Study Title:

EVALUATION OF EFFICACY AND SAFETY OF PROFHILO STRUCTURA® FOR THE CORRECTION OF ACNE SCARS ON THE FACE

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E0222

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EVALUATION OF EFFICACY AND SAFETY OF PROFHILO STRUCTURA® FOR THE CORRECTION OF ACNE SCARS ON THE FACE

1. AIM OF THE STUDY

Aim of the study is to evaluate the efficacy and the safety of the deep injection of Profhilo Structura® in acne scars of the face (ice picks, rolling, boxcars).
It is also aim of this study to evaluate volunteer's satisfaction with the treatment effects and physicians satisfaction with the study products use.

2. MATERIALS

- Profhilo Structura® (IBSA Farmaceutici Italia S.r.l. - see Appendix 1)
-25 G, 40 mm Magic Needles (Cannula) (with 23 G Needle for entry point)
-25 G Terumo Needle
- Digital camera
- Primos compact portable (GFMesstechnik)

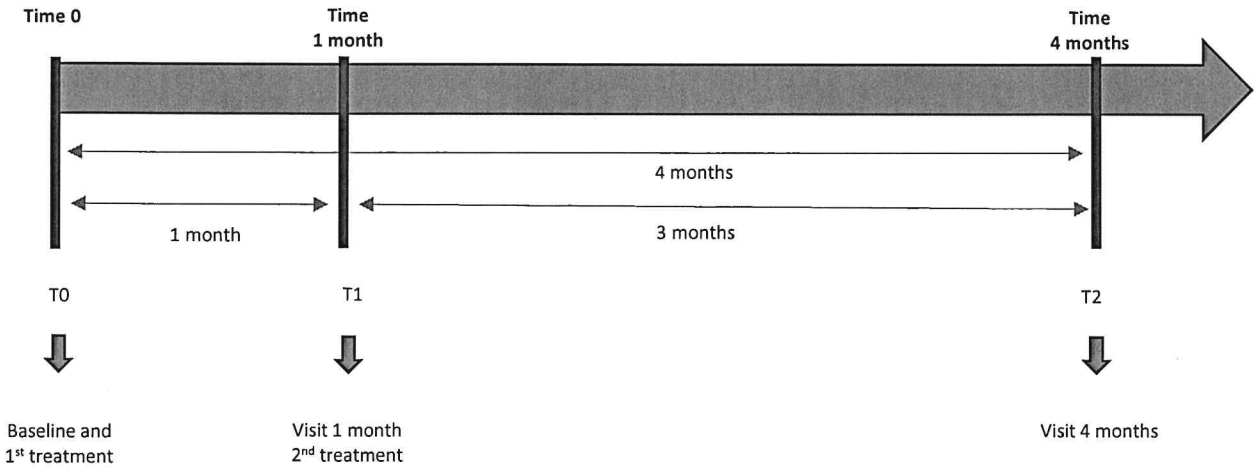
3. STUDY DEVICE

ProfhiloStructura® (IBSA Farmaceutici Italia S.r.l.) is a resorbable medical device 2 ml non-pyrogenic pre-filled syringe, containing 2 ml of 4,5% hyaluronic acid for intradermal use (45 mg H-HA + 45 mg L-HA dissolved in 1,5 ml of saline buffered sodium chloride – IBSA Farmaceutici Italia S.r.l. – ITALY. The principal component of the medical device is Hyaluronic Acid of non-animal origin, produced by bacterial fermentation.
To note that in the clinic preliminarily tested 8 subjects volunteers with the product under study, with no adverse events occurrence.

4. STUDY DESIGN

4.1. Study plan
Open clinical trial, conducted by 1 center under dermatological control.
3 visits will be performed during the study:

- T0 (baseline) clinical and instrumental evaluations, followed by the 1st injection procedure
- T1 (1 month after the 1st injection procedure) - clinical and instrumental evaluations, followed by the 2nd injection procedure
- T2 (3 months after the 2nd injection procedure) - clinical and instrumental evaluations.



4.2. Experimental design

The 1st treatment will be performed during T0 visit, after the basal evaluations planned by the study procedure. Treatment of acne scars of the face by using a subcision+injection technique: the needle (25 G) or cannula (25 G) (wider areas are treated with the cannula) is inserted into the skin and made to move with a back-and-forth motion in order to detach scar collagen bundles. Then the product is injected. The 2nd treatment will be performed after 4 weeks (1 month from T0). Results of the study will be elaborated after the completion of the clinical phase.

4.3. Investigators

The study will be conducted by and under the supervision of a dermatologist.

5. RECRUITMENT OF THE VOLUNTEERS

5.1. Characteristics of the population

The study will be conducted on Caucasian of both sexes volunteers aged >18 years

5.2. Number of volunteers

A total of 30 subjects will be enrolled in the trial.

5.3. Inclusion criteria

Volunteers with the following characteristics will be included in the study:

- caucasian subjects of both sexes;
- age >18years
- asking for acne scars treatment;

- presenting acne scars (ice picks, rollings, boxcars);
- available and able to return to the study site for the post-procedural follow-up examinations;
- agreeing to present at each study visit without make-up;
- accepting to not change their habits regarding food, physical activity, make-up use, face cosmetic and cleansing products;
- accepting not to expose their face to strong UV irradiation (UV session, or sun bathes) during the entire duration of the study, without appropriate sun protection;
- accepting to sign the Informed consent form.

5.4. Exclusion criteria

5.4.1. Dependent on the volunteers' characteristics:

- smokers;
- performing in the 6 month before the trial beginning HA injections, radiofrequency treatment, toxin treatment;
- contraindication or know allergy to the devices' components or to the treatment;
- participation in a similar study actually or during the previous 3 months
- known pregnancy
-occurrence of pregnancy during the study

5.4.2. Dependent on a clinical condition

5.4.2.1. Dermatological disease

- Dermatitis;
- presence of cutaneous disease on the tested area,different from those under study
- recurrent facial/labial herpes;
- clinical and significant skin condition on the test area (e.g. active eczema, psoriasis, severe rosacea, scleroderma, local infections and severe acne).

5.4.2.2. General disease

- Diabetes, coagulation disorders, connective tissue disorders, lipodystrophy or other systemic disease;
- HIV and/or immunosuppressive disease;
- cancerous or precancerous lesions in the either right or left midface;
- severe allergies manifested by a history of anaphylaxis, or history or presence of severe multiple allergies;
- alcohol or drug abusers.

5.4.3. Dependent on a pharmacological treatment

- Anti-inflammatory drugs, anti-histaminic, topic and systemic corticosteroids, narcotic, antidepressant, immunosuppressive drugs (with except of contraceptive or hormonal treatment starting more than 1 year ago);
- assumption of drugs able to influence the test results in the investigator opinion.

The use of other drugs, not mentioned above, can be authorized by the Investigator. The trade name, the dosage, the start and stop date of the therapy will be reported on Case Record Form (CRF).

5.4.4. Restrictions

The volunteers accept to respect the rules fixed in the list of recruitment criteria and not to deviate from their normal life habits. Moreover, the month preceding the inclusion visit and during the entire period of treatment, sun and UV light exposure, will be avoided. In the case of UV exposure, very high protection cream must be used.

6. CASE RECORD FORM

For each volunteer a Case Record Form is filled and a progressive number is assigned to each one. Personal data, subject's history, inclusion/exclusion criteria, clinical evaluations are registered in the CRF.

7. SAMPLE ACCEPTANCE, IDENTIFICATION AND APPLICATION

The Sponsor supplies directly each study center and samples will be save as indicated by the Sponsor. The products to be tested are recorded, with a reference number, in the Human Studies Record Book together with additional information such as the arrival date, the test requested, Sponsor's name, the product code, the order number and any other information reported on the container.
During the twelve months following the issue date of the report, a counter-sample will be kept in the same conditions as those described above.

8. TREATMENT EVALUATION

8.1. Inclusion visit
Each volunteer is submitted to a careful clinical examination in order to check the selection criteria.

8.1. Clinical evaluations
Clinical assessment will be performed during the basal visit (T0) and then at T1 (1 month, 2nd aesthetic procedure) and T2 after 3 months since the 2nd aesthetic procedure. The grade of scarring will be evaluated by Goodman and Baron scale:

TABLE 1. Goodman and Baron Grading Scale of Postacne Scarring

GRADE	SEVERITY GRADE	CHARACTERISTICS	EXAMPLES OF SCARS/LESIONS
1	Macular	Erythematous, hyper- or hypopigmented flat marks visible to patient or observer irrespective of distance	Erythematous, hyper- or hypopigmented flat marks
2	Mild	Mild atrophy or hypertrophy that may not be obvious at social distances of 50cm or greater and can be adequately covered by makeup, the normal shadow of shaved beard in males, or normal body hair if extrafacial	Mild rolling, small soft papular
3	Moderate	Moderate atrophic or hypertrophic scarring that is obvious at social distances of	More significant rolling, shallow, boxcar, mild-to-

		50cm or greater and is not able to be covered by makeup, the normal shadow of shaved beard in males, or normal body hair if extrafacial, but is still able to be flattened by manual stretching of the skin	moderate hypertrophic or papular scars
4	Severe	Severe atrophic or hypertrophic scarring that is obvious at social distances of 50cm or greater and is not able to be covered by makeup, the normal shadow of shaved beard in males, or normal body hair if extrafacial, and is not able to be flattened by manual stretching of the skin	Punched-out atrophic (deep boxcar), ice pick, bridges and tunnels, gross atrophy, dystrophic scars, significant hypertrophy or keloid

8.2.3. Non-invasive instrumental evaluations

A measurement of the skin surface affected by acne scars is taken thanks to Primos compact portable device (GFMesstechnik); Primos software is able to measure skin principal profilometric parameters in vivo or on skin replicas, according to the law DIN EN ISO 4228; moreover, the software compares directly the different images obtained at the times foresee by the protocol.

As a measuring method Primos compact uses a digital stripe projection based on micro mirrors which allows for fast and highly precise measuring data acquisition (the speed of under 70ms for the measuring data admission provide perfect results of measurement).

An assortment of different measuring fields, realized by means of different precise recording optics ensures a wide spectrum of measuring possibilities with ranges up to micrometres.

The portable probe assures a constant distance from the skin as well as a fixed illumination angle of incidence; in this way is possible to acquire standardized and reproducible measurements.

8.2.3 Digital images

Clinical pictures are taken at the level of treated scars at each considered evaluation time, in order to compare them and assess the efficacy of the treatment.

8.3. Standard conditions for the treatment evaluations

8.3.1. Volunteers

During 3 hours before the visit the volunteer must not smoke, drink coffee or alcohol. Any cosmetic product can be used on the skin test areas from 2 hours before each visit.

All study evaluations are performed at room temperature; no temperature/humidity recording is required.

8.3.3. Acclimatization
Before each visit the volunteer will get acclimatized under relax conditions for at least 10-15 min.

8.4. Self assessment questionnaire (subjects' judgment)
At T2 each volunteer fills a questionnaire regarding:

- the efficacy of the study treatment on acne scars (score: very marked; marked; medium; light; absent);
- the treatment tolerance (score: bad; poor; medium, good; excellent).

9. TOLERANCE

9.1. Tolerance evaluation
Product tolerance will be evaluated considering:

- local expected events/reactions induced by the micro-injection (tardive swelling, pain, erythema, bruise)
- any other adverse event/reaction, also of systemic source occurred during the study

9.2. Adverse event
9.2.1. Definition and classification
Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects undergoing a clinical investigation, users or other persons which does not necessarily have a causal relationship with the product under investigation. AEs may manifest as new findings (signs, symptoms, diagnoses, laboratory results) or alterations in pre-existing conditions.

NOTE 1: This definition includes events related to the investigational 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 investigational medical devices.

Adverse Device Effect (ADE): an Adverse Device Effect (ADE) is defined as adverse event related to the use of the investigational medical device.
Note 1: This definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation or any malfunction of the investigational medical device.
Note 2: This definition also includes any event resulting from user error or from intentional abnormal use of the investigational medical device.

Serious Adverse Event (SAE): an Adverse Event that:

a. Led to death,
b. Led to a serious deterioration in health of subject, user, or others that:
Resulted in a life-threatening illness or injury, or

Resulted in persistent or significant disability or incapacity and/or permanent impairment of a body function or permanent damage to a body structure, or
Required in-patient hospitalization or prolongation of existing hospitalization, or
Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if
a) suitable action had not been taken, or
b) intervention had not been made, or
c) if circumstances had been less fortunate.
NOTE 2: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a SAE.
The term "life-threatening" in the definition refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Serious Adverse Device Effect (SADE): a Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.

Incident:

a. any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.
b. Any technical or medical reason in relation to the characteristics or performance of a device for the reasons referred to in subparagraph (a), leading to systematic recall of devices of the same type by the manufacturer.

Device Deficiencies (DDs): any inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling. A malfunction is 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. A use error is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user (including slips, lapses, and mistakes). An abnormal use is an act or omission of an act by the operator or user of a medical device as a result of conduct which is beyond any means of risk control by the Manufacturer.

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Definition of the severity of an Adverse Event/Reaction:
The severity/intensity of adverse events/reactions can be graded either on a three-point scale:

- **Mild or Grade 1**: discomfort noted, but no disruption to normal daily activities.
- **Moderate or Grade 2**: discomfort sufficient to reduce or affect normal daily activities.
- **Severe or Grade 3:** inability to work or to carry out normal daily activities.

Relationship with the tested product:
The investigator evaluates the cause-effect relation of each adverse event to the experimental product. Each AE will be classified according to 5 different levels of causality":

- **not related**
- **unlikely**
- **possible**
- **probable**
- **certain**

If there is insufficient or incomplete evidence to make a clinical judgment of the causal relationship, the causality can be evaluated as "not assessable". All adverse events judged by either the reporting Investigator or the sponsor as having a reasonable causal relationship to a medical device qualify as adverse device effects.

9.2.2 Categories of Adverse Events

Table 1. Categories of Adverse Events

ADVERSE EVENTS	Non-device-related	Device- or procedure-related	
Non-serious	Adverse Event (AE)	Adverse Device Effect (ADE)	
Serious	Serious Adverse Event (SAE)	Serious Adverse Device Effect (SADE)	
		Anticipated	Unanticipated
		Anticipated Serious Adverse Device Effect (ASADE) [1]	Unanticipated Serious Adverse Device Effect (USADE) [2]

[1] ASADE: is an effect which by its nature, incidence, severity or outcome has been identified in the IFU / Manual
[2] USADE: is an effect which by its nature, incidence, severity or outcome has not been identified in the current version of the IFU / Manual

9.2.2.2 AEs/Incidents reporting procedure

All incidents and adverse events (AEs) or adverse device effect (ADE) regardless the seriousness must be reported in the source file (if applicable) and in the "Adverse event form" (see "CRF " enclosed in Appendices section). Investigators are responsible for documenting adverse events in the eCRF section created for this purpose.
Moreover, the investigator must determine:

(a) if the event is serious or not
(b) if the event is related or not related to the study treatment.

Any adverse event, related or not related to the study treatment, must be documented and will be followed until completed resolution (see paragraph 8.2.3.).
Then, the investigator will decide to:

(a) interrupt definitively the study treatment

(b) continue the study as protocol directed
(c) interrupt temporary the study treatment
(d) end the study

In case a subject's withdraws from the trial, the form "End of Study" should be filled in and the reasons for discontinuation recorded. The withdrawal subject should be encouraged to attend the final visit for the last study assessment.

9.2.2.3 AEs submission

The investigator must immediately notify to Sponsor (IBSA) all Incidents/SAEs/SADEs occurred during the study by fax, or e-mail and within 24 hours of the investigator becoming aware of the event to the below dedicated contact details:

IBSA Drug Safety Unit (DSU)
Telephone n.: 0371 617378
Fax n.: +41 58 360 1695 / 0371 617290
Email: farmacovigilanza@ibsa.it

using the Adverse Event MD form (Appendix 1) provided by the Sponsor.

The Sponsor will confirm the receipt of the concerned Incident/SAE to the investigator by e-mail within 48 hours after the first report was received.
Without acknowledgement of receipt of the e-mail, a letter with acknowledgement of receipt is also sent to the Sponsor accompanied by the form.

Day 0 is the day that the Sponsor receives a notification report from an Investigator and will be the reference to calculate the due date for reporting to the concerned Authorities.

The general provisions for reporting to the concerned Authorities by the Sponsor are into the MEDDEV 2.7/3 guideline.
According that the Sponsor must notified to Independent Ethics Committee, copying also Ministero della Salute:

a) any SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other subjects, subjects, users or other persons or a new finding to it: immediately, without delay after awareness by Sponsor of a new reportable event or of new information in relation with an already reported event.
b) Any other reportable events, or a new finding or 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.

For the purpose of safety reporting within this study, National Laws must be taken into account and will be mandatory.

9.2.2.4. Incidents submission
The Manufacturer is responsible to assess if a SAE meets the criteria for Incident reporting. If the SAE meets the criteria for Incident Reporting, the Manufacturer will observe all reporting requirements to the Competent Authority and the Notified Body in conformance with the applicable

law (European directives 93/42/CEE and 90/385/CE reviewed for directive 2007/47/CE) without delay according to MEDDEV 2.12-1 guideline timelines:

- **Serious public health threat**: immediately (without any delay that could not be justified) but not later than **2 calendar days** after awareness by the Manufacturer of this threat.
- **Death or unanticipated serious deterioration in state of health**: immediately (without any delay that could not be justified) after the Manufacturer established a link between the device and the event but not later than **10 elapsed calendar days** following the date of awareness of the event.
- **Others**: immediately (without any delay that could not be justified) after the Manufacturer established a link between the device and the event but **not later than 15 elapsed calendar days** following the date of awareness of the event

9.2.3. Adverse event follow up

All SAEs should be followed-up by the Investigator in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or the subject is lost to follow-up.

If the study product causes an adverse event, the Investigator could withdraw the subject from the study. During the final visit the Investigator will determine whether the adverse event is ongoing or resolved. In any case it must be followed up to complete resolution.

The Investigator could decide to momentarily suspend the treatment and then to reintroduce it, only if the subject agrees and if the adverse event has been classified "mild/moderate" and its relationship to the study product results unlikely/possible.

All further follow up visits necessary to monitor the adverse event, will be recorded in the adverse event form.

9.2.4. Occurrence of Pregnancy

The investigator must immediately, at the latest within 24 hours from the investigator first notice of the event, inform the Sponsor of the pregnancy using specific form.

Women who become pregnant during the study will be withdrawn from the study but followed until the outcome of the pregnancy is known, and reported to the Sponsor (baby health) using a pregnancy outcome form.

10. SCHEDULE OF STUDY PROCEDURE

10.1. Baseline (T0)

The visit includes:

- detailed explanation of the study procedures and informed consent signature
- filling in the CRF (personal data, subject's history, concomitant medications)
- check of inclusion/exclusion criteria, with particular attention to the assessment of a possible subject's sensitivity to the test product or its ingredients
- clinical and instrumental assessments
- Profilometry measurement
- 1st micro-injection procedure.

10.2. Intermediate visit (T1 1 month after the 1st aesthetic procedure)
The visit includes:
- record of possible adverse events or intervened illness
- clinical and instrumental assessments
- Profilometry measurement
- 2nd injection procedure.

10.3. Final visit (T2, 4 months after the 1st aesthetic procedure)
The visit includes:
- record of possible adverse events or intervened illness
- clinical and instrumental assessments
- Profilometry measurement
- self assessment questionnaire at T2

10.4. Premature end of the study
This visit is identical to the final visit.

11. PREMATURE END OF THE STUDY/ END OF THE STUDY

11.1. Withdrawal criteria
Any person who in the course of the trial:
- decides to withdraw the consent for any reason
- does not present to the study visits
- does not comply with the treatment
- develops any of the conditions specified in the original exclusion criteria
- contracts a serious illness that does not allow the study continuation
- other reason of the patient to quit.

11.2. Procedure
All breaks in a volunteer's participation in the trial have to be recorded in the study termination form the reasons for discontinuation being mentioned.
In case of volunteers did not perform the expected visit, the Investigator has to try to understand the reason of the absence.

11.3. Restrictions
The volunteers, who stop the trial, cannot be enrolled again or be replaced by other volunteers with the same randomization number.

12. STATISTICAL ANALYSIS PLAN

12.1. Main criteria
The statistical evaluations of clinical and instrumental data (adjusted means and standard deviation) and relative graphs will be performed at the times required by the protocol. The values will be rounded off to the decimal in accordance to our internal procedures.

12.2. Population description
This sample includes all subjects that completed the study according to the protocol.

12.3. Clinical data
The statistical analysis of clinical data is carried out with not parametric test.

12.4. Instrumental data
The analysis of all numeric parameters (arithmetic mean, standard deviation) and their relative graphs are carried out:

- by non parametric test when the normality hypothesis is rejected by the Shapiro-Wilk test at the threshold inferior to 5%.
- by parametric test, when the normality hypothesis is confirmed by Shapiro-Wilk test.

12.5. Statistical plan
The activity of the test product at each study time will be expressed in absolute values versus baseline (T0).

13. ETHICS

13.1. Ethic Committee Approval
A final version of the study protocol and appendices will be submitted to an independent Ethic Committee (E.C.) to be examined; a copy of the E.C. decision has to be sent to the Sponsor. Moreover a copy of the E.C. approval has to be enclosed to the study documentation, while the Informed Consent Form has to be stored separately in order to respect the volunteers' privacy. Any subject must be included in the trial before the Ethic Committee study approval. Moreover any volunteer must sign the Informed Consent Form before protocol inclusion. Finally the Sponsor and the Investigator agree to inform the Ethic Committee in case of protocol amendments and of serious or unexpected adverse events which could damage volunteers' safety or the study continuation. This study will be conducted according to the ethic of the "Helsinki Declaration" (see Appendix 6). A list of the members of the E.C., who examined the protocol, has to be enclosed in the Investigator and Sponsor's file.
The approval documentation has to enclose these information:
* the protocol title, the issue date, the Sponsor and the Investigator's name.
* an approval declaration for the protocol and the CRF, with the annotations of each possible change.
* a list of E.C members
* the E.C President signature
* E.C. address (c/o DermIng S.r.l., Clinical Research and Bioengineering Institute, Via Valassina, 29 – 20159 Milan).
The study will start only after Indipendent Ethical Committee approval.

13.2. Consent form for the volunteer
Each volunteer is precisely informed about the study and the personal data processing according to the Bioethics Committee approval and Italian law indications (Guidelines July 24, 2008); before the inclusion each subject reads the information form related to the study and its methodology. Once informed the volunteer will complete and sign the consent form. At the end of the study the investigator will declare to have informed all the volunteers who participated in the protocol, signing and dating the relative form.

13.3. Products conformity to the current regulations
The test starts only after the evaluation of the documentation provided by the Sponsor (with products identification, date and Sponsor signature).

This documentation contains: the declaration that the products are submitted to the E.C.C. legislation, the qualitative composition of the products with the declaration that any component presents a serious toxicological effects at the established concentration, all available data about toxicological and tolerability pre-clinical tests, the normal conditions of the products use, a Sponsor attestation of insurance/statement of responsibility related to the risks for the volunteers who will use the products according to the foresee conditions of use. The administration of the products can be stopped immediately as soon as the Investigator judges it necessary.

13.4. Insurance
The study is covered by insurance policy company for damages related to the study product and by involved doctors' insurance policies for damages induced by the micro-injection procedure.
0260/03/0024707 and 0260/03/0024695 of Reale Mutua company for damages induced by the microinjection
procedure.

14. CONFIDENTIALITY

15.1. Final report
The final report contains: the identification of the tested product, a summary of the procedure, results' evaluation and conclusions about the clinical test.

14.2. Publication
Everything concerning this study must be considered confidential. DermIng Institute and the Sponsor commit themselves to respect confidentiality and to divulge the whole study or part of it on the basis of a written consent of the counterpart. The documentation can be reproduced only for DermIng internal use.

15. REFERENCES

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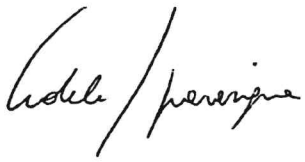
STUDY PROTOCOL APPROVAL

I certify to have checked and approved this study protocol

DermIng S.r.l., Research Director: Dr. Adele Sparavigna - Main investigator

Signature :  Date : 21/10/2022

IBSA Farmaceutici Italia S.r.l. Sponsor's representatives: Dr. G. Bellia

Signature :  Date : 21/10/2022