Study Title:

AESTHETIC PERFORMANCE AND TOLERANCE OF AN INJECTIVE INTRADERMAL TREATMENT FOR THE SKIN ROUGHNESS AND LAXITY OF BACK OF THE HANDS

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AESTHETIC PERFORMANCE AND TOLERANCE OF AN INJECTIVE INTRADERMAL TREATMENT FOR THE SKIN ROUGHNESS AND LAXITY OF BACK OF THE HANDS

1. RATIONALE AND AIM OF THE STUDY

People lose collagen all over the body, not just in the face; skin roughness and laxity of the dorsum of the hands can result from chrono and photo-aging.

This skin roughness and laxity can range from very mild to severe; injection procedures can provide new tone and firmness to the skin of the hand dorsum.

Dermal fillers are the most used non-permanent injectable materials available today to correct skin flaccidity and roughness on the dorsum of the hands. They give immediate aesthetic effect due to elastic gel matrix injected and impart longer term effects due to bio stimulation, promoting new collagen formation.

The objective of this study is to investigate the aesthetic performance of the Hyaluronic acid (HA)-based dermal filler Profhilo® Body injected by a blunt tip microcannula (25G or 22G, preferably 22G), with fanning technique through a single entry point performing 5 passages and injecting 0,3 ml per passage, 1,5 ml for each hand. Volunteers of both sexes, aged 18-65 years with mild-moderate skin roughness and laxity at the level of hand dorsum are to be treated.

Primary endpoint of the study is the evaluation of performance and tolerance of Profhilo Body (3ml) treatment in the back of the hands (or dorsum of the hands).

Secondary endpoint is self-assessment questionnaire by both doctors and volunteers.

2. MATERIALS

- Profhilo Body® (IBSA Farmaceutici Italia S.r.l. - see Appendix 1)
- 22 G, 40mm, Magic needles
- Digital camera
- Dermal Torque Meter (Dia-Stron LTD)
- MoistureMeterD (Delfin Technologies, Kuopio - Finland)
- Primos compact portable (GFMesstechnik).

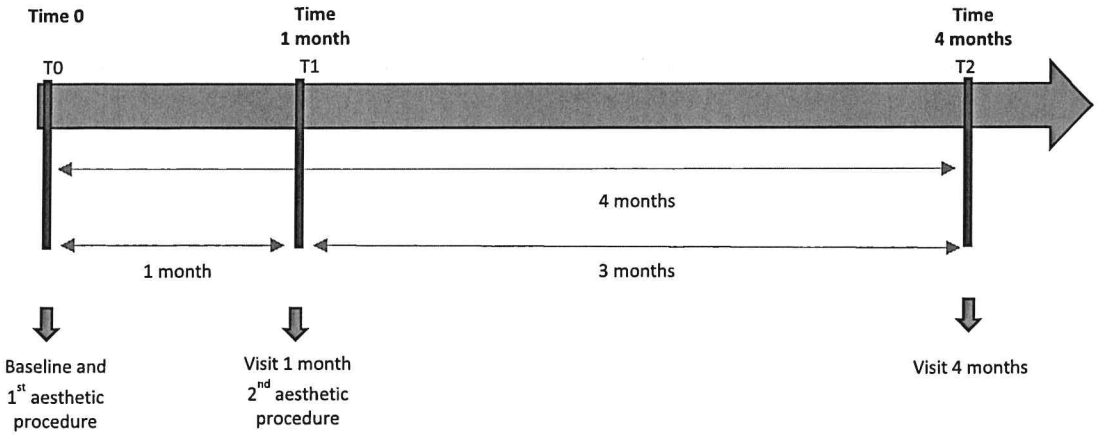
3. STUDY DEVICE

Profhilo® Body (IBSA Farmaceutici Italia S.r.l.) is a resorbable medical device 3.25 ml non-pyrogenic pre-filled syringe, containing 3 ml of 3.2% hyaluronic acid for intradermal use (48 mg H-HA + 48 mg L-HA) dissolved in 3 ml of saline buffered sodium chloride. – IBSA Farmaceutici Italia S.r.l. – ITALY. The principle component is cross-linked Hyaluronic Acid of non-animal origin, produced by bacterial fermentation (see Appendix 1).

On the basis of preceding trials with Profhilo® product, no reaction like injection site reaction, allergies and hypersensitivity reactions (see appendices 1) have been observed. This is due to the fact that this hyaluronic acid is not derived from animal tissue. Some side effects, like little bleeding and/or ecchymosis can happen shortly after injection.

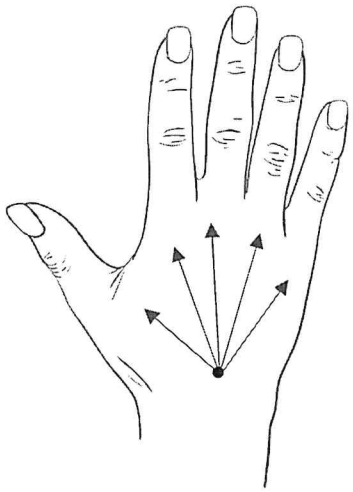
4. DESIGN OF THE STUDY
Open, monocentric.
3 visits, 55 subjects.
T0: inclusion/exclusion criteria**, instrumental and clinical evaluation*, 1° treatment
T1 (after 1 month): instrumental and clinical evaluation, 2° treatment
T2 (3 months after T1; 4 months after T0): instrumental and clinical evaluation, NO treatment

Visit number	Study Activities	Treatment
1 T0	Information and consent form provided. If participants agreeable, to sign consent form. Photographic assessment: - Clinical photography Clinical assessment Instrumental assessment First treatment of Profhilo® (refer to study protocol)	Profhilo Body 3 ml 1.5 ml per hand injected by a blunt tip microcannula (25G or 22G, preferably 22G), with fanning technique through a single entry point performing 5 passages and injecting 0,3 ml per passage.
2 T1 (1 month after T0)	Photographic assessment: - Clinical photography Clinical assessment Instrumental assessment Second treatment of Profhilo® (refer to study protocol) Self-evaluation questionnaire	Profhilo Body 3 ml 1.5 ml per hand injected by a blunt tip microcannula (25G or 22G, preferably 22G), with fanning technique through a single entry point performing 5 passages and injecting 0,3 ml per passage.
3 T2 (4 months after T0)	Photographic assessment: - Clinical photography Clinical assessment Instrumental assessment NO treatment Self-evaluation questionnaire	No



4.1 INJECTION METHOD

Fanning technique with single entry point, 5 passages with cannula (25G or 22G, preferably 22G), 0,3 ml per passage, 1,5 ml for each hand.



5. RECRUITMENT OF THE VOLUNTEERS

5.1. Characteristics of the population

The study will be conducted on volunteers of both sexes, aged between 18 and 65 years, who meet the inclusion and exclusion criteria required by the study procedure.

5.2. Number of volunteers

In order to obtain at least 50 evaluable cases, 55 volunteers will be enrolled in the trial

5.3 Inclusion criteria

Will be included in the study volunteers with the following characteristics:

- female and male sex, not necessarily 1:1 ratio;

- age 18-65 years;
- asking for hands restoration;
- available and able to return to the study site for the post-procedural follow-up examinations;
- accepting to not change their habits regarding food, physical activity, cosmetic and cleansing products for the hands;
- accepting not to expose their hands to strong UV irradiation (UV session, or sun bathes) during the entire duration of the study, without appropriate sun protection;

5.4 Exclusion criteria

- Pregnancy;
- lactation;
- smokers;
- alcohol or drug abusers;
- subjects not in menopause who do not use adequate contraceptive precautions in order to avoid pregnancies during the study;
- Body Mass Index (BMI) variation (± 1) during the study period;
- performing non-surgical skin aesthetic procedures for hands in the 6 months prior to the study start;
- aesthetic surgical procedure for the hands in the past;
- change in the normal habits regarding food, physical activity, cosmetic products and cleansing for the hands during the month preceding the test;
- sensitivity to the test product or its ingredients (to be assessed by the investigator during the baseline visit);
- subjects whose insufficient adhesion to the study protocol is foreseeable;
- participation in a similar study currently or during the previous 6 months.)
- presence of cutaneous disease on the tested area, as lesions, scars, malformations;
- clinical and significant skin condition on the test area (e.g. active eczema, psoriasis, sclerodermia, local infections).

5.4.1Exclusion criteria due to systemic disease

- Diabetes;
- endocrine disease;
- hepatic disorder;
- renal disorder;
- cardiac disorder;
- pulmonary disease;
- cancer;
- neurological or psychological disease;
- inflammatory/immunosuppressive disease;
- drug allergy

5.4.2. Exclusion criteria due to ongoing pharmacological treatment

- Anticoagulants and antiplatelet drugs, anti-histaminic, topic and systemic corticosteroids, narcotic, antidepressant, immunosuppressive drugs (with the except of contraceptive or hormonal treatment starting more than 1 year ago);
- using 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 concomitant medication form.

5.4.3. Restrictions
The volunteers accept to respect the rules fixed in the list of recruitment criteria and not to deviate from their normal life habits; particular attention should be paid to the cosmetic products and detergents for the hands, which must remain the same during the entire study period. During the entire period of treatment, the exposure to strong UV irradiation (UV session, or sun bathes) without appropriate sun protection, will be avoided. Moreover the use of NSAID drugs is not admitted in the 5 days preceding the two injective procedure.

6. CASE RECORD FORM (CRF)
The investigator will use an electronic CRF (eCRF) specially "ad hoc" engineered for each study by a trained and specialized DERMING technician. In the eCRF all information about subjects (personal data, subject's history, inclusion/exclusion criteria, clinical evaluations, instrumental data etc.) will be recorded directly on a tablet (interactive form). The tabulation of the collected data is direct and totally automatic (not manual), assuring an higher level of quality and security. Every step of the eCRF creation and filling processes are performed in accordance to DERMING internal quality procedure assuring the validation of data and the prevention of data loss.

7. SAMPLE ACCEPTANCE, IDENTIFICATION AND APPLICATION
IBSA will supply directly the study center and samples will be stored as indicated by the Instruction for Use. Samples are handled by DERMING in accordance with the methods described in the company operating procedures (SOP).
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, Company'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.
8.2. Efficacy evaluation
The assessment of the aesthetic result will be established through the use of qualitative (clinical evaluations) and quantitative assessments (instrumental measurements) and supported by photographic documentation.
All clinical and instrumental evaluations will be carried out mono-laterally on hands,
right or left side according to a subjects' randomization list defined by the investigator before the subjects' inclusion. The evaluation side assigned at each enrolled subject will be recorded in the eCRF.

8.2.1. Clinical evaluations
Clinical assessment of hand dorsum (according to a reference photographic scale)
roughness and laxity will be performed at each study time according to a visual score from 1 (no roughness and flaccidity) to 5 (very severe roughness and flaccidity).
8.2.2. Photographic documentation
2D pictures of the dorsum of both hands for all included volunteers will be taken. In order to assure comparable images, the pictures will be taken with standardised methods, concerning especially:
• magnification factor

• intensity of illumination source (photographic lamps)
• angle of incidence and inclination of illumination
More-over the subject during the photo execution must keep still, with relaxed body muscles.

8.2.3. Non-invasive instrumental evaluations
8.2.3.1. Tissue dielectric constant of superficial and deep skin layers
The MoistureMeterD measures non-invasively the dielectric constant of the skin and subcutaneous fat. The dielectric constant is a dimensionless physical quantity and it is directly proportional to the water content in the measured tissue. The MoistureMeterD generates a high frequency, low power electromagnetic (EM) wave which the tissue is exposed to. The reflected EM wave is registered and the obtained value is a dielectric constant, which is proportional to the water content of the measured tissue; the measured value increases when water content increases.
The dielectric constant of water molecules depends on the used radiofrequency. Free and bound water behave electrically differently with different frequencies. At around 300 MHz, the electrical properties of free and bound water are quite identical, thus the MoistureMeterD measures changes in the total water content of the tissue.
The measurement depth can be determined by using differently sized probes. There are four probes of different sizes. The corresponding effective measurement depths are 0.5 mm, 1.5 mm, 2.5 mm and 5 mm. The probe should be selected after the measurement site has been determined. The deeper the measurement need the larger the probe. For the present study 0.5 mm and 1.5 mm probes will be used.
8.2.3.2. Skin density evaluation (profilometry)
A little skin area of about 7 cm_2 (2.5x2.8 cm) at level of the dorsum of the hand is pinched.
A picture of the obtained profile is taken thanks to Primos compact portable device (GFMesstechnik); Primos software is able to elaborate 3D representations of skin wrinkles as well as to measure skin 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 micrometers.

8.2.3.3. Torsiometry (skin plastoelasticity)
Torsion is demonstrated to be one of the most effective method used for measuring skin elasticity, being very sensible to skin mechanical properties variation. Measurements will be performed thanks to the instrument Dermal Torque Meter (Dia-Stron Ltd., UK).
By a probe made of two circles adhering to the skin through shaped adhesive tapes, skin surface under-go to a torsion. The distance between the 2 circles delimits the skin area submitted to the mechanical torsion. The internal circle rotation, while the external circle is still, exerts a constant twist of the skin (torsion time = 10 second with a torque = 9mMm); the instrument measures the torsion angle (θ) during the mechanical stimulus ("torque on") and after it stops ("torque off").
For each of the considered curve ("torque on" and "torque off", see Appendix) the cutaneous torque ratio relative to the defined measured times could be measured, obtaining the parameters listed below:
U_e: immediate extensibility ("torque on" at 0.2 sec.)
U_f: final extensibility ("torque on" at 9 sec.)
U_v: viscoelasticity
U_r: immediate elastic recovery ("torque off" at 0.2 sec.)

8.2.4. Standard conditions for the treatment evaluations
8.2.4.1. Volunteers
During 3 hours before the visit the volunteer must not drink coffee or alcohol. No cosmetic product can be used on the skin test areas in the 2 hours preceding each visit.
8.2.4.2. Conditions for the measurement execution
All measurements are performed under standard environmental conditions (Temperature=22+\-2ÆC; Relative Humidity<60%).
8.2.4.3. Acclimatization
Before each visit the volunteer will get acclimatized under relax conditions for at least 10-15 min.

8.3. Evaluation of the treatment efficacy and tolerance (volunteers' judgment)
At the end of the study (T2), each volunteer fills a questionnaire (Appendix 5) regarding:
• the efficacy of the study treatment over skin roughness and laxity of the treated areas, skin suppleness, skin smoothness, skin hydration, skin lifting, contour redefinition/remodeling (score: very marked; marked; medium; light; absent);
• the treatment tolerance (score: bad; poor; good; excellent).

9. TOLERANCE
9.1. Tolerance evaluation
Products tolerance will be evaluated considering:
§ local expected events/reactions induced by the injection procedure (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:
1) Resulted in a life-threatening illness or injury, or

2) Resulted in persistent or significant disability or incapacity and/or permanent impairment of a body function or permanent damage to a body structure, or
3) Required in-patient hospitalization or prolongation of existing hospitalization, or
4) 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 foetal distress, foetal 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

9.2.3. 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.
9.2.3.1 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 has to 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.
9.2.2.2. 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 30 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 followup.
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
- pregnancy test (only for women not in menopause)
- clinical and instrumental assessments
- photographic documentation
- 1st 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
- pregnancy test (only for women not in menopause)
- clinical and instrumental assessments
- photographic documentation
- 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
- photographic documentation
- 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. ETHIC

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. 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. No subject can be included in the trial before the Ethic Committee study approval. Moreover no volunteer can sign the Informed Consent Form before protocol inclusion. Finally 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 7). A list of the members of the E.C., who examined the protocol, has to be enclosed in the Investigator's file.

The approval documentation has to enclose these information:

* the protocol title, the issue date, the Company 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 n. 29 – 20159 MILANO).

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 European General Data Protection Regulation (GDPR 2016/679 see Appendix 6); before the inclusion each subject reads the information form related to the study and its methodology (see Appendices 3). 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 (see Appendix 4).
13.3. Product conformity to the current regulations
The test starts only after the evaluation of the documentation provided by the Investigator (with products identification, date and IBSA representatives' signature for knowledge).
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 no 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 Company 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 the insurance policy n. ..... of the ..... insurance company for damages related to the study product and by insurance policies n. 0260/03/0024707 and 0260/03/0024695 of Reale Mutua insurance company for damages induced by the micro-injection procedure.
14. CONFIDENTIALITY
14.1. 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 IBSA 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. APPENDICES
1) Product information and complications of injectable fillers
2) Adverse event and concomitant medication forms
3) Informed consent form and subjects'enrolment form
4) Certificate of subjects information
5) Volunteers' self assessment questionnaire
6) Consent form to the personal data processing (European General Data Protection Regulation - GDPR 2016/679)
7) Helsinki declaration
8) Inner arm reference photographic scale
9) "Torque on" and "torque off" curves.

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