

CLINICAL STUDY PROTOCOL

Complife Italia Study no: IT0000844/25 rev02

Study code: H.E.HU.MP.NAA00.040.35.00

“CLINICAL-INSTRUMENTAL EVALUATION OF THE EFFICACY OF TWO COSMETIC PRODUCTS IN COMPARISON. PLACEBO CONTROLLED STUDY.”

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VERSION N° 01– 10th November 2025

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GENERAL INFORMATION

TITLE:		
CLINICAL-INSTRUMENTAL EVALUATION OF THE EFFICACY OF TWO COSMETIC PRODUCTS IN COMPARISON. PLACEBO CONTROLLED STUDY.		
STUDY CODE/STUDY NO.		
H.E.HU.MP.NAA00.040.35.00_IT0000844/25		
PROTOCOL NO. AND VERSION		
IT0000844/25_Rev.02 by 03/10/2025		
SPONSOR:		
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OTHER LABORATORIES		
None		
OTHER DEPARTMENTS		
Not applicable		

PROTOCOL APPROVAL

I have read the protocol IT0000844/25_Rev.02 by 03/10/2025 - Study code: H.E.HU.MP.NAA00.040.35.00 titled "CLINICAL-INSTRUMENTAL EVALUATION OF THE EFFICACY OF TWO COSMETIC PRODUCTS IN COMPARISON. PLACEBO CONTROLLED STUDY." 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



Dr. Maryam Ghanbarirad
Quality manager, Repolar Pharmaceuticals OY

Date

11 / 11 / 2025

Principal Investigator

Signature



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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	13/10/2025	Enza Cestone Francesca De Gennaro Federica Ruggeri	First drafting
	01	10/11/2025	Enza Cestone Francesca De Gennaro Federica Ruggeri	Update of Products composition and Product name

2. BACKGROUND

Repolar Pharmaceuticals (the sponsor of the study) aims the repairing, soothing, and hydrating effects of cosmetic products formulated for atopy-prone and sensitive skin. The test formulations are based on gentle, skin-friendly ingredients with properties suitable for maintaining the well-being of compromised skin barriers.

One of the key active components included is spruce resin extract, which is enriched in lignans through dedicated purification methods.

Spruce resin has a long tradition in traditional medicine, particularly for its purifying, antimicrobial, and skin-calming properties [1,2]. Modern studies have demonstrated that resin components, particularly lignans like, may stimulate keratinocyte proliferation and reduce the secretion of pro-inflammatory cytokines such as TNF- α and IL-1 β , suggesting a direct mechanism in supporting skin renewal and reducing inflammatory discomfort [3].

Clinical and in vitro data also suggest that spruce resin may have antimicrobial activity against wound pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and may accelerate wound healing and improve skin surface condition [4,5]. The documented antimicrobial and regenerative properties suggest potential benefits for skin with compromised barriers, such as in sensitive or atopy-prone individuals.

By combining these characteristics with moisturizing and barrier-supporting excipients, the product is intended to deliver hydration, soothing sensations, and improved overall skin comfort, particularly for individuals with sensitive or easily irritated skin.

[1] Jokinen JJ, Sipponen A. Refined spruce resin to treat chronic wounds: Rebirth of an old folkloristic therapy. *Adv Wound Care (New Rochelle)*. **2016** May 1, 5(5):198–207. doi: 10.1089/wound.2013.0492. PMID: 27134764; PMCID: PMC4827294.

[2] Sipponen A, Kuokkanen O, Tiihonen R, Kauppinen H, Jokinen JJ. Natural coniferous resin salve used to treat complicated surgical wounds: pilot clinical trial on healing and costs. *Int J Dermatol*. **2012** Jun, 51(6):726–32. doi: 10.1111/j.1365-4632.2011.05397.x. PMID: 22607295.

[3] Haapakorva E, Raunio H, von Wright A, Harvima I. Pinoresinol stimulates keratinocyte proliferation and downregulates TNF- α secretion in peripheral blood mononuclear cells: An experimental in vitro study. *Health Sci Rep*. **2023** Jan, 6(1):e998. doi: 10.1002/hsr2.998. PMID: 36544622; PMCID: PMC9758476.

[4] Sipponen A, Peltola R, Jokinen JJ, Laitinen K, Lohi J, Rautio M, Mannisto M, Sipponen P, Lounatmaa K. Effects of Norway spruce (*Picea abies*) resin on cell wall and cell membrane of *Staphylococcus aureus*. *Ultrastruct Pathol*. **2009**, 33(3):128–35. doi: 10.1080/01913120902889138. PMID: 19479653.

[5] Rautio M, Sipponen A, Peltola R, Lohi J, Jokinen JJ, Papp A, Carlson P, Sipponen P. Antibacterial effects of home-made resin salve from Norway spruce (*Picea abies*). *PMI*. **2007** Apr, 115(4):335–40. doi: 10.1111/j.1600-0463.2007.apm_548.x. PMID: 17504300.

2.1 Summary of potential risk and benefits to human subjects

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 products could be related to biological phenomenon that are not avoidable and cannot be considered as AEs due to products 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 associated with product use are amelioration of the skin parameters related to atopy prone skin.

3. OBJECTIVES

The study is aimed to assess the repairing effect of 2 cosmetic formulations after a period of use.

To reach this goal a multi-site clinical trial* is carried out on 60 (66 enrolled) healthy female and male subjects enrolled according to specific inclusion and non-inclusion criteria (see section 5).

In particular, subjects will be divided in 3 study groups:

- 20 subjects (22 enrolled) will use Atopic cream with *Picea abies* extract;
- 20 subjects (22 enrolled) will use Atopic cream without *Picea abies* extract (placebo);
- 20 subjects (22 enrolled) will use a benchmark product;

**The study will be carried out under dermatological control in accordance with the ethical principles applicable to medical research, based on the following protocol; the study protocol and informed consent will be submitted to the approval of an Independent Ethical Committee.*

3.1. Primary objectives

The primary objective of this study is to assess the repairing efficacy of the a cosmetic formulation vs a placebo product and vs a benchmark by evaluating transepidermal water loss (TEWL) and skin moisturization in subjects with atopy prone and sensitive skin.

Furthermore, the study aims to assess the soothing effect of the products through the dermatologist's evaluation of improvement of physical (skin dryness, skin desquamation, skin redness) and functional (Stinging/itching sensation, burning sensation and tight feeling) signs.

3.2. Secondary objectives

Secondary objectives of this study are evaluating the possible effect of the product on skin inflammation (TNF α , TSLP and TARC dosage) and the evaluation of the volunteers' perceived efficacy by self-assessment questionnaire.

4. STUDY DESIGN

The study will be a randomized, double-blind, placebo-controlled, parallel-group trial carried out on a total of 66 healthy female and male subjects. Participants will be randomly assigned, in equal proportions (1:1:1), to one of three treatment groups.

One third of the subjects will receive the product with Picea abies extract. Another third will receive the product without Picea abies extract. The remaining third will receive the bechmark cream. All participants will apply the assigned product twice daily, for a total duration of 21 consecutive days, following the directions for use. Participants attend clinic visit at baseline (T0) and after 21 (T21 \pm 2) days of product use.

4.1. Population characteristics

The study is planned to enrol 60 (66 enrolled) healthy female and male subjects, aged between 18 and 60 years old, according to inclusion/non-inclusion criteria reported in section 5.

4.2. Study structure

The study will be carried out by Complife Italia Srl, placed in Via Monsignor Angelini, 21 - 27028 San Martino Siccomario (PV), Italy, and Complife Italia S.r.l., Piazzale Siena, 11 – 20146 Milano (MI), Italy, and in Via Signorelli, 159 – 20024 Garbagnate Milanese (MI), Italy, and in Corso S. Maurizio, 25 – 13900 Biella (BI), Italy; in Nutratch S.r.l., Via Francesco Todaro, 20/22 – 87036 Rende (CS), Italy and in Complife Romania Strada Orzari, 92A - 021554 Bucuresti – Romania.

The principal investigators are Dr. Enza Cestone, MD, Specialist in Dermatology and Venereology and Ioana Ciurea, MD. The principal co-investigators are Dr. Valentina Cortale, Efficacy Clinical Trial Technician Senior and Alina Nanu, General Manager Romania. The in-site study director is Dr Francesca De Gennaro, Clinical Trial Project Manager.

5. STUDY POPULATION

A total of 60 female and male subjects will be enrolled. The study is carried out on 66 subjects to ensure that a minimum of 60 complete the study. The estimated drop out of the study is 10%. Withdrawn/lost to follow-up/drop-out subjects will not be replaced. All inclusion and non-inclusion criteria will be checked by the principal investigator (Dermatologist) or delegate (co-investigator), through a questionnaire during the screening visit.

5.1. Inclusion criteria

5.1.1. Generic inclusion criteria

- ✓ Healthy female and male subjects
- ✓ Caucasian ethnicity
- ✓ Subjects aware of the study procedures and having signed an informed consent form and the privacy policy
- ✓ Subjects registered with National 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 and to respect the instructions given by the investigator as well as able to respect the study constraints and specific requirements
- ✓ 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 having signed their written Informed Consent form (ICF) and privacy form for their participation in the study and a photograph authorization.

5.1.2. Specific inclusion criteria

- ✓ Aged between 18 and 60 years old
- ✓ Subject with atopy-prone skin on cheekbones and forearm, with sensitive and reactive skin, showing skin redness complaining itching sensation and other skin discomforts e.g. tightness, stinging,
- ✓ Subjects meeting the following transepidermal water loss (TEWL) thresholds at screening will be included:
 - Cheekbones TEWL $\geq 20 \text{ g/m}^2/\text{h}$
 - Forearms TEWL $\geq 10 \text{ g/m}^2/\text{h}$

5.2. Non-inclusion criteria

- ☐ Subjects who do not fit 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 (14 days)
- ☐ 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 with known hypersensitivity or allergy to one of the active ingredients;
- ☐ 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 and/or probiotic 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 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 attend to 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 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/he completes the entire treatment, and she/he is undergone all the check visits.

5.6. Subjects risk and benefit

Risks associated with the product application are considered from low to very low, in absence of allergy/intolerances to product ingredients.

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 the skin parameters related to atopy prone skin.

6. STUDY FLOW CHART

The duration of the study will be 21 days. Clinical visits are planned at baseline (T0) and after 21 days (T21) of product use.

6.1. Study schedule

Study schedule is as follows:

Study phases	Initial visit Start of the study (T0)	Final visit (T21±2)
Signed Informed consent and Privacy Policy	X	--
Subject eligibility*	X	--
Products distribution	X	--
Subject's demographic data and medical history recording	X	--
Product collection	--	X
Product weight	X	X
Instrumental evaluations	X	X
Clinical evaluations	X	X
Skin stripping	X	X
TNFα, TSLP and TARC dosage	X	X
Self-assessment questionnaire	X	X
AE and local tolerance assessment	--	X

*The experimenter checks the compliance of the subjects with all inclusion/non-inclusion criteria.

6.2.1 Screening – Initial visit (T0)

Subjects are screened as follows:

- screening in the Complife volunteers' database**. The subjects identified by Complife volunteers management database 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 in the study and the date for the screening visit will be planned;

** 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.

During the screening visit (T0) the principal investigator or her designee evaluates if the subject is eligible to participate in the study. The following procedures are carried out:

- signature of the Informed Consent Form and the Privacy Policy

- recording of the subject demographic data
- checking of the current and previous subject's medical history and concomitant therapies
- checking of subject eligibility
- in order to check the compliance to the product use, the product is previously weighted
- supplying of the product
- instrumental evaluations on cheekbones and forearm of:
 - Transepidermal water loss (TEWL)
 - Skin moisturization
- clinical evaluations on cheekbones and forearm:
 - Dermatological evaluation of skin basal conditions
- skin stripping procedure on forearm and in vitro biochemical evaluation of cytokine dosage
- fixing the date of the following visits after 21 days of product use.

6.2.2. Final visit (T21)

The following procedures are carried out:

- checking of subject eligibility
- product collection: subjects are asked to bring back to the laboratory the product given at T0 in order to check the compliance to treatment by weighting
- instrumental evaluations on cheekbones and forearm of:
 - Transepidermal water loss (TEWL)
 - Skin moisturization
- clinical evaluations:
 - Dermatological evaluation on cheekbones and forearm for skin soothing effect
- supplying and collecting of the self-assessment questionnaire
- skin stripping procedure on forearm and in vitro biochemical evaluation of cytokine dosage
- recording reactions (AE, SAE)

7. TREATMENT

7.1. Products

7.1.1. Qualitative formula

Atopic cream with *Picea abies* extract: AQUA, BETAINE, XYLITOL, SODIUM PHYTATE, C14-22 ALCOHOLS AND C12-20 ALKYL GLUCOSIDE, CETEARYL ALCOHOL, HELIANTHUS ANNUUS (SUNFLOWER) SEED OIL *, CETYL PALMITATE, ISOPROPYL MYRISTATE, EMOGREEN (C15-19 ALKANE), BUTYROSPERMUM PARKII (SHEA) BUTTER *, TOCOPHEROL, PROPYLENE GLYCOL, GLYCERIN, SODIUM CHLORIDE, PICEA ABIES, ACACIA SENEGAL GUM, XANTHAN GUM, SODIUM BENZOATE, POTASSIUM SORBATE, AQUA, SODIUM DEHYDROACETATE, LACTIC ACID.

Atopic cream without *Picea abies* extract (placebo): AQUA, BETAINE, XYLITOL, SODIUM PHYTATE, C14-22 ALCOHOLS AND C12-20 ALKYL GLUCOSIDE, CETEARYL ALCOHOL, HELIANTHUS ANNUUS (SUNFLOWER) SEED OIL *, CETYL PALMITATE, ISOPROPYL MYRISTATE, EMOGREEN (C15-19 ALKANE), BUTYROSPERMUM PARKII (SHEA) BUTTER *, TOCOPHEROL, PROPYLENE GLYCOL, GLYCERIN, SODIUM CHLORIDE, ACACIA SENEGAL GUM, XANTHAN GUM, SODIUM BENZOATE, POTASSIUM SORBATE, AQUA, SODIUM DEHYDROACETATE, LACTIC ACID.

Benchmark cream: AQUA, CAPRYLIC/CAPRIC TRIGLYCERIDE, ISOPROPYL PALMITATE, GLYCERYL STEARATE, GLYCERIN, CETYL ALCOHOL, PEG-30 STEARATE, CETEARETH-20, ETHYLHEXYLGLYCERIN, PHENOXYETHANOL.

7.1.2. Products dosage and way of use

During the clinical study, participants are instructed to apply the product twice daily on clean and dry skin of face and body.

7.1.3. Product supply, labelling, 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. Francesca De Gennaro - T. +39 0382 25504

7.1.3.2. Labeling

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

Figure 1. Atopic cream with Picea abies extract

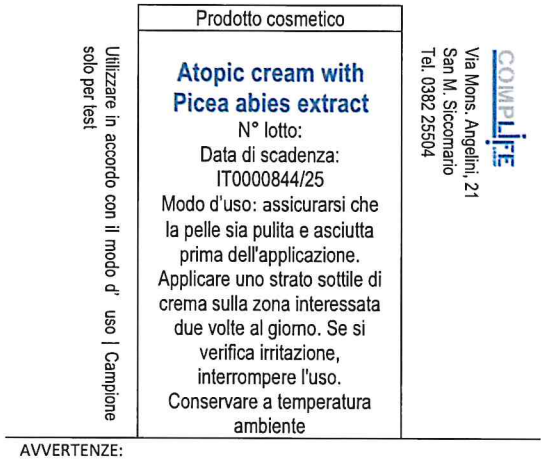


Figure 2. Atopic cream without Picea abies extract (Placebo)

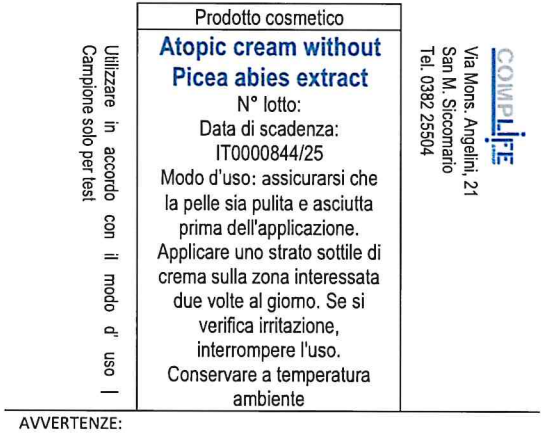
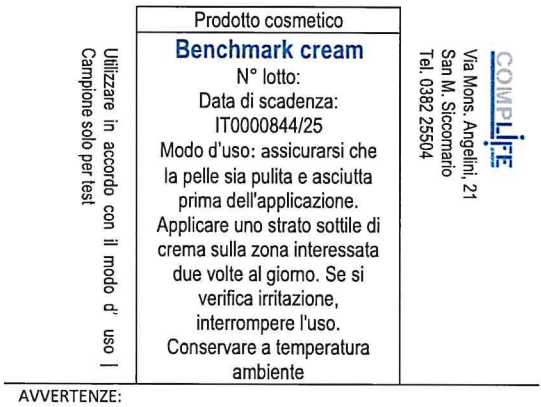


Figure 3. Benchmark cream



7.1.3.3. Storage

All products are stored at room temperature (between 15 and 25°C) at COMPLIFE ITALIA srl, protected from direct light, heat and source of water safe place with restricted access.

7.1.3.4. Accountability

The principal investigator and his collaborators maintain a record of the products delivered to the subjects at the study beginning and received by the subjects at the study ending. The returned product at 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) subjects will receive product sample(s) previously weighted by the experimenter. The compliance to treatment is assessed by the principal investigator by weighting the delivered samples after 21 days of treatment.

7.1.4. Randomization

Restricted randomization list is generated using an appropriate statistic algorithm ("Wey's urn"). An independent technician will dispense either active products 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 21 days.

7.1.7. Study completion

The study completion will be achieved by a subject when she/he will have performed all the treatment and the evaluation visits.

8. EFFICACY ENDPOINTS AND EVALUATIONS

Parameters below reported are assessed under controlled environmental conditions (T = 18-26°C and RH = 40-60%). Subjects are left to acclimatize to ambient condition for 15-20 minutes before the check visit.

8.1. Transepidermal water loss (TEWL).

Transepidermal water loss is measured using a Tewameter® TM 300/TM HEX (Courage+Khazaka, electronic GmbH). The measurement is based on the diffusion law, as described by the equation here below:

$$\frac{dm}{dt} = -D \cdot A \cdot \frac{dp}{dx}$$

where: A is the surface in m²; m is the water transported (in g); t is the time (h); D is the diffusion constant (0.0877 g/m(h(mm Hg))); p is the vapor pressure of the atmosphere (mm Hg); s is distance from skin surface to point of measurement (m)

The diffusion flow dm/dt indicates the mass of water, which is transported per cm² in a specific period. It is proportional to the area A and the change of concentration per distance (dp/dx). D is the diffusion coefficient of water vapor in the air. The resulting density gradient is measured indirectly by two pairs of sensors (temperature and relative humidity) and is analyzed by a microprocessor. The measuring head of the probe is a narrow hollow cylinder (10 mm diameter and 20 mm height), in order to minimize influences of air turbulence inside the probe.

8.2. Skin moisturization

Skin moisturization is evaluated by means of Corneometer® measurement. This measurement is based on the completely different dielectric constant of water (81) and other substances (mostly < 7). The measuring capacitor shows changes of capacitance according to the moisture content of the skin. A metallic lamina separates the metallic tracks (gold) in the probe head from the skin in order to prevent current conduction in the measured area. An electric field between the tracks with alternating attraction develops. One track builds up a surplus of electrons (minus charge) the other a lack of electrons (plus charge). The scatterfield penetrates the very first layer of the skin (10-20 µm) during the measurement and the capacitance is determined.

8.3. Clinical evaluations

8.3.1 Dermatological evaluation for soothing efficacy

Before the study start and after 21 days of product use, the experimenter assesses physical signs (erythema, oedema, desquamation, skin dryness) and reports functional signs referred by the subject (itching, stinging sensation, burning sensation, skin tightness, other) according to scores reported in box 1a/1b.

Box 1a. Physical signs	Score	Box 1b. Functional signs	Score
No/None	0	No/None	0
Very mild	1	Very mild	1
Mild	2	Mild	2
Moderate	3	Moderate	3
Severe	4	Severe	4

Both the improvement of pre-existing conditions and the occurrence of new clinical signs are evaluated. The intensity, location, duration and frequency of each event are recorded, in order to define a relationship to the study product and (if needed) the subject would be asked to stop the product use as long as the symptomatology resolves and then to try to use it again.

All reactions related to the product-use are recorded and reported in the final report.

8.3.2 Assessment of itching sensation

Itching sensation will be scored according to an internal clinical score scale (absent itching, very mild itching, mild itching, moderate itching, severe itching).

Data will be expressed as % of improved subjects vs T0.

8.3.3. Assessment of skin redness

Redness will be scored according to an internal clinical score scale (absent redness, very mild redness, mild redness, moderate redness, severe redness).

Data will be expressed as % of improved subjects vs T0.

8.4. *In vitro* biochemical evaluations

Skin anti-inflammatory properties are assessed by the cytokine dosage on the subject's first skin layers (stratum corneum). Samples of the first layers of the stratum corneum are collected by means of tape stripping procedure using Corneofix® (Courage+Khazaka, electronic GmbH); in particular, for each evaluations consecutive tape strips are collected from two adjacent skin areas.

8.4.1. Skin stripping

Skin stripping is performed using Corneofix® (Courage+Khazaka). This technique allows to collect serial layers of the stratum corneum. The first stripped layer is discarded and 10 strips for each *in vitro* biochemical evaluations (two adjacent areas) are collected and stored at - 80°C upon further analysis. In accordance with the standard operative procedure, skin stripping is performed using a device that allows to standardize the pressure applied on the stripping.

Skin stripping procedure will be performed at T0 (before treatment) and T21 (21 days of treatment).

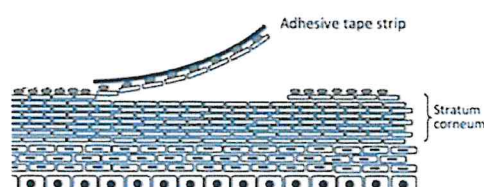


Figure 4. Skin stripping technique. Different layers of the stratum corneum are collected using an adhesive tape strip (Corneofix)

8.4.2 Cytokine dosage

In order to evaluate the possible effect of the product on cytokines expression during the inflammatory answer, 10 tape stripping (Corneofix) are collected by a specialized technician at T0 and T21. After each collection stripping will be stored at -80 ° for further cytokine dosage.

In particular TNF-alpha cytokine, TSLP cytokine and TARC cytokine concentration will be dosed by means ELISA kit (Enzyme-Linked Immunosorbent Assay). The quantification is performed by immunoenzymatic method on the

extraction solution where the collected stripping for each subject are immersed.

8.5. Self-assessment questionnaire

At the end of the study (T21) subjects will be asked to express their opinion on the tested product by answering to a questionnaire about product's acceptability and effects.

9. SAFETY ENDPOINTS AND EVALUATIONS

Tolerability of the treatment are closely followed by the study principal investigator during the course of the study. Subjects have access to the investigators in case of intolerance reactions via a contact phone number provided with the informed consent form (contact at Complife: Enza Cestone: +39 0382 25504). If a subject reports a reaction, the principal investigator must decide if it is related to the investigational product use. If yes, she reports it as an adverse event.

Any unexpected, related side effect judged as severe by the principal investigator is reported to the Sponsor. Upon investigator judgment, the subject may be withdrawn from the study and the side effect is followed until resolution (maximum until the end of the study).

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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a tested 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 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 (tilaukset@repolar.com) with a copy to the project manager. SAE must be sent within 24 hours after the observation. Reactions related to the product must be reported as soon as possible. If pictures 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. Tolerance assessment

For each sign, intensity, location, duration (hours, minutes), and frequency are 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 is 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 is done in conjunction with clinical expertise, knowledge of the product (type of product, conditions of use...), identification of concomitant events.

9.1.1. Causality assessment of local tolerance

Five levels of causality can be described.

- **Very likely/likely**

Very likely

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

- **Not clearly attributable/Unlikely**

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 application 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 application 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 application 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 application 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 application 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 application 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 application and rechallenge is negative.

- **Excluded**

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 Investigation Centre. If required, they would be assessed by the Dermatologist/Ophthalmologist who would perform the clinical assessment and decide the appropriate measures to take (i.e. medical treatment, withdrawal ...).

For each reaction with a physical sign with an intensity of 3 (moderate) and higher and/or for each relevant reaction, photographs are taken, and joined to results at the end of the study.

10. STATISTICS

10.1. Study population for analysis

A total of 66 subjects will be enrolled in the study: 22 subjects will use Atopic cream with Picea abies extract, 22 subjects will use Atopic cream without Picea abies extract, 22 subjects will use benchmark product.

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 one or more evaluation visit; or they do not use the product properly during the study period (as referred by the subject itself). Analysis of safety will be based on the Intent to Treat Population that is defined as all subjects that have been assigned a subject number and received at least one study treatment.

10.2. Descriptive analysis

Demographic variables (sex, age, ethnicity) 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

For each parameter under study Intra-group statistical analysis (T21 vs. T0) and Inter-group statistical analysis (Atopic cream with Picea abies extract vs Atopic cream without Picea abies extract vs benchmark cream) will be carried out.

An appropriate statistical model (parametric or not parametric) will be applied based on data distribution.

Statistical analysis is performed using NCSS 10 software.

p values < 0.05 will be considered as statistically significant.

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 principal 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 initialled/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 Italia under Microsoft® Excel. 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.

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, extracted raw data, administrative file including all the correspondence) is kept in the records of the

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 Italia 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 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 the people 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 Efficacy results based on the Per Protocol Population.

13.3. Contractual and Financial Details

The principal investigator and the Sponsor signs a clinical study agreement prior to the beginning 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 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.

ANNEX 1 - SELF-ASSESSMENT QUESTIONNAIRE

N°	Item Domanda	Completely agree Completamente d'accordo	Agree D'accordo	Disagree In disaccordo	Completely disagree Completamente d'accordo
01	The odour is pleasant L'odore è gradevole	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
02	The texture is pleasant. La texture è gradevole	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
03	The product is quickly absorbed Il prodotto si assorbe velocemente	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
04	The product is easy to apply Il prodotto è facile da applicare	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
05	The product does not leave the skin sticky Il prodotto non lascia la pelle appiccicosa	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
06	The skin is hydrated La pelle è idratata	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
07	The skin is nourished La pelle è nutrita	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
08	The skin is repaired La pelle è riparata	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
09	The product improves the overall appearance of the skin Il prodotto migliora l'aspetto generale della pelle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	The product provides a feeling of comfort Il prodotto fornisce una sensazione di comfort	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11	The skin is soothed La pelle è lenita	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12	The product soothes feelings of discomfort Il prodotto lenisce le sensazioni di discomfort	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13	The product leaves a protective film on the skin Il prodotto lascia un film protettivo sulla pelle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14	My skin is more supple La mia pelle è più elastica	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15	The product preserves the skin Il prodotto preserva la pelle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16	The skin is softer La pelle è più morbida	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17	The product protects the skin against external factors Il prodotto protegge la pelle dai fattori esterni	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18	The skin seems to be less sensitive La pelle sembra essere meno sensibile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

19	The product reduces redness La pelle sembra essere meno sensibile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20	The product is suitable for my skin type Il prodotto è adatto al mio tipo di pelle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
N°	Item Domanda	Yes Sì		No	
21	Would you consider using this product again? Prenderesti in considerazione l'idea di utilizzare nuovamente questo prodotto?	<input type="checkbox"/>		<input type="checkbox"/>	
N°	Item Domanda	Very satisfied Molto soddisfatto	Satisfied Soddisfatto	Unsatisfied Insoddisfatto	Very unsatisfied Molto insoddisfatto
22	How satisfied are you with the product? Quanto sei soddisfatto del prodotto testato?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
N°	Item Domanda				
23	What did you especially like about this product? Cosa ti è piaciuto particolarmente di questo prodotto?	Free comment Commento libero			
24	What did you especially dislike about this product? Cosa non ti è piaciuto particolarmente di questo prodotto?	Free comment Commento libero			