# CLINICAL STUDY PROTOCOL

**Complife Italia Study no: IT0005576/22**
**Study code: H.E.HU.HV.NAC00.060.09.00**

# "PLACEBO CONTROLLED ASSESSMENT OF THE EFFICACY OF A FOOD SUPPLEMENT IN IMPROVING FACE SKIN CONDITIONS AND CELLULITE DERIVED SKIN IMPERFECTIONS"

| | |
|---|---|
| Principal investigator: | Dr Enza Cestone, MD, Specialist in Dermatology and Venereology |
| Co-investigators: | Dr Valentina Salogni<br>Dr Valentina Cortale |
| Sponsor: | ROELMI HPC Srl |
| In-site study Director: | Dr Ileana De Ponti, Chemist and Pharmaceutical Technologist |
| Study sites: | Complife Italia srl<br>Corso San Maurizio, 25<br>13900 Biella (BI)<br><br>Complife Italia srl<br>Via Fratelli Signorelli, 159<br>20024 Garbagnate Milanese (MI) |

**VERSION N° 01 – 30th January 2023**

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## GENERAL INFORMATION

| | | |
|---|---|---|
| **TITLE:** | | |
| PLACEBO CONTROLLED ASSESSMENT OF THE EFFICACY OF A FOOD SUPPLEMENT IN IMPROVING FACE SKIN CONDITIONS AND CELLULITE DERIVED SKIN IMPERFECTIONS. | | |
| **STUDY CODE:** | | |
| **H.E.HU.HV.NAC00.060.09.00** | | |
| **PROTOCOL NO. AND VERSION:** | | |
| **IT0005576/22 rev.01 by 30/01/2023** | | |
| **SPONSOR:** | | |
| **NAME AND ADDRESS:** | **PERSONS AUTHORIZED TO SIGN THE PROTOCOL AND ITS AMENDMENTS:** | **MEDICAL STAFF:** |
| **ROELMI HPC Srl**<br>Via Celeste Milani, 24/26<br>21040 Origgio (VA)<br>Tel. +39 02 3351 0150 | **Federica CARLOMAGNO**<br>R&D Manager<br>Via Celeste Milani, 24/26<br>21040 Origgio (VA)<br>Mobile: +39 345 800 1081<br>@ federica.carlomagno@roelmihpc.com | Non applicabile |
| **MONITOR:** | | |
| Not applicable | | |
| **FACILITY:** | | |
| **NAME AND ADRESS:** | **INVESTIGATING SPECIALIST:** | **CO-INVESTIGATOR:** |
| Complife Italia srl<br>Corso San Maurizio, 25<br>13900 Biella (BI)<br>Italy | Dr. Enza Cestone, MD, Dermatologist | Valentina Salogni, Biotechnologist |
| Complife Italia srl<br>Via Fratelli Signorelli, 159<br>20024 Garbagnate Milanese (MI)<br>Italy | | Valentina Cortale, Chemical Engineer |
| **MONITOR:** | | |
| **NAME AND ADRESS:** | **MONITOR:** | |
| Complife Italia S.R.L<br>Via Guido Rossa, 1<br>20024 Garbagnate Milanese (MI)<br>Italy - T. 0382 490286 | Dr. Ileana De Ponti, Chemist and Pharmaceutical Technologist | |
| **STUDY MANAGEMENT** | | |
| **NAME AND ADDRESS:** | **PERSONS AUTHORIZED TO SIGN THE PROTOCOL AND ITS AMENDMENTS:** | |
| Complife Italia S.R.L<br>Via Mons. Angelini, 21<br>27028 San Martino Siccomario (PV)<br><br>Via Guido Rossa, 1<br>20024 Garbagnate Milanese (MI) - Italy<br><br>Italy - T. 0382 49028 | Dr. Enza Cestone, MD, Dermatologist<br><br><br><br>Dr. Ileana De Ponti,<br>Chemist and Pharmaceutical Technologist | |
| **OTHER LABORATORIES** | | |
| None | | |
| **OTHER DEPARTMENTS** | | |
| Not applicable | | |

## PROTOCOL APPROVAL

I have read the protocol **IT0005576/22 rev.01 by 30/01/2023 - Study code: H.E.HU.HV.NAC00.060.09.00,** titled **"PLACEBO CONTROLLED ASSESSMENT OF THE EFFICACY OF A FOOD SUPPLEMENT IN IMPROVING FACE SKIN CONDITIONS AND CELLULITE DERIVED SKIN IMPERFECTIONS."** and I agree. I am aware of my responsibilities as an Investigator under the declaration of Helsinki, local regulations and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

**For and on behalf of the Study Sponsor**

Signature Date

_____ ____/____/___

Dr. Federica Carlomagno
*R&D Manager*
*ROELMI HPC SRL*

**Principal Investigator**

Signature Date

_____ ____/____/____

Dr Enza Cestone, MD
*Dermatologist*

**Study Director**

Signature Date

_____ ____/____/____

Dr Ileana De Ponti
*In Vivo Safety & Efficacy Technician and Sales Manager*

# SUMMARY

**1. PROTOCOL AMENDMENTS HISTORY**

The table here below reports the list of the amendments to the protocol.

| Amendments no. | Protocol vers. | Date | Author | Description |
|---|---|---|---|---|
| | 00 | 10/11/2022 | Enza Cestone<br>Ileana De Ponti | First drafting |
| | 01 | 30/01/2023 | Enza Cestone<br>Ileana De Ponti | Second drafting - Amendment |
| | | | | |
| | | | | |

## 2. BACKGROUND

ROELMI HPC SRL (the Sponsor of the study) is interested to evaluate the efficacy of a food supplement in improving face skin conditions and in reducing cellulite-derived skin imperfections.

### 2.1 Summary of potential risk and benefits to human subjects

**Food supplement**. Test product is manufactured according to the applicable national and international rules and regulation. All ingredients included in the product formula are approved for their use in food/food supplements. The potential risks associated with the use of the product are related to both subjective and objective adverse events (AEs) (e.g., bloating, diarrhea, stomachache). The occurrence of AEs related to individual susceptibility to specific ingredients in the product could be related to biological phenomenon that are not avoidable and cannot be considered as AEs due to product intake. Potential risks are assumed to be from mild to moderate and are not expected to pose a risk to human health.

**Cosmetic products**. The test products conform to Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast) (Text with EEA relevance) and to its annexes. All the ingredients included in the products formula are approved for their use in cosmetic products and are used at the permitted concentration. The potential risks associated with the use of the products are related to both subjective and objective adverse events (AEs) (e.g. skin irritation, sensitization, etc.). The occurrence of AEs related to individual susceptibility to specific ingredients in the product could be related to biological phenomenon that are not avoidable and cannot be considered as AEs due to product use. Potential risks are assumed to be from mild to moderate and are not expected to pose a risk to human health. Risks associated with the procedures involved in this study are judged as minor. All the measurements carried out are not invasive and no skin side effects are expected from the measurement process.

The potential benefits due to product use are related to an improvement of face skin parameters (skin profilometry – wrinkledness and eyebags volume), skin moisturization, skin brightness, skin evenness, skin pinkish, eyebags and dark circles appearance, skin homogeneity and cellulite derived skin imperfections (skin smoothness, body circumferences, skin microcirculation, “orange peel” skin appearance)

## 3. OBJECTIVES

The study is aimed to assess the efficacy of a food supplement in improving face skin conditions and in reducing cellulite-derived skin imperfections after 28 and 56 days of product intake.

In order to reach this goal a multicentric, parallel groups, placebo-controlled, inter- (active product vs placebo) and intra-group (T28 vs T0; T56 vs T0) comparison study is carried out on 60 healthy male and female subjects (66 enrolled) aged between 35 and 65 (extremes included) years old, phototype from I to IV included according to Fitzpatrick classification, showing fine lines/light wrinkles, dull skin, uneven skin tone and mild to moderate cellulite-derived skin imperfections with 10 subjects per group showing visible dark circles and 10 subjects per group showing visible eyebags will be included.

The study foresees 56 days of product consumption. Evaluations of the parameters under study will be performed at baseline (T0), after 28 (T28) and 56 days (T56) of product intake.

The study is integrated with the self-assessment questionnaire filled-in by the volunteers after 28 days and at the end of the study (T56).

According to a previously defined randomization list subjects will be divided in 2 study groups:

- 30 subjects (33 included) will take the active food supplement
- 30 subjects (33 included) will take the placebo food supplement

In order to standardize the volunteer’ cosmetic habit, Complife will provide the volunteers a base face and body cream without any cosmetic activity to use during the whole study period instead of the day/night face cream normally used by each volunteer and as body cream if they are used to it. Volunteers will not apply the cream in the morning of the day when measurements will be performed.

The study foresees the intake of 1 capsule per day: with a glass of still water for the 56 days of treatment.

### 3.1. Primary objectives

The aim of this study is to evaluate the efficacy of a food supplement in improving face skin conditions and in reducing cellulite-derived skin imperfections. In particular evaluation of face skin profilometry – wrinkledness and eyebags volume, skin moisturization, skin brightness, skin evenness, skin pinkish, eyebags and dark circles appearance, skin homogeneity and cellulite derived skin imperfections (skin smoothness, body circumferences, skin microcirculation, “orange peel” skin appereance) are evaluated.

**3.2. Secondary objectives**

Secondary objective of this study is the assessment of product acceptability and volunteers' perceived efficacy by self-assessment questionnaire.

**4. STUDY DESIGN**

A multicentric, parallel groups, randomized, placebo-controlled clinical study is carried on 2 groups of 33 subjects as follows: one group will take the active food supplement and one group will take the placebo food supplement.

**4.1. Population characteristics**

It is planned to enroll 66 female subjects, phototype from I to IV included according to Fitzpatrick classification, showing fine lines/light wrinkles, dull skin, uneven skin tone and mild to moderate cellulite-derived skin imperfections with 10 subjects per group showing visible dark circles and 10 subjects per group showing visible eyebags will be included. Subjects are enrolled only if they satisfy all the inclusion/non-inclusion criteria reported in the sections 5.
Subjects will be randomly attributed to each group of treatment.

**4.2. Study structure**

The clinical study will be carried out by Complife Italia srl placed in Corso San Maurizio, 25 - 13900 Biella (BI), and Complife Italia srl placed in Via Fratelli Signorelli, 159 - 20024 Garbagnate Milanese (MI) – Italy.
The principal investigator is Dr. Enza Cestone. The co-investigators are: Valentina Salogni, Biotechnologist and Valentina Cortale, Chemical Engineer
The in site Study Director is Dr. Ileana De Ponti, Chemist and Pharmaceutical Technologist

**5. STUDY POPULATION**

A total of 66 female subjects will be enrolled. Withdrawn/lost to follow-up/drop-out subjects will not be replaced. All inclusion and non-inclusion criteria will be checked by the investigators or delegate (co-investigator), through a questionnaire during the screening visit.

**5.1. Inclusion criteria**

- ✓ Healthy female subjects,
- ✓ Age between 35 and 65 (extremes included) years old,
- ✓ Phototype I to IV included, according to Fitzpatrick classification,
- ✓ Subjects showing fine lines/light wrinkles, dull skin and uneven skin tone
- ✓ Subjects showing mild to moderate cellulite-derived skin imperfections
- ✓ 10 subjects per group showing visible dark circles
- ✓ 10 subjects per group showing visible eyebags
- ✓ Subjects who have not been involved in any other similar in the last 3 months,
- ✓ Subjects registered with Nation Health Service (NHS),
- ✓ Subjects certifying the truthfulness of the personal data disclosed to the investigator,
- ✓ Subjects able to understand the language used in the investigation center and the information given by the investigator,
- ✓ Subjects able to respect the instructions given by the investigator as well as able to respect the study constraints and specific requirements,
- ✓ The pharmacological therapy (except for the pharmacological therapy in the non-inclusion criteria) should be stable for at least one month without any changes expected or planned during the study,
- ✓ Commitment not to change the daily routine or the lifestyle,
- ✓ Subjects who have not been recently involved in any other similar study,
- ✓ Subjects having signed their written Informed Consent form (ICF) for their participation in the study and a photograph authorization.

**5.2. Non-inclusion criteria**

- × Subject does not meet the inclusion criteria,
- × Subjects with acute or chronic diseases able to interfere with the outcome of the study or that are considered dangerous for the subject or incompatible with the study requirements,
- × Subjects participating or planning to participate in other clinical trials,
- × Subjects deprived of freedom by administrative or legal decision or under guardianship,
- × Subjects not able to be contacted in case of emergency,
- × Subjects admitted to a health or social facility,
- × Subjects planning a hospitalization during the study,
- × Subjects who participated in a similar study without respecting an adequate washout period,

- Subjects having an acute, chronic or progressive illness liable to interfere with the study data or considered by the Investigator hazardous for the subject or incompatible with the study requirements,
- Subjects under pharmacological treatments that are considered incompatible with the study requirement by the investigator,
- Subjects having a skin disease or condition liable to interfere with the study data or considered by the Investigator hazardous for the subject or incompatible with the study requirements,
- Subjects that have shown allergies or sensitivity to cosmetic products, drugs, patch or medical devices,
- Subject breastfeeding, pregnant or not willing to take necessary precautions to avoid pregnancy during the study (for the women of childbearing potential).

**5.3. Subject withdrawal criteria**

In compliance with the Helsinki Declaration (1964) and its successive, subjects have the right to exit from the study at any time and for any reason. In all cases, the Investigator should attempt to contact the subject as soon as possible for a final assessment in order to: i) have the subject's decision written on the consent form, ii) obtain the reason(s) of their withdrawal so they can be recorded, iii) evaluate the subject's clinical condition, iv) if necessary, take appropriate therapeutic measures (management of an AE or concomitant disease), v) recover the investigation product given to the subject. The Investigator can also interrupt the subject participation in the study prematurely in the case of a disease occurrence, a pregnancy or the occurrence of adverse reactions or a serious adverse event, particularly if it is considered by the Investigator liable to threaten the health of the subject or if necessitates the prescription of a medication incompatible with the pursuit of the study. In this case, the Sponsor will be informed by phone or fax and a letter or report explaining the withdrawal will also be forwarded to him as soon as possible. Any premature discontinuation linked to an AE or a SAE will have to be followed-up (until final outcome). The Sponsor can demand that any subject be excluded from the study for major infringements to the protocol, for administrative reasons or any other motive. Nevertheless, premature removal of a high percentage of subjects from the study can make it difficult or impossible to interpret. Consequently, any premature exit without valid reasons should be avoided as much as possible and is carefully documented in the case report form, the final report and, if necessary, in the AE form. Every premature exit must be classified as follows: i) presence of a non-inclusion criteria, ii) AE occurrence, iii) SAE occurrence, iv) withdrawal of consent, v) lost to follow-up, vi) appearance of non-inclusion criteria, vii) non-adherence to the protocol, viii) other reason (to be clearly specified).

**5.4. Subject discontinuation**

The subjects are entitled to discontinue the study for any reason at any time if they desire. Should this occur, the Investigator or designee determines the reasons in order to know if it is linked to the study or not and the primary reason will be recorded in the data collection sheet. If the subject has withdrawn due to Serious Adverse Event (SAE), the subject will be followed until Serious Adverse Event (SAE) resolution.

In the case where subject does not present for a visit, the investigator or designee must attempt to contact the subject by telephone on two consecutive occasions. The subject will be considered as lost to follow-up if the investigator or designee fails to reach him/her. These attempts and the result must be recorded on source document.

**5.5. Study completion**

The study completion is achieved by a subject when she completes the entire treatment and she is undergone all the check visits.

**5.6. Subjects risk and benefit**

Risks associated with the products intake/application are considered from low to very low, in absence of allergy/intolerances to product ingredients; other ingredients in the product formula are commonly used in dietary supplements.

All the measurements carried out are not invasive and no skin side effects are expected from the measurement process.

The potential benefits associated with product use are amelioration of skin conditions in terms of skin profilometry – wrinkledness and eyebags volume, skin moisturization, skin brightness, skin evenness, skin pinkish, eyebags and dark circles appearance, skin homogeneity and cellulite derived skin imperfections (skin smoothness, body circumferences, skin microcirculation, "orange peel" skin appearance).

**6. STUDY FLOW CHART**

The study duration is 56 days (8 weeks). Clinical visits are planned after 28 ($T_{28d}$) and 56 ($T_{56d}$) days of product intake.

### 6.1. Study schedule

Study schedule is as follows:

| Study phases | Initial visit – Start of the study (T0) | Intermediate visit (T28) | Final visit (T56) |
|---|---|---|---|
| Informed consent signature and photograph authorization form signature | X | - | - |
| Subject eligibility* | X | X | X |
| Demographics data/Medical history | X | - | - |
| Products distribution | X | X | - |
| Base cream distribution (face and body) | X | X | - |
| Products collection and counting | - | X | X |
| Daily diary for compliance/tolerance/dietary habits | X | X | X |
| Skin profilometry of face (periocular area and under eyebags volume) | X | X | X |
| Instrumental evaluations of face (dark circles colour analysis, skin deep moisturization, skin brightness) | X | X | X |
| Digital pictures of face | X | X | X |
| Clinical evaluations of face (skin evenness complexion, skin pinkish, eyebags and dark circles appearance) | X | X | X |
| Skin profilometry of body (evaluation of skin smoothness) | X | X | X |
| Evaluation of body circumferences | X | x | X |
| Instrumental evaluation of body (skin microcirculation) | X | X | X |
| Digital pictures of body | X | X | X |
| Clinical evaluation of body (“orange peel” skin appearance) | X | X | X |
| Self-assessment questionnaire | - | X | X |
| AE and local tolerance assessment | - | X | X |

*The experimenter checks at each visit the compliance of the subjects with all inclusion/exclusion criteria

#### 6.1.1. Screening – Initial visit (T0)

Subjects are screened as follows:

- screening in the Complife volunteers database*. The subjects identified by Complife volunteers management database are screened by appropriate personnel (authorized by the investigator, pursuant to and for the effects of the legislation on protection of personal data). Screened subjects are then invited to participate to the study and it is make the date for the screening visit;

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  * The database will be used only for screening purposes, without storing additional data that can allow the identification of the subject as a potential participant in the clinical study.

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During the screening visit (T0) the investigator / co-investigator evaluates if the subject is eligible to participate in the study. The following procedures are carried out:

- signature of the Informed Consent Form and photograph authorization Form
- recording of the subject demographic data
- checking of the subject’s medical history and previous and concomitant therapies
- checking of the inclusion/non-inclusion criteria
- supplying of the daily diary
- supplying of the product/placebo in accordance with the randomization list
- face and body base cream face distribution
- skin profilometry (periocular area and under eyebags volume)
- instrumental evaluations of face (dark circles color analysis, skin deep moisturization, skin brightness)
- digital pictures of face
- clinical evaluations of face (skin evenness complexion, skin pinkish, eyebags and dark circles appearance)
- skin profilometry of body (evaluation of skin smoothness)

- evaluation of body circumferences
- instrumental evaluation of body (skin microcirculation)
- digital pictures of body
- clinical evaluation of body ("orange peel" skin appearance)
- fixing the date of the first check visit after 28 days of treatment.

**6.1.2. 1st check visit (T28)**

The following procedures are carried out:

- checking of subject eligibility
- checking of the daily diary
- product collection: subjects are asked to bring back to the laboratory bottle of product given at T0 in order to check the compliance to the product use
- supplying of the product/placebo in accordance with the randomization list
- face and body base cream distribution
- skin profilometry (periocular area and under eyebags volume)
- instrumental evaluations of face (dark circles color analysis, skin deep moisturization, skin brightness)
- digital pictures of face
- clinical evaluations of face (skin evenness complexion, skin pinkish, eyebags and dark circles appearance)
- skin profilometry of body (evaluation of skin smoothness)
- evaluation of body circumferences
- instrumental evaluation of body (skin microcirculation)
- digital pictures of body
- clinical evaluation of body ("orange peel" skin appearance)
- filling of the self-assessment questionnaire
- fixing the date of the final check visit after 56 days of treatment.

**6.1.3. Final check visit (T56)**

The following procedures are carried out:

- checking of subject eligibility
- daily diary collection
- product collection: subjects are asked to bring back to the laboratory bottle of products given at T0/T28 in order to check the compliance to the product use
- skin profilometry (periocular area and under eyebags volume)
- instrumental evaluations of face (dark circles color analysis, skin deep moisturization, skin brightness)
- digital pictures on face
- clinical evaluations of face (skin evenness complexion, skin pinkish, eyebags and dark circles appearance)
- skin profilometry of body (evaluation of skin smoothness)
- evaluation of body circumferences
- instrumental evaluation of body (skin microcirculation)
- digital pictures of body
- clinical evaluation on body ("orange peel" skin appearance)
- filling of the self-assessment questionnaire

## 7. TREATMENT

### 7.1. Products

**7.1.1. Qualitative formula**

**-Food supplement active:**

*Selectsieve Rainbow:* 300 mg
*Maltodextrin:* 19 mg
*Vegetal Magnesium Stearate:* 31 mg
*CPS HPMC:* 95 mg

**-Food supplement placebo:**

*Maltodextrin:* 300 mg
*Purple dye:* 20 mg
*Vegetal Magnesium Stearate:* 30 mg
*CPS HPMC:* 95 mg

**Face cream C.SK.21.127(A)HPC**
*Aqua, Tripelargonin, Neopentyl Glycol Dipelargonate, Polyglyceryl-3 Stearate, Triolein, C10-18 Triglycerides, Cetearyl Alcohol, Glyceryl Dioleate, Sunflower Seed Oil Glycerides, Hydroxyethylcellulose, Caprylyl Glycol, Ethylhexylglycerin, o-Cymen-5-ol, Parfum.*

**Body cream C.SK.21.127(C)HPC**
*Aqua, Tripelargonin, Neopentyl Glycol Dipelargonate, Polyglyceryl-3 Stearate, Triolein, C10-18 Triglycerides, Cetearyl Alcohol, Glyceryl Dioleate, Sunflower Seed Oil Glycerides, Hydroxyethylcellulose, Caprylyl Glycol, Ethylhexylglycerin, o-Cymen-5-ol, Parfum.*

### 7.1.2. Products dosage and way of use

**- Food Supplement:** 1 capsule per day with a glass of still water for the 56 days of treatment.
**- Face and Body cream:** use the FACE CREAM instead of the day/night cream normally used by making one application in the morning and one in the evening; use BODY CREAM, if you are used to it, instead of the cream you normally use. NB. Not apply the cosmetic product on the morning of the visit day.

### 7.1.3. Product supply, labeling, storage and accountability

#### 7.1.3.1. Product supply

Products are supplied to COMPLIFE ITALIA srl by the Sponsor.
The shipment address is:

COMPLIFE ITALIA srl
Via Mons. Angelini, 21
27028 San Martino Siccomario (Pavia) - Italy
Contact person: dr. Ileana De Ponti - T. +39 0382 25504

#### 7.1.3.2. Labeling

Products will be supplied with an anonymous packaging and Complife will affix on each product the following label.

**Figure 1**. Face and body cream label

COMPLIFE GROUP

Codice studio: **H.E.HU.HV.NAC00.060.09.00-IT0005576/22**
Codice prodotto: Formula n.
N° di lotto:
Data scadenza:

**Modo d'uso**: utilizzare la CREMA VISO al posto della crema giorno/notte normalmente usata effettuando una applicazione al mattino e una alla sera; utilizzare anche la CREMA CORPO, se abituati a farlo, al posto della crema normalmente usata.
N.B. non applicare il prodotto cosmetico la mattina del giorno in cui verranno effettuate le misurazioni

**Figure 2**. Food supplement label

Integratore alimentare

N° lotto:
Data di scadenza:
IT0005576/22

Modo d'uso: assumere 1 capsula con un bicchere di acqua non gasata per i 56 giorni di trattamento.

Utilizzare in accordo con il modo d' uso | Campione solo per test

Via Mons. Angelini, 21
San M. Siccomario
Tel. 0382 25504
COMPLIFE GROUP

*AVVERTENZE: Tenere al riparo da fonti di luce e di calore, tenere al di Fuori della portata dei bambini, non assumenre il prodotto oltre la dose Giornaliera consigliata.*

#### 7.1.3.3. Storage

All products are stored at room temperature at Complife facilities, protected from direct light, heat and source of water safe place with restricted access.

#### 7.1.3.4. Accountability

The investigator and her collaborators maintain a record of the products delivered to the subjects at the study starting and received by the subjects at the study ending.
The returned product the end of the study will be destroyed according to the current internal procedures.

#### 7.1.3.5. Compliance to treatment

At the beginning of the study (T0) and after 28 days (T28) experimenter provides products necessary to complete the study. The compliance to treatment is assessed by the investigator by counting and recording the remaining capsules in each bottle after 28 days and 56 days of treatment.
The investigator may withdraw the subject in case of suspicion and/or if she has the evidence that the subject was not compliant to the treatment regimen.
Compliance to treatment will be calculated by product accountability, as follows:

$$\text{Compliace to treatment} = \frac{\text{number of intake product}}{\text{number of product to intake}} \text{x} 100$$

The average of overall compliance shall be > or = 80%. The returned product (if remained on the basis of the provided and used product) at the end of the study will be destroyed according to the current internal procedures.
Moreover subjects will fill in a daily diary specifying any significant change in the alimentary habits, product tolerance and use.

### 7.1.4. Randomization

A restricted randomization list is generated by the in site Study Director using an appropriate statistic algorithm ("Wey's urn"). An independent technician will dispense either active product or placebo product according to the randomization list. The study will adhere to establish procedures to maintain separation between the investigators and its collaborators and the staff that will deliver the intervention. Investigators and its collaborators who will obtain outcome measurements will be not informed on the product group assignment. Staff who will deliver the intervention will not take outcome measurements. Subjects, investigators and collaborators are kept masked to products assignment.

### 7.1.5. Blinding

Products will be supplied in the same packaging without any obvious differences among products.

### 7.1.6. Duration of subjects participation

The expected duration of subjects participation in the study is 8 weeks.

### 7.1.7. Study completion

The study completion will be achieved by a subject when she will have performed all the treatments and the evaluation visit.

## 8. EFFICACY ENDPOINTS AND EVALUATIONS

Parameters below reported are assessed under controlled ambient conditions (T = 22±2°C and RH = 40-60%).
Subjects are left to acclimatize to ambient condition for 15-20 minutes before the check visit.

### 8.1. Skin profilometry (T0, T28, T56)

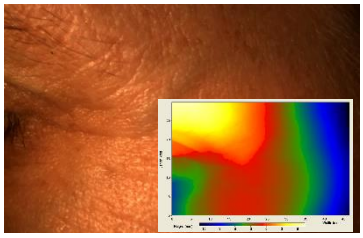
Skin surface is quantitatively assessed by Primos 3D (GFMesstechnik GmbH). Primos 3D is a non-contact in vivo skin measurement device based on structured light projection. In conjunction with a comprehensive 3-D measurement and evaluation software, the sensor allows to evaluate skin surface properties (i.e. wrinkle depth, volume, skin roughness, etc.). In this study the following parameters are evaluated in the periocular area:

- Rz parameter which represents the average depth of roughness, index of skin roughness
- Ra parameter which represents the mean roughness and its' related to skin smoothness.

For further information see Figure 3.

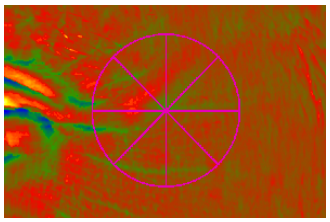
**Figure 3 - Skin profilometry by means of Primos 3D analysis**

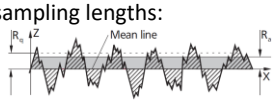
**The technique**. Primos 3D is a 3D scanner that create a point cloud (set of vertices in a three-dimensional coordinate system) of geometric samples on the surface of the subject. These points are then used to extrapolate the shape of the subject (a process called reconstruction). Like cameras, 3D-scanner has a cone-like field of view, and like cameras, they can only collect information about surfaces that are not obscured. While a camera collects color information about surfaces within its field of view, 3D scanners collect

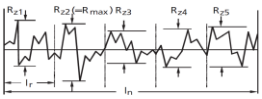


distance information about surfaces within its field of view. The "picture" produced by a 3D scanner describes the distance to a surface at each point in the picture (see the image in the insert).

**Calculation of roughness**. For the calculation of a star roughness, intersections are arranged in a star shape by the program. The calculation of the parameter occurs accordingly to the determination of the line roughness (separate for every star shape arranged intersection).
In this study roughness is calculated through the Ra and Rz parameters.
Ra parameter is the arithmetic average of the absolute values of the roughness profile ordinates (see the picture here below).
Rz is the arithmetic mean value of the single roughness depths Rzi of 5 consecutive sampling lengths:





Ra is mathematically calculated as:

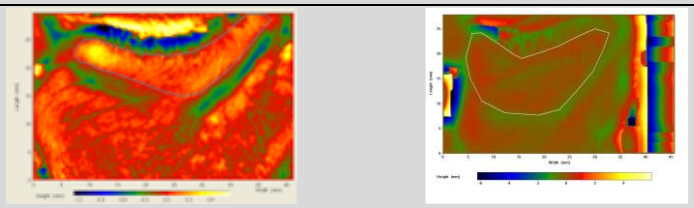
$$R_a = \frac{1}{l}\int_0^l |Z(x)|\, dx$$

Rz is mathematically calculated as:

$$R_z = \frac{1}{n}\left(R_{z1} + R_{z2} + \ldots + R_{zn}\right)$$

**8.2. Skin profilometry: under eye bags volume (10 vol per group) - (T0, T28, T56)**
By means of Primos 3D (GFMesstechnik GmbH) is calculated the volume of eye bags.
For further information see Figure 4.

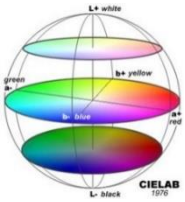
**Figure 4 - Eye bags volume**



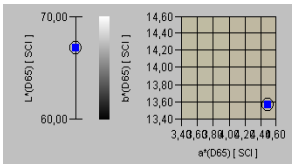
The technique allows to: a) take a high resolution image of the skin, b) take a 3 dimensional image and c) analyze by means of image analysis the profilometrical information of the 3D image.

**8.3. Evaluation of the intensity of dark circles color analysis (10 vol per group) - (T0, T28, T56)**
The intensity of dark circle is measured by means of a spectrophotometer/colorimeter CM-700D (Konica Minolta, Milan, Italy). L* and b* values are taken. These data are then interpolated using a mathematical formula that allows to calculate the ITA° (Figure 5). A low ITA° value indicates a dark pigmentation, while a high ITA° value indicates a very light pigmentation. The measure of the colour is done in the standardized CIElab chromatic space.
The probe sends out white LED light, arranged circularly to uniformly illuminate the skin. The emitted light is scattered in all directions, some parts travel through the layers and some is scattered out of the skin, the light reflected from the skin is measured in the probe and expressed accordingly.

**Figure 5. Calculation of ITA° (individual typology angle)**

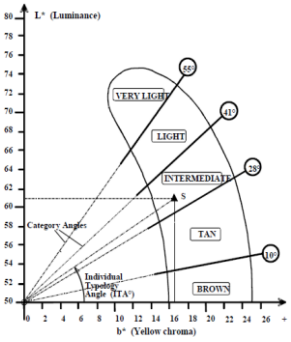



**The technique.** The spectrophotometer CM-700d measure the skin color in the CIELab chromatic space. CIELab is a standardized color space in which the color is defined - under standard illumination conditions (illuminant) and observer angle - by the values called a* and b* that defines hue and color saturation and by the value called L* that defines the color brightness. The instrument, which principle of function is the reflectance spectrophotometry, emits an intense white light that re-emitted from the object (at an angle of 10 °) is collected by 36 photodiodes each with different spectral sensitivity (from 400 nm to 700 nm). The sensitivity of the photodiodes is regulated according to a "standard observer" simulating the sensitivity of the human eye. This information is then elaborated by a microprocessor is displayed graphically.




ITA° calculation. ITA° is calculated as follows:

$$ITA° = \text{ArcTan}\frac{(L^* - 50)}{b^*} x \frac{180}{3.14159}$$




Based on ITA° it is possible to define the following skin colour categories:

| | |
|---|---|
| ITA°>55° | "Very light" |
| 55°>ITA°>41° | "Light" |
| 41°>ITA°>28° | "Intermediate" |
| 28°>ITA°>10° | "Tan" |
| ITA°<10° | "Brown" |

COLIPA "Guideline for the colorimetric determination of skin colour typing and prediction of the minimal erythemal dose (MED) without UV exposure".

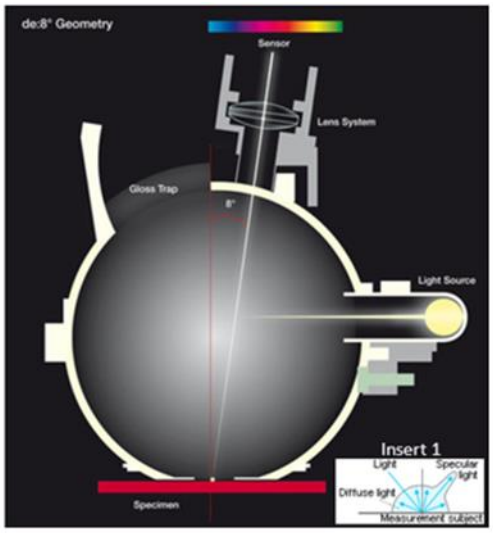
### 8.4. Evaluation of deep skin moisturization (T0, T28, T56)

The MoistureMeterEpiD is an all-in-one measurement unit that is composed of an integrated probe, a built-in contact force sensor and a display. The LCD display shows non-invasively measured values in percentage of local tissue water (0 to 100 %) effectively in the epidermis (500µm). The MoistureMeterEpiD generates a high frequency, 300 MHz, 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.

### 8.5. Skin brightness (T0, T28, T56)

Skin radiance/skin brightness is the ability of the skin to reflect the light and it is measured by using the spectrophotometer/colorimeter CM-700D (Konica-Minolta). The instrument emits diffuse light that reaches the skin through an opening located at the extreme of the lighting sphere. A sensor located at 8° compared to the vertical axis of the opening detects then the reflected light and calculates a parameter known as "gloss". The gloss value is used in the management of the brilliance of the color and for the evaluation of the improvement of dull skin.

**Figure 6. Gloss measurement**




When light reach a surface it is reflected at the equal but opposite angle from the light source; this is called specularly reflected light. This specular component is reflected as if reflected by a mirror. The light that is not specularly reflected, but scattered in many directions, is called diffuse reflectance (insert 1). The sum of the specular reflectance plus the diffuse reflectance is called the total reflectance. For objects with shiny surfaces, the specularly reflected light is relatively strong and the diffused light is weaker. On rough surfaces with a low gloss, the specular component is weak and the diffused light is stronger. The measuring geometry d: 8° features an optical device which provides diffuse illumination (Ulbricht sphere). The light (Xenon lamp) is projected into a sphere. The interior of the sphere is coated with a white highly reflecting substance (barium sulphate, ceramic, special plastic) which reflects the light manifold. A shutter, an optical element inside the sphere, prevents the directional rays from reaching the measuring sample directly. The sample is positioned at an opening of the sphere and is illuminated from all directions with a close to perfect diffuse light. Through an opening at the top of the sphere the sensor is viewing the surface being measured with an angle of 8° to the vertical. In order to prevent reflection of specular light from the sample surface, the instrument feature a gloss trap. When the trap which is arranged with an angle of -8° to the viewing opening, is open, the light which would otherwise be reflected from the interior wall of the sphere, will be eliminated and can therefore not Illuminate the sample. The relation between directional and diffuse reflection allows calculating the gloss component. The measuring system including gloss is named di: 8° whilst the measuring system excluding gloss is described as de: 8°.

### 8.6. Digital pictures (T0, T28, T56)

At each timepoint digital pictures of the face are acquired by means of Visioface device (Courage+Khazaka). The instrument ensures a reproducible subject positioning between timepoints. The best digital pictures (active ingredient) (2* cases showing the improvement of skin brightness – 2* cases showing the improvement of skin color evenness – 2* cases showing the improvement of skin roughness – 2* cases showing the improvement of dark circles and eyebags appearance) are delivered to the sponsor in jpg format.

### 8.7. Clinical evaluations (T0, T28, T56)

Clinical evaluations of skin evenness complexion, skin pinkish and improvement of eyebags and dark circles are carried out by the experimenter according to internal clinical scales:

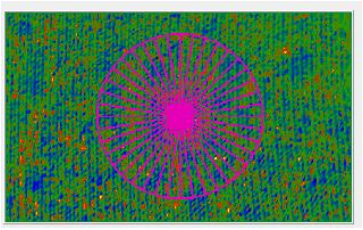
- Skin evenness complexion improvement (4-point scales)
- Skin pinkish (VAS scale)
- Improvement of eyebags and dark circles appearance – 10 volunteers per group (from 0, no eyebags/no dark circles → to 7, remarkable eyebags/remarkable dark circles)

### 8.8. Skin profilometry – evaluation of skin smoothness on thighs (T0, T28, T56)

Skin surface is quantitatively assessed by Primos 3D (GFMesstechnik GmbH). Primos 3D is a non-contact in vivo skin measurement device based on structured light projection. In conjunction with a comprehensive 3-D measurement and evaluation software, the sensor allows to evaluate skin surface properties. Ra parameter is measured as index of skin smoothness.

For further information see Figure 7.

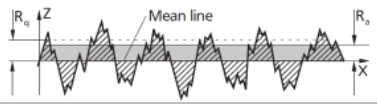
**Figure 7 - Skin profilometry by means of Primos 3d analysis**



**The technique.** Primos 3D is a 3D scanner that create a point cloud (set of vertices in a three-dimensional coordinate system) of geometric samples on the surface of the subject. These points are then used to extrapolate the shape of the subject (a process called reconstruction). Like cameras, 3D-scanner have a cone-like field of view, and like cameras, they can only collect information about surfaces that are not obscured. While a camera collects colour information about surfaces within its field of view, 3D scanners collect distance information about surfaces within its field of view. The "picture" produced by a 3D scanner describes the distance to a surface at each point in the picture.

**Calculation of roughness.**

For the calculation of a rectangle roughness, intersections are arranged in a star shape by the program. The calculation of the parameter occurs accordingly to the determination of the line roughness (separate for every star shape arranged intersection). In this study roughness is calculated as the Ra parameter. Ra parameter is the arithmetic average of the absolute values of the roughness profile ordinates (see the picture here below).




Mathematically Ra is calculated as:

$$R_a = \frac{1}{l}\int_0^l |Z(x)|\, dx$$

### 8.9. Evaluation of body circumferences (T0, T28, T56)

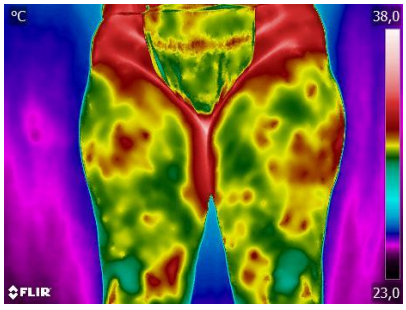
The measurement of body circumferences is carried out by using a flexible meter at the level of the following body zones: thigh, waistline and hips. The measurement of waistline circumference is carried out in the point of maximum protrusion of adiposity localized in the region of the abdomen; the measurement of thigh circumference is carried out in the point of maximum protrusion of localized adiposity on thigh; the measurement of hips circumference is carried out in the point of maximum protrusion of localized adiposity on hips (love handles).

### 8.10. Measurement of cellulite-induced alteration of skin microcirculation (T0, T28, T56)

Cellulite-derived blood and lymphatic microcirculation alterations are objectively measured by means of a thermal camera (FLIR infrared camera – FLIR Systems AB). Skin thermal images are taken on the thighs and cellulite is then objectively scored according to clinical scores reported in figure 8.

*The best digital pictures (active ingredient) showing an improvement of skin microcirculation (3 cases) will be delivered to the sponsor in jpg format.*

**Figure 8**. Example of thermal picture. Cellulite stage and improvement can be scored based on the temperature variation.



**8.11. Digital pictures (T0, T28, T56)**

Digital images of the cellulite affected zones will be taken using a reflex digital camera. Images will be taken under standard lighting conditions.

*The best digital pictures (active ingredient) showing a reduction of orange peel (3 cases) will be delivered to the sponsor in jpg format.*

**8.12. Clinical evaluation (T0, T28, T56)**

Clinical evaluations of "orange peel" skin appearance (thighs) is carried out by the experimenter according to internal clinical scales:

- "Orange peel" skin appearance (thighs) (4-point scales)

**8.13. Self-assessment questionnaire (T28, T56)**

After 28 days and at the end of the study after 56 days subjects are asked to express their personal opinion on the tested treatment by answering to a questionnaire about products acceptability and effects.

**ASSESSMENT OF SAFETY**

***9.1. Adverse Events (AE) and Serious Adverse Events (SAE)***

**9.1.1. Definition of Adverse Event (AE)**

An Adverse Event is any untoward medical occurrence in a clinical investigation subject administered a test product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a test product, whether or not related to the test product.

**9.1.2. Definition of Serious Adverse Event (SAE)**

A Serious Adverse Event is any untoward medical occurrence that: i) results in death, ii) is life-threatening, iii) requires inpatient hospitalization or prolongation of existing hospitalization, iv) results in persistent or significant disability/incapacity, or v) is a congenital anomaly/birth defect.

**9.1.3. Documentation of AE and SAE**

All concomitant treatments are reported in the data collecting sheet and the study report. All Adverse Events likely to be related to the studied product (adverse reactions) are reported in the data collecting sheet and the study report. All Serious Adverse Events are reported in the data collecting sheet and the study report.

**9.1.4. Notification to the Sponsor**

***9.1.4.1. Notification of reaction to the Sponsor***

AEs occurring during the study or after the study must be reported to the Sponsor's vigilance officer by email (federica.carlomagno@roelmihpc.com) with a copy to the project manager, using the appropriate notification forms. SAE must be send within 24 hours after the observation. Reactions related to the product must be reported as soon as possible. If picture of the reactions are available, they should be enclosed with the notification.

**9.1.5. Follow-up**

SAE and reactions related to the product must be followed up until resolution or stabilization. To inform Sponsor's vigilance officer of any new information the investigator must use the appropriate forms filled in with results collected from the examination carried out. Reports of hospitalization must be enclosed with the notification form.

**9.2. Tolerability**

The tolerability of the product will be closely followed by the study investigators during the study period. Subjects will have access to the investigator in case of intolerance reactions via a contact phone number provided with the study information sheet. If a subject report an event, the investigator must decide if it is related to the product or not. If yes, he will report it as an intolerance. Any unexpected, related side effect judged as severe by the investigator will be reported to the Sponsor. Upon investigator judgment, the subject may be withdrawn from the study and the side effect will be followed until resolution.

**9.2.1. Tolerance assessment**

For each sign, intensity, location, duration (hours, minutes), and frequency is recorded. Moreover, the investigator collects all discomfort or reactions reported by the subjects. Each time a sign (physical or functional) appears (new sign or worsened compared to the baseline evaluation i.e evaluation at day 1), a reaction must be recorded. All the reactions observed by the dermatologist and reported by the subject are

recorded. The following information is recorded: i) subject characteristics, ii) details about study product (product code or name, date of first use, way of use), iii) description of the reaction (functional and physical signs, intensity of the signs, location, date/time of onset, timeframe between product use and onset of the reaction, date/time of end or duration (hours, minutes), frequency, diagnosis/nature of the reaction), iv) significant medical history , v) concomitant events: cutaneous diseases (atopic dermatitis flare), medical treatments, sunscreen product application, food, external factors (weather conditions), other diseases, vi) outcome and actions taken (use modalities modification, temporary interruption, definitively discontinuation, medical treatment, care), and viii) relationship to the product (study product and/or associated product) (causality assessment): analysis of the probability that the reaction is attributable to the product(s) used in the study. This assessment must be done in conjunction with clinical expertise, knowledge of the product (type of product, conditions of use…), identification of concomitant events.

**9.2.2. Causality assessment of local tolerance**

Five levels of causality can be described.

- **Very likely**

Clinical signs suggest a link with the product; the reaction follows a definite reasonable temporal sequence from the time of the product use and rechallenge is positive.

- **Likely**

Clinical signs suggest a link with the product; the reaction follows a definite reasonable temporal sequence from the time of the product intake and there hasn't been a rechallenge or results of rechallenge are ambiguous. Or Clinical signs suggest a link with the product; the reaction follows a partially reasonable or unknown temporal sequence from the time of the product intake and rechallenge is positive. Or Clinical signs only partially suggest or do not suggest a link with the product, the reaction follows a definite reasonable temporal sequence from the time of the product intake and rechallenge is positive

- **Not clearly attributable**

Clinical signs suggest a link with the product; the reaction follows a definite reasonable temporal sequence from the time of the product intake and rechallenge is negative. Or clinical signs suggest a link with the product; the reaction follows a partially reasonable or unknown temporal sequence from the time of the product intake and there hasn't been a rechallenge or results of rechallenge are ambiguous. Or clinical signs only partially suggest or do not suggest a link with the product; the reaction follows a definite reasonable temporal sequence from the time of the product intake and there hasn't been a rechallenge or results of rechallenge are ambiguous. Or clinical signs only partially suggest or do not suggest a link with the product; the reaction follows a partially reasonable or unknown temporal sequence from the time of the product intake and rechallenge is positive.

- **Unlikely**

Clinical signs suggest a link with the product; the reaction follows a partially reasonable or unknown temporal sequence from the time of the product intake and rechallenge is negative. Or: clinical signs only partially suggest or do not suggest a link with the product; the time sequence between use of the product and occurrence of the symptoms is compatible; and rechallenge is negative. Or clinical signs only partially suggest or do not suggest a link with the product; the reaction follows a partially reasonable or unknown temporal sequence from the time of the product intake and there hasn't been a rechallenge or results of rechallenge are ambiguous. Or clinical signs only partially suggest or do not suggest a link with the product; the reaction follows a partially reasonable or unknown temporal sequence from the time of the product intake and rechallenge is negative.

- **Excluded**

Causality can only be excluded if another aetiology has been medically validated or when time sequence between exposure and signs occurrence is incompatible. If necessary, in case of adverse events, subjects can also contact the Study Manager. If required, they would be assessed by the Dermatologist who would perform the clinical assessment and decide the appropriate measures to take (i.e. medical treatment, withdrawal …).

## 10. STATISTIC

### 10.1. Study population for analysis

A total of 66 subjects will be enrolled in the study. Efficacy analysis is based on the Per Protocol Population. The per-protocol (PP) population is defined as all subjects who will complete the study without any major protocol violations.

Subjects will be excluded from the per-protocol population if: they miss the one or more evaluation visit; or they do not used the product properly during the study period (as referred by the subject itself).

**10.2. Descriptive analysis**

Demographic variables (sex, age, skin type, phototype) will be reported for the PP population. Data will be summarized using frequency distributions (number and percentage) for categorical/ordinal variables. For continuous variables the following figures will be calculated: i) the mean value, ii) the minimum value, iii) the maximum value, iv) the standard deviation, v) the standard error of the mean (SE), vi) the individual variation , vii) the mean variation, viii) the individual percentage variation, ix) the mean percentage variation.

**10.3. Statistical analysis**

An appropriate statistical model (parametric or not parametric) will be applied based on data distribution. For each parameter under study Intra-group statistical analysis (T28 vs T0; T56 vs T0) and Inter-group statistical analysis (active product vs placebo) will be carried out. A p values < 0.05 will be considered as statistically significant.
Statistical analysis is performed using NCSS 10 software.

**11. STUDY MANAGEMENT**

**11.1. Data recording of Study Data**

The medical records/medical notes, etc., are clearly marked and permit easy identification of a subject's participation in the specified clinical trial. The investigator records manually all data with respect to protocol procedures, safety data and efficacy ratings related to the treatment on the data collecting sheet.
The investigator may delegate the authority to fill the data collecting sheet to appropriately qualified staff to complete data collecting sheet, by authorizing and completing the signature log.

**11.2. Source Data Verification**

The Investigator must, as a minimum, review and sign all SAE forms, and the data collecting sheet to attest the accuracy and completeness of all the data. All corrections on data collecting sheet and on source documents must be made by the originator (or authorized delegate) in a way that does not obscure the original entry. The correct data must be inserted, dated and initialed/authorized by study site personnel. If it is not obvious why a change has been made, a reason must be provided.

**11.3. Data Quality**

The entire file (protocol, results, final reports and study-related documents) is subject to quality assurance procedures in compliance with regulatory requirements. The investigating laboratory authorizes the inspections by the Regulatory Body and the audit or the control by the Sponsor and allows them to access to raw data.

**11.4. Data Management**

The investigator allows direct access to all relevant files (for all subjects) for the purpose of verifying entries made in the data collecting sheet, and assists with the monitor's activities, if requested.
The subject must have consent to their records being viewed by sponsor-authorized personnel, and by local and possibly foreign Competent Authorities. This information should be included in the informed consent documents.
Data must be entered onto collecting data sheet. All forms must be completed in blue ballpoint pen. All study documents must provide adequate verification of the content of the collecting data sheet.
Definition of source data and source documents are given below:

| | |
|---|---|
| Source Data: | All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) |
| Source Documents: | Original documents, data and records (subject file, collecting data sheet notes, evaluation check list) |

All information, data and results of the study are confidential. All people having access to such data are informed of its confidentiality. In all cases, nominative information shall not be transmitted to the study sponsor. Whenever a subject name is revealed on a document required by the Sponsor (e.g., photographs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification. Data capture is performed by Complife under Microsoft® Excel 2010 (vers. 14.0.4760.1000; Microsoft, USA) worksheet running on Microsoft® Windows 8.1 Professional (Microsoft, USA). Data entry and quality control are performed by two different persons. Calculated cells and formulas in Excel are also checked by the quality assurance. Statistical analysis was carried out using NCSS 10 statistical software (NCSS, LLC. Kaysville, Utah, USA) running on Windows Server 2008 R2 Standard (Microsoft, USA).

### 11.5. Record Archiving and Retention

An original copy of all the data of the study (signed protocol, safety assessment letter of the Sponsor, case study report form, all raw data, administrative file including all the correspondence) is kept in the records of Complife Italia for 10 years. The archives are destructed only after reception of a written and signed permission from the Sponsor. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The archiving arrangements will be addressed by the monitor when closing-out the site. The Sponsor will inform Complife srl, in writing, as to when these documents no longer need to be retained.

## 12. COMPLIANCE WITH DECLARATION OF HELSINKI

### 12.1. Compliance with declaration of Helsinki

This study is carried out in the spirit of informed consent regulations, and the Declaration of Helsinki.

### 12.2. Informed Consent

Prior to study entry, the investigator, or a person designated by the investigator, explains the nature, purpose, benefits and risks of participation in the study to each subject. Informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure). Sufficient time is allowed to discuss any questions raised by the subject.

The final informed consent form must be agreed by the Sponsor and must contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject and by the person who conducted the informed consent discussion, is retained by the investigator. The investigator supplies all enrolled subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments.

It is the investigator's responsibility to ensure that the amended form is signed by all subjects subsequently entered into the study and those currently in the study. This is documented in the same way as previously described.

### 12.3. Subjects Confidentiality

In accordance with applicable law on data protection (EU Regulation 679/2016), the personal data, which may be sensitive, including date of birth, sex, race, etc.., the information resulting from clinical studies and on your health status (that you freely supply to us) are processed by Complife Srl in confidence, only for research purposes in relation with this study. If the results arising from the clinical study should be published or disseminated in scientific journals or conferences, this is done in confidence. For this purpose, the subject medical information, cosmetic information and information related to subject lifestyle as well as, if necessary for this research, the data about ethnic origins are forwarded to the Sponsor of the study or to Sponsor partners in France or abroad. In each case, data are anonymized and are identified by a code number and initials. The investigator has the responsibility to keep the list of codes to enable the link between the subject assigned number and the subject name. The data remain strictly confidential and are not made public. At any time during or after the study, health authorities may have direct access to the records to check the accuracy of the information collected. In such circumstances, it is possible that the subject identity will be known. All of the person mentioned here above are bound by professional secrecy.

## 13. ADMINISTRATION PROCEDURES

### 13.1. Publication Policy

The results of the study as well as any other data disclosed or generated in the context of the study are confidential. Any publication in relation to the study shall be subject to Sponsor's prior written approval.

### 13.2. Clinical Study Report

Clinical study report contains Safety results based on the Safety Population and Efficacy results based on the Intent to Treat and Per Protocol Population.

### 13.3. Contractual and Financial Details

The principal investigator and the Sponsor sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration covers the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the terms of payment are described in the contract.

### 13.4. Insurance

A product liability insurance is provided by the Sponsor

**13.5. Protocol Amendments (If applicable)**

All amendments to the protocol shall be agreed upon by the sponsor and the principal investigator. Deviations should be reviewed to determine the need to amend the protocol or to terminate the investigation.

However, when there are changes to the initial list of investigators and Centre this list will not be formally updated by amendments at each change; the sponsor maintains an updated list which is available on request. The definitive list of all Centre and investigators is provided with the final report.