zones within the past 12 months prior to study start.
7. Subject with subcutaneous retaining structure on the studied zones (meshing, threads, gold strand).
8. Subject having received injections of permanent or semi-permanent filling products in the studied zones.

[redacted]

**Related to previous or ongoing treatment:**

24. Subject under anti-coagulant treatment or treatment liable to interfere with the healing process or hemostasis, during the previous month and during the study.
25. Subject receiving or is planning to receive anti-inflammatory drugs (oral/injectable corticosteroids or NSAIDs, e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (herbal supplements with garlic or ginkgo biloba, etc) for 10 days prior to study treatment and 3 days after.
26. Subject under immunosuppressive therapy.

[redacted]

### 6.3.3 Withdrawal criteria

Any deviation to the CIP that can affect:
- the primary evaluation criterion,
- the adherence of the subjects to the study schedule,
- the adherence relative to the products use,
- the inclusion / exclusion criteria,

can be considered as an exclusion criterion. Before any exclusion of the subject from the study, each case will be discussed with the Sponsor who will make the final decision if the subject must be excluded from the study.

### 6.3.4 Restrictions and recommendations

**Recommendations after injection**:
- Subjects are recommended not to use cosmetic products on the zone injected during 16 hours.
- Subjects are recommended to avoid intensive exposure to sunlight or UV rays, temperatures below 0°C, as well as any sauna or hammam sessions during the 2 weeks following the injection treatment.
- To limit bleeding and bruising, subjects are recommended not to use aspirin, anti-inflammatories and anti-coagulants during 1 week after injection.

[redacted]

**Restrictions**:
- Subjects must not take part in any other clinical study on human beings.
- Subjects must continue using their usual cleansing and care products on the studied zones for the whole study period.
- Subjects must not apply any care product to the studied area 24 hours before each visit to the site.
- Subjects must keep their dietary habits.

### 6.3.5 Recruitment procedure

Subjects will be recruited by phone from Dermscan data base according to inclusion and exclusion study criteria. This data base is constituted from registration files of people wishing to participate in clinical studies at Dermscan.
Advertisement will be placed in Dermscan website and reception.

### 6.3.6 Subjects identification

Each subject having signed a consent form will be assigned a “screening subject number” according to

[redacted]

### 6.3.7 ID card

[redacted]

## 6.4 PROCEDURES

### 6.4.1 Study schedule

[redacted]

[redacted]

[redacted]

[redacted]

### 6.4.2 Description of performance procedures

6.4.2.1 Summary of performance assessments

**Table 2- Summary of performance parameters**

| Instrument | Measurement of interest | Parameters studied |
|---|---|---|
| MoistureMeter D® 0.5 mm | Hydration (epidermis+ dermis) | Hydration rate (TDC) |
| MoistureMeter D® 1.5mm | Hydration (epidermis + dermis) | Hydration rate (TDC) |
| Corneometer® | Hydration (superficial layers of epidermis) | Hydration rate (A.U.) |
| Cutometer® | Elasticity | Uf (R0), Ur, Ua (R8), Uf – Ua (R1), Ua/Uf (R2), Ur/Ue (R5), Uv/Ue (R6), Ur/Uf (R7) (mm), Q1, Q2, Q3 |
| Elastimeter® | Elasticity | ISE (N/m) |
| Skin Scanner® | Skin thickness and density | % of non-echogenic surface (skin density), skin thickness (mm) |
| Vivosight OCT® | Skin roughness, density and vascularity | For roughness: Ra, Rq, Re, Sp, Sv, Sz<br>For density: A-scan in mm and AU<br>For vascularity: unitless |
| Glossymeter® | Brightness | Brightness Index (GU) |
| Spectrophotometer® | Colour | L*, a*, b* (A.U.), ITA°(°) |
| Mexameter® | Melanin content | Melanin Index (A.U.) |

[redacted]

6.4.2.2 MoistureMeter D®

**MoistureMeter D® (Delfin Technologies)** allows to measure water content of biological tissues.

[redacted]

6.4.2.3 Corneometer®

Epidermis hydration measurements will be performed [redacted]

6.4.2.4 Cutometer®

**Cutometer®**

[redacted]

6.4.2.5 Elastimeter®

**The ElastiMeter® (Delfin Technologies)**

[redacted]

[redacted]

6.4.2.6 SkinScanner®

Measurements are performed directly *in vivo*, using the high frequency echograph **DUB® SkinScanner (TPM).**

[redacted]

6.4.2.7 Vivosight OCT®

The Vivosight Dx is a Multi-Beam Optical Coherence Tomography (OCT) system indicated for use in the two-dimensional, cross-sectional, real-time imaging of external tissues of the human body. [redacted]

[redacted]

6.4.2.8 Glossymeter®

The **Skin-Glossymeter® GL200 (*Courage & Khazaka*)** measures both the fraction of light being reflected directly from the sample (skin) and the scattered fraction of reflected light. [redacted]

[redacted]

6.4.2.9 Spectrophotometer®

Skin colorimetric measurement will be done with a **MINOLTA CM700-d Spectrophotometer®**, [redacted]

[redacted]

[redacted]

6.4.2.10 Mexameter®

**Mexameter® MX18 is a Courage and Khazaka** device, [redacted]

6.4.2.11 Serology checking

A blood sample will be taken before subject inclusion in order to ascertain volunteer serologic status for Hepatitis B and C, and HIV to ensure the safety of the biological samples taken during the course of the study.

[redacted]

6.4.2.12 Cutaneous biopsies

[redacted]

[redacted]

### 6.4.3 Description of safety parameters

6.4.3.1 Local tolerance

Immediately after injection, one and three months after injection, the investigator will evaluate the local tolerance of the tested device with the following 4-point numerical rating scale (NRS):

**Table 4- List of ISR**

| Parameter | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| Redness / Erythema | ☐0 | ☐1 | ☐2 | ☐3 |
| Pain / Tenderness | ☐0 | ☐1 | ☐2 | ☐3 |
| Induration | ☐0 | ☐1 | ☐2 | ☐3 |
| Swelling / Oedema | ☐0 | ☐1 | ☐2 | ☐3 |
| Lumps / Bumps | ☐0 | ☐1 | ☐2 | ☐3 |
| Bruising / Hematoma | ☐0 | ☐1 | ☐2 | ☐3 |
| Itching | ☐0 | ☐1 | ☐2 | ☐3 |
| Discoloration/ pigmentation | ☐0 | ☐1 | ☐2 | ☐3 |

Each local reaction will be described by the intensity as follows:

| | Qualification | Definition |
|---|---|---|
| 0 | None | |
| 1 | Mild | Discomfort noted, but no disruption to normal daily activities. No treatment considered |
| 2 | Moderate | Discomfort sufficient to reduce or affect normal daily activities; treatment may be needed. |
| 3 | Severe | Inability to work or to carry out normal daily activities; treatment is required. |

Moreover, the subjects will be given a daily-log in order to grade each ISR described above, each day during 28 days after injection. The ISR will not be reported in the Adverse Event Form except if still present at D28, if they require a medical treatment of if judged abnormal by the investigator.

6.4.3.2 General tolerance

Collection of adverse events by the investigator.

### 6.4.4 Description of activities performed by Sponsor representatives

The Sponsor has delegated the following activities to the CRO (Dermscan):

- Submission of the study files to the EC and regulatory authorities
- Monitoring
- Data management
- Statistical analysis and clinical investigation report writing.
- Management and transportation of biopsies

### 6.4.5 Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results

None.

## 6.5 MONITORING

The monitoring of the study will be done by a CRA, ofDermscan France. The monitor has the responsibility to familiarise the investigator(s) and the centre staff involved in the study with all study procedures if necessary. The monitor has the responsibility of reviewing the ongoing study with the investigator(s) to verify adherence to the CIP and to deal with data queries as well as any problems that arise during the conduct of the study. After each visit, a monitoring report will be sent to the sponsor.

### 6.5.1 Monitoring visits

[redacted]

### 6.5.2 Access to source data

In accordance with good clinical practices and the standards of the data protection law, data obtained during a research involving human beings must be treated confidentially to guarantee the subjects' privacy.

The investigator agrees that, subject to local regulations and ethical considerations, the Sponsor representatives' designee and/or and any regulatory agency have direct access to all study records, CRFs, corresponding subject/patient medical records, study drug dispensing records and study drug storage area, and any other documents considered source documentation. The investigator also agrees to assist the representative, if required.

# 7- STATISTICAL CONSIDERATIONS

The statistical analysis will be performed by Dermscan Biostatistician.

## 7.1 STATISTICAL DESIGN, METHOD AND ANALYTICAL PROCEDURES

### 7.1.1 Intermediary analysis

An intermediary analysis will be planned after D94 visit for safety and performance endpoints.
The final analysis will be done at the study end with the last safety data.

### 7.1.2 Analysis population

The following analysis populations will be studied and will be considered for the statistical analysis:

- Safety population: any subject having used the tested device.
- FAS (Full Analysis Set): Any subject included in the study with at least a post-basal value.

The analysis of the safety/tolerance parameters will be performed on the “safety” population. The analysis of the performance parameters will be performed on the FAS.

### 7.1.3 Descriptive statistics

Descriptive statistics will be presented for each parameter. Categorical variables will be summarized with frequency and relative frequency. Continuous variables will be summarized by number of subjects, mean, median, standard deviation, minimum, and maximum. Where appropriate, 2-sided 95% CIs for population mean, or population proportion, will be provided as part of the descriptive summary.

### 7.1.4 Patient accountability

A flow diagram will be drawn with the number of patients enrolled, the number and % of screen failures and reason for exclusion, the number and % of patients receiving the medical device, the number and % of patients dropping out before and reason for dropping out, and the number and % of patients completing the study.

### 7.1.5 Demographic data and other baseline characteristics

The studied population will be described on the demographic and injection parameters recorded at the screening and inclusion visits. The listing of medical history and prior medications will also be provided.

### 7.1.6 Performance endpoints

#### 7.1.6.1 Skin quality measurements

Descriptive statistics will be provided on both primary endpoint (one month change) and secondary endpoints (comparison zones for both one- and three months changes). Considering primary criterion of change between baseline and one month, descriptive statistics is a requirement while ANOVA model is served as exploratory analysis.

All parameters listed in Table 2 of paragraph 6.2.4.1 ([redacted]) will be analysed using a mixed ANOVA model for repeated measures (*MIXED procedure of SAS*®) fitted to raw data.

The following factors will be included in the model:

- Zone as fixed (2 levels: treated and control)
- Time as fixed (3 levels: D0, D28 and D84)
- Zone by time interaction

To capture the correlation between data obtained from a same subject, an unstructured variance - covariance matrix (*UN@UN*) is set.

The specific contrasts of interest will be built (*LS-Means statement*) to:

- Assess the change from baseline value (D0) on D28 and D84 within each zone
- To compare the zones for the change (D28-D0) and (D84-D0)

The underlying assumptions (residual normality and homoscedasticity) will be analyzed with Shapiro-Wilk test and graphs to judge the model validity. In case of strong deviation, a data transformation or a non-parametric approach (Wilcoxon signed rank test) will be carried out.

[redacted]

### 7.1.7 Safety Endpoints

For each parameter of ISR evaluation, the score distribution will be summarized in frequency and percentage by time point.

In addition, for each parameter of ISR evaluation, the proportion of the subjects presenting the sign will be also computed and summarized in frequency and percentage.

The individual listing of AE will be provided.
AEs, ADEs, SAEs and SADEs will be summarized by presenting the number and percentage of patients having any sign or symptom. AEs will be classified by System Organ Class (SOCs) and Preferred Term (PTs) using MedDRA.

### 7.2 SAMPLE SIZE AND ITS STATISTICAL JUSTIFICATION

This study is an exploratory study, no formal sample size calculation has been performed.
11 subjects will be included to have at least 10 subjects analysed (10% of drop-out rate expected).

### 7.3 LEVEL OF SIGNIFICANCE AND POWER OF THE CLINICAL INVESTIGATION

All statistical tests will be assessed at $\alpha$ = 5% level of significance in a bilateral approach.

### 7.4 EXPECTED DROP-OUT RATES

It is considered as acceptable to lose a maximum of 10% of subjects in the final analysis population.

### 7.5 STATISTICAL PASS/FAIL CRITERIA TO BE APPLIED

Not applicable, exploratory study.

### 7.6 CRITERIA FOR THE TERMINATION OF THE CLINICAL INVESTIGATION ON STATISTICAL GROUNDS

As no interim statistical analysis has been planned, no statistical criteria for the termination of the clinical investigation has been defined.

### 7.7 DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any modification to the statistical analysis plan due to a substantial modification of the CIP will be documented as an amendment and will be described in the final study report if applicable.

### 7.8 TREATMENT OF MISSING, UNUSED OR SPURIOUS DATA, INCLUDING DROP-OUTS AND WITHDRAWALS

No strategy for taking in charge missing data has been defined. Data that are not valid or missing will be considered and treated as missing data.

# 8- DATA MANAGEMENT

### 8.1 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING AND ISSUING/RESOLVING DATA QUERIES

#### 8.1.1 Identification of source data

The data related to the subject characteristics, to their actual or previous medical state and to the safety of the device will be notified in the subject's source document and the Case Report Form (CRF).

The data relative to the device efficacy will only be collected in the CRF and/or directly in specific software and will be considered as source data.

### 8.1.2 Data collection

All data for this study will be recorded on CRF or directly recorded within data capture software for measurement instruments.

[redacted]

### 8.1.3 Data entry

[redacted]

### 8.1.4 Data coding

Not applicable.

### 8.1.5 Data Review

[redacted]

### 8.1.6 Preparation of the Database and Locking

[redacted]

### 8.1.7 Data unblinding

Not applicable, open study.

### 8.1.8 Final Report

A final report according to ISO 14155:2012 will be written by the Project Manager. A draft will be sent to the Sponsor for validation. This final report will be signed by the principal investigator, the Project Manager, the Biostatistician and the Sponsor.

## 8.2 PROCEDURES FOR VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEMS, IF APPLICABLE

Verification, validation and securing of electronic clinical data systems is done according to Dermscan Standard Operating Procedure (SOP). No e-CRF will be used for the study.

## 8.3 PROCEDURES FOR DATA RETENTION

The Sponsor must archive the CIP, documentation, approvals and all other essential documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out, for 30 years. Dermscan will archive all documents concerning the study as detailed below:

- All documents must be archived in a secure place and treated as confidential material.
- Paper documents relating to this study are stored maximum during one year on site before to be transmitted for archiving to an approved service provider.
- Data will be archived securely as digital and paper version for 15 years from the date of dispatch of the final report's acceptance.

At the end of this period of 30 years, the study archives will be destroyed unless otherwise stipulated in writing by the Sponsor.

## 8.4 OTHER ASPECTS OF CLINICAL QUALITY ASSURANCE

In order to ensure the conformity of the studies entrusted to Good Clinical Practices and regulatory requirements, DERMSCAN has implemented a quality management system which has been certified ISO 9001:2008.

# 9- AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

The Sponsor or the Investigator might modify the CIP for ethical, medical or scientific reasons.
No change can be implemented at investigational sites, unless to eliminate an immediate hazard to study subjects, without having obtained the favourable opinion of the Sponsor.

These changes will be documented in the Trial Master File (TMF) and communicated to investigational centres as soon as possible.

If applicable, changes will be submitted as substantial or non-substantial modification (according to its nature) to EC.

# 10- DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

The Investigators are not allowed to deviate from the CIP, excepted under emergency circumstances, to protect the rights, safety and well-being of the subjects. In this case, such deviations shall be documented and reported to the Sponsor and the EC as soon as possible.

### 10.1 PROCEDURES FOR EVALUATING SUBJECT COMPLIANCE

The device under investigation will not be dispensed to the subject but will be injected at D0 at the study centre.
Subjects will be given a daily log to report any adverse event or concomitant treatment.

### 10.2 PROCEDURES FOR RECORDING, REPORTING AND ANALYSING CIP DEVIATIONS

All CIP deviations will be managed according to Dermscan Standard Operating Procedure (SOP).

Deviations to the CIP should be classified as:

- **Minor** if they don't impact the rights, safety or well-being of the subjects. They do not increase the risk or do not diminish the benefit for the subject and/or do not have a significant effect on the integrity of the data collected,
- **Major (or CIP violations**) if they affect the rights, safety or well-being of participants. They increase the risk or diminish the benefit for the subject and/or have a significant effect on the integrity of the data in the study.

If the deviation is reported/observed during the study, the sponsor/the investigator may decide to drop-out the subject of the study or not.
If the deviation is detected after the study end, the case will be discussed during the « data review » which occurs before data analysis.

### 10.3 CORRECTIVE AND PREVENTATIVE ACTIONS AND PRINCIPAL INVESTIGATOR DISQUALIFICATION CRITERIA

If major deviations from the investigator is observed during the study, the CRA/study monitor will warn the investigator of the importance to respect the CIP. An investigator who continuously violates the CIP despite CRA warnings could be excluded from the investigation after agreement of the Sponsor.

## 11- DEVICE ACCOUNTABILITY

The device will be used only under conditions defined in this CIP and only for included subjects.

The CRO must keep an updated dispensation form which contains the subject number, the number of Medical Device (MD) injected to each subject, with the corresponding dates. This will be collected on a specific form.

All MD supplies (empty containers, as well as partly used and unused MD) must be available for inspection at every monitoring visit. The study monitor should verify the investigational site's devices accountability records against record of administrated doses in the CRF. All MD (wasted and unused) must be returned by the Investigator to the Sponsor at the end of the study.

## 12- STATEMENTS OF COMPLIANCE

### 12.1 REGULATORY ASPECT

The study will be performed on healthy subjects, in accordance with:

- the study CIP,
- the Good Clinical Practices (GCP),
- the ISO 14155:2012 standard and its updates, and any regional or national regulations,

- the ethical principles that have their origin in the Declaration of Helsinki and its later modifications.
- the polish law

### 12.2 ETHICS COMMITTEE

It is the responsibility of the Sponsor or its legal representative to submit a copy of the CIP and detailed subject information sheet and consent form to an ethics committee in order to obtain independent approval to conduct the study. Ethics committee approval must be obtained before the study is started. The Ethics Committee submission is delegated by the Sponsor to the CRO Dermscan.
The approval of the ethics committee must be sent in writing, to the Sponsor or its legal representative and then to the investigator. The Ethics Committee approval letter must mention the Ethics Committee members and their function. Any additional requirements imposed by the EC must be followed, if appropriate.

### 12.3 PERSONAL DATA PROTECTION

In this study, DERMSCAN processes personal data of subjects on behalf of the Sponsor, in accordance with the rules on the protection of personal data and, in particular, the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data,. For this purpose, DERMSCAN limits the collection and use of personal data to that which is needed for analysis and control purposes, by insuring their security and integrity and by guaranteeing their confidentiality.
DERMSCAN makes sure beforehand and throughout the duration of the data-processing:
- of the compliance with the obligations of the applicable data protection law,
- to inform subjects of their personal data-processing and obtain their consent on it,
- to implement and maintain appropriate technical and organisational measures.

An identification code is attributed to each subject for the purpose to keep his/her identity confidential. This code consists of: the first letter of the subject's first name and the first letter of his/her last name.

According to Article 14 of GDPR, the concerned subject must be informed of the identity and the contact details of the Controller and, where applicable, of the controller's representative.

### 12.4 INSURANCE

The Sponsor has subscribed an insurance contract to cover the financial consequences of the liability of all investigators, the Sponsor itself and anyone involved in the study.

The collaboration agreements are established by the Sponsor/service provider, as defined in the requirements specification.
The copy of the insurance certificate is presented separately in the EC submission file.

## 13- INFORMED CONSENT PROCESS

Voluntary written informed consent form must be obtained from each subject prior to perform any study related procedures in compliance with the recommendations of the Declaration of Helsinki. Subject should not be screened or enrolled before the subject has signed an approved informed consent form, written in a language that is understandable to the subject.

Each subject should be given both verbal and written information describing the nature and duration of the clinical study. The informed consent form should be signed and personally dated in two originals by the subject and the person who conducted the informed consent discussion. The investigator, or the attending physician, will explain the nature, purpose and risks of the study. The subject will be informed that he has the right to withdraw at any time from the study, without giving reasons. The informed consent process should

take place under conditions where the subject has adequate time to consider the risks and benefits associated with her participation in the study.

The investigator is responsible for assuring the appropriate content of the informed consent form and that informed consent is obtained from each subject in accordance with all applicable regulations. The informed consent form will be reviewed and approved by the Sponsor.

Each subject should receive one original of the signed and dated written informed consent form and any other information provided to the subject.

The second original of the signed and dated informed consent form should be retained in the investigator's file. The investigator should maintain a log of all subjects who sign the informed consent form.

No copy will be given to the Sponsor.

# 14- ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

## 14.1 DEFINITIONS

Table below presents categorization of adverse events:

| ADVERSE EVENTS | Non-device-related | Device- or procedure-related | |
|---|---|---|---|
| **Non-serious** | **Adverse Event (AE)**[a] | **Adverse Device Effect (ADE)** | |
| **Serious** | **Serious Adverse Event (SAE)**[b] | **Serious Adverse Device Effect (SADE)** | |
| | | **Anticipated** | **Unanticipated** |
| | | **Anticipated Serious Adverse Device Effect (ASADE)** | **Unanticipated Serious Adverse Device Effect (USADE)** |

a Includes all categories
b Includes all categories that are serious

### 14.1.1 Adverse event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device.

NOTE 1: This definition includes events related to the medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to medical devices.

### 14.1.2 Adverse device effect (ADE)

Adverse event related to the use of a medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the l medical device.

### 14.1.3 Device deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE 1: Device deficiencies include malfunctions, use errors and inadequate labelling.

### 14.1.4 Serious adverse event (SAE)

A serious adverse event is defined as an adverse event that led to:

a) death (death is the result and not the event),

b) serious deterioration in the health of the subject, that either resulted in

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient or prolonged hospitalization, or
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

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

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

### 14.1.5 Serious adverse device effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

### 14.1.6 Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse device effect whose nature, incidence, severity, or outcome have not been identified in the current version of the risk analysis report."

NOTE: anticipated serious adverse device effect (ASADE) is an effect whose nature, incidence, severity or outcome have been identified in the risk analysis report.

### 14.1.7 Severity definition

The severity of adverse events/reactions can be graded on a three-point scale:

* **Mild**: discomfort noted, but no disruption to normal daily activities.

* **Moderate**: discomfort sufficient to reduce or affect normal daily activities.
* **Severe**: inability to work or to carry out normal daily activities.

### 14.1.8 Relationship to the medical device(s)

The Investigator must determine the relationship (if any) between an adverse event and the device or CIP.

For the purpose of harmonizing reports, each AE will be classified according to five different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device[1] or procedures (MEDDEV 2.7/3 revision 3, May 2015).

**Not related**: relationship to the device or procedures can be excluded when:

- the event is not a known side effect[2] of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the device or the procedures;
- the serious 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 event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious 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 device used for diagnosis[3], when applicable;
- harms to the subject are not clearly due to use error;
- 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 event.

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

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

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

**Causal relationship**: the serious event is associated with the device 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;

[1] Investigational device: any device object of the clinical investigation, including the comparators.
[2] When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered “not related”. Yet, the unexpected effect shall not be excluded from evaluation and reporting.
[3] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

- the event has a temporal relationship with device use/application or procedures;
- the event involves a body-site or organ that
  - the device or procedures are applied to;
  - the device or procedures have an effect on;
- the serious 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 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 device used for diagnosis2, 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 event.

The Sponsor and the Investigators will distinguish between the adverse events related to the 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 device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of device use/application. In some particular cases the event may be not 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.

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

## 14.2 PROCESS FOR REPORTING ADVERSE EVENTS AND DEVICE DEFICIENCIES

### 14.2.1 Documentation

All adverse events shall be documented in a timely manner throughout the clinical investigation in the source document and in the “adverse event documentation” form in the CRF.
Investigators are responsible for documenting adverse events in the table provided for this purpose.
All AE reports should contain:

- a brief description of the event, localization,
- date and time of onset,
- severity of symptoms,
- treatment required,
- relationship with device and CIP procedures,
- action taken with the device,
- outcome,
- date of resolution,
- duration of the event,
- and whether the event is classified as serious.

This information is reported at the end of the study in the clinical report.

All device deficiencies shall be documented throughout the clinical investigation and appropriately managed by the Sponsor.
Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

shall be reported as specified below.

### 14.2.2 Reporting by the Investigator

The declaration of Serious Adverse Event (Events, Reactions, or suspicion of Serious Adverse Reactions) is a legal requirement. Timelines for reporting adverse events to the Sponsor are described in the table below:

| | **Reporting by the Investigator** |
|---|---|
| **What to report?** | • All AEs will be reported to Allergan Product Surveillance Department.<br>• all SAEs (except for those recorded in the CIP or the investigator's brochure as not requiring an immediate notification)<br>• the results of abnormal analyses defined in the CIP as determining factors for the evaluation of the safety of individuals participating in the research |
| **To whom?** | • For SAE, to Vigilance/Materiovigilance Department at Allergan: [redacted]<br>• For AE, to Product Surveillance Department at Allergan: [redacted] |
| **How to report?** | **1- First notification:**<br>**SAEs immediately upon awareness** by telephone, fax, or e-mail.<br><br>**2- Completed form sending:**<br>the first notification is confirmed by sending the completed SAE form and AE documentation form by fax or e-mail with an acknowledgement of receipt, **within 48 hours of knowledge by the investigator**.<br>The AEs will be notified within 72 hours of knowledge by the investigator.<br><br>**3- Additional follow-up reports:**<br>send by fax or e-mail.<br><br>*Note: As a part of monitoring of serious adverse events, if necessary, this first notification will be followed by additional detailed written reports. In notifications, individuals participating in research are identified by a code number.* |

### 14.2.3 Reporting by the Sponsor

Sponsor will submit any post market vigilance reports as required.

## 14.3 PROCESS FOR REPORTING A PREGNANCY

The occurrence of a pregnancy (reported or diagnosed) after screening but before inclusion (first use of the device) in the study is not reported to the Sponsor unless severity criteria (like SAE related to CIP procedures). If the pregnancy is confirmed, the studied device must not be administered and the subject immediately withdrawn from the study.

The Investigator must immediately notify the Sponsor of the pregnancy using specific form and reports the withdrawn from the study in the CRF (study end).
Women who become pregnant during the study will be followed until the outcome of the pregnancy is known and reported to the Sponsor (baby health).

### 14.4 LIST OF FORESEEABLE ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

The anticipated adverse device effects and foreseeable adverse events are described in section 4.2.

### 14.5 INFORMATION REGARDING THE DATA MONITORING COMMITTEE (DMC)

For the purposes of this study, no data monitoring committee will be formed, because:
- studied population is not considered to be high-risk population: healthy subjects, young (< 50 years old) and female subjects of childbearing potential should use a medically accepted contraceptive regimen,
- medical device contains known components and is available on the market.
- lastly, study duration is short enough (94 days).

## 15- VULNERABLE POPULATION

Not applicable. The population studied during the clinical investigation is not considered as a vulnerable population.

## 16- SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

### 16.1 STUDY END

The study end is defined as the last subject last visit.

### 16.2 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

#### 16.2.1 Criteria and modalities for suspension or premature termination of the whole clinical investigation

Urgent security measures in case of a new fact, which involves the premature termination of the study, might occur.
They are followed, according to the case, by a study end declaration or by a substantial modification request. The opinion request is submitted in a 15 days delay after the implementation of urgent security measures to the Ethics Committee and to the Competent Authority if applicable.

#### 16.2.2 Criteria for access and to breaking the blinding/masking code

Not applicable.

#### 16.2.3 Requirements for subjects follow-up

Subjects participating in the study are informed of the urgent security measures by the Investigator. A first information is made by phone, followed by a written document sent by email or post mail with receipt confirmation. A visit with the Investigator is then planned as soon as possible.

# 17- PUBLICATION POLICY

The Sponsor reserves the right to review all the manuscript(s) and abstract(s) before their submission for publication or presentation. Publication of data will be at the discretion of the Sponsor.

This is not intended to restrict or hinder publication or presentation, but to allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator(s).

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