MULTICENTER, OPEN LABEL, UNCONTROLLED CLINICAL INVESTIGATION ON THE PERFORMANCE AND SAFETY OF DERMORELIZEMA ECOFOAM IN THE MANAGEMENT OF SOME DERMATITIS IN THE ADULT

Clinical Investigation Plan (CIP) code: *ReGl/20/Dec-Der/001*

Version 1.0, 06/11/2020

Sponsor

Relife S.r.l.
Via dei Sette Santi 3
50131 Florence, ITALY
Phone: +39 055 56809345
Fax: +39 055 56809346

Coordinating Principal Investigator

Prof. Gabriella Fabbrocini
Unità Operativa Complessa di Dermatologia Clinica
Azienda Ospedaliera Universitaria "Federico II" - Napoli
Via Sergio Pansini 5, 80138 Napoli - Italy

Sponsor's Approval Page

Study Medical Expert: Martina Manni
Relife S.r.l.

Signature & Date: _____ 19-11-2020

Head of Scientific Affairs: Silvia Innocenti
Relife S.r.l.

Signature & Date: _____ 19/11/2020

Coordinating Investigator's Approval Page

I understand that all information concerning the product DermoRelizema ecofoam supplied by Relife Srl and/or Latis Srl in connection with this study protocol are confidential information. This information include: CIP, Case Report Form, product documents.

I understand that any change in this study protocol must be approved in writing by Relife Srl the Co-ordinating Investigator and the Ethics Committee before implementation, except where necessary to eliminate apparent immediate hazard to patients.

I confirm that I will conduct the study according to this protocol (except when mutually agreed to in writing with Relife Srl or its delegate Latis Srl), the Good Clinical Practice (GCP), the UNI EN ISO 14155, the Declaration of Helsinki current edition and laws and regulations in the Country where the study is to be conducted.

I confirm that I will record and report all adverse events occurring during the study, according to this protocol.

I confirm that I am informed about the need of data records retention, according to current regulations and that no data can be destroyed without the written consent of Relife Srl.

I confirm that I will transfer adequate ownership of my responsibilities for the clinical investigation and will inform the Sponsor, in case I retire from my PI role.

I confirm that in case the Trial Center File is stolen or anyhow damaged, I will promptly inform the Sponsor and declare it to the Competent Authorities.

Coordinating Principal Investigator: PROF. SSA GABRIELLA FABBROCINI

Signature & Date: 26/11/2020

Investigator's Approval Page

I understand that all information concerning the product DermoRelizema ecofoam supplied by Relife Srl and/or Latis Srl in connection with this study protocol are confidential information. This information include: CIP, Case Report Form, product documents.

I understand that any change in this study protocol must be approved in writing by Relife Srl the Co-ordinating Investigator and the Ethics Committee before implementation, except where necessary to eliminate apparent immediate hazard to patients.

I confirm that I will conduct the study according to this protocol (except when mutually agreed to in writing with Relife Srl or its delegate Latis Srl), the Good Clinical Practice (GCP), the UNI EN ISO 14155, the Declaration of Helsinki current edition and laws and regulations in the Country where the study is to be conducted.

I confirm that I will record and report all adverse events occurring during the study, according to this protocol.

I confirm that I am informed about the need of data records retention, according to current regulations and that no data can be destroyed without the written consent of Relife Srl.

I confirm that I will transfer adequate ownership of my responsibilities for the clinical investigation and will inform the Sponsor, in case I retire from my PI role.

I confirm that in case the Trial Center File is stolen or anyhow damaged, I will promptly inform the Sponsor and declare it to the Competent Authorities.

Principal Investigator: ……
……..

Signature & Date: _____

General information

Sponsor Representative Contact	Martina Manni *Study Medical Expert* Phone. +39 055 56807184 E-mail. mmanni@relifecompany.it Silvia Innocenti *Head of Scientific Affairs* Phone. +39 055 5680536 E-mail. sinnocenti@relifecompany.it Lia Fabbri *Clinical Trial Coordinator* Phone. +39 055 56809528 E-mail. lfabbri@relifecompany.it Manuela Chelo *Study Safety Manager* Phone.+39 055 56807111 E-mail. mchelo@relifecompany.it
Clinical CRO	Latis Srl – Viale Sauli 39/5 – 16121 Genova Phone. +39 010 562234 Fax. +39 010 540699 E-mail. info@latiscro.it
Contacts for safety reporting	
CRO Contact for Serious Adverse Events (SAEs)	Latis Srl – Viale Sauli 39/5 – 16121 Genova Phone. +39 010 562234 Fax. +39 010 540699 Laura Michellini *Scientific Director* Mobile. +39 347 4785898 E-mail. michellini@latiscro.it

TABLE OF CONTENTS

1. SYNOPSIS OF THE CLINICAL INVESTIGATION PLAN

Study Title	MULTICENTER, OPEN LABEL, UNCONTROLLED CLINICAL INVESTIGATION ON THE PERFORMANCE AND SAFETY OF DERMORELIZEMA ECOFOAM IN THE MANAGEMENT OF SOME DERMATITIS IN THE ADULT
Study Code	ReGl/20/Dec-Der/001
Study Acronym	NA
Study type and design	Multicenter, open label, uncontrolled, single arm, post-market clinical follow-up study.
Pre/post Marketing study	Post Marketing Study
Version/Date	1.0 - 06/11/2020
Sponsor	RELIFE S.r.l.
Countries and Sites	Unità Operativa Complessa di Dermatologia Clinica - Azienda Ospedaliera Universitaria "Federico II" – Napoli Coordinating PI - Prof. Gabriella Fabbrocini Unità Operativa di Dermatologia - Azienda Ospedaliero-Universitaria Sant'Andrea – Roma PI - Prof. Severino Persechino
Indication	Some types of dermatitis, including atopic dermatitis (AD), contact dermatitis (CD), or dermatitis caused by solar radiation.
Objectives	*Primary objective* The primary objective of this clinical investigation is to evaluate and confirm the performance of the DermoRelizema ecofoam in the improvement of the dermatitis severity, by alleviating the symptomatology. The disease severity will be clinically measured through the Investigator Global Assessment (IGA) after 28 days of treatment. *Secondary objectives* ▪ To evaluate the performance of the DermoRelizema ecofoam in the improvement of dermatitis severity (IGA) after 14 and 42 days of treatment. ▪ To evaluate the eczema improvement through the EASI (Eczema

	Area and Severity Index) score; ▪ To evaluate itching, burning, pain and pruritus improvement as reported by the subject at visits by VAS; ▪ To evaluate the improvement in the Quality of Life (QoL) of the subject related to his/her dermatitis, through the DLQI (Dermatology Life Quality Index) questionnaire; ▪ To evaluate the subject's adherence to treatment. ▪ To evaluate the subject's and Investigator's global evaluation of performance of DermoRelizema ecofoam; ▪ To evaluate the subject's overall acceptability of the treatment. *Safety objectives* ▪ To evaluate the local and general tolerability of DermoRelizema ecofoam.
Study Treatment	DermoRelizema ecofoam
Study Duration	For each subject the investigation will be of 1,5 month (42 days ±1). The recruitment phase will be of 3 months. The overall project duration (from "First Subject In" to "Last Subject Out") will be of about 4,5 months.
Number of Patients	40
Target Study Population	Adult outpatients of both sexes, affected by mild to moderate dermatitis, like atopic or contact dermatitis.
Selection Criteria	*Inclusion Criteria:* 1. Subject's written informed consent obtained prior to any study-related procedures; 2. Generally healthy male and female aged ≥ 18 years; 3. Presence of dermatitis of any typology, including atopic dermatitis (AD), irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD), of mild-moderate severity: ▪ IGA score 2 (=mild) or 3 (=moderate); 4. Dermatitis affecting one or more body areas (face, legs, arms, etc.); 5. Subjects with cooperative attitude, able to comprehend the full nature and the purpose of the investigation, including possible risks and side effects, and able to comply with the requirements of the entire investigation (including ability to attend the planned

	visits according to the time limits), based on Investigator's judgement. *Exclusion criteria:* 1. Severe dermatitis at inclusion; 2. Pregnant and breastfeeding women; 3. Concomitant other skin disorders including skin infections; 4. Currently or previously diagnosed or treated (chemotherapy and/or radiotherapy) for cancer in the past 5 years; 5. History of previous skin cancer (history of non-metastatic squamous or basal cell carcinoma of the skin is allowed); 6. Active infections or use of antibiotics in the past 7 days; 7. Diabetic subjects; 8. History of congenital or acquired immunodepression; 9. Immunologic or infectious disease (e.g. hepatitis, tuberculosis, HIV or AIDS, any typology of lupus, rheumatoid arthritis) which could place the subject at risk or interfere with study results; 10. Use of any topic medication for dermatitis in the past 14 days; 11. Use of any topic product for dermatitis in the 2 days before study treatment start; 12. Any systemic treatment or procedure that could influence dermatitis activity within the past 30 days (or 5 half-lives); 13. Use of any corticosteroids, immunosuppressant drugs or immunotherapy within the past 30 days (or 5 half-lives); 14. Use of oral antihistamines and antidepressants in the past 30 days; 15. Subjects with any other clinically significant or unstable concurrent disease or skin condition or general condition that, in the Investigator's opinion, might interfere with the study evaluations; 16. Allergy, sensitivity or intolerance to the components of the investigational device formulations ingredients; 17. Concomitant or previous participation in other interventional clinical study in the past 3 months; 18. Subjects planning sun exposure or tanning booths or UV sources throughout the course of the study.
Concomitant	*Non-permitted treatments*:

Treatments	▪ any topic product for dermatitis ▪ oral antihistamines and antidepressants ▪ corticosteroids (by any route) ▪ antibiotics ▪ immunosuppressant drugs and immunotherapies ▪ any systemic treatment or procedure that could influence dermatitis ▪ chemo and radiotherapies ▪ sun exposure or tanning booths or UV sources.
Primary study endpoint	Change in dermatitis severity from baseline (Visit 1) to 28 days of treatment (Visit 3) in the IGA (Investigator Global Assessment) score.
Secondary study endpoints	*Performance endpoints* 1. Change in dermatitis severity from baseline (Visit 1) to 14 and 42 days of treatment (Visit 2 and 4) in the IGA (Investigator Global Assessment) score 2. Change from baseline (Visit 1) to 14, 28 and 42 days of treatment (Visit 2, 3 and 4) in the EASI score 3. Change from baseline (Visit 1) to 14, 28 and 42 days of treatment (Visit 2, 3, 4) of treatment in the itching, burning, pain and pruritus severity as reported by the subject on VAS scale, administered at visits 4. Change from baseline (Visit 1) to 14, 28 and 42 days of treatment (Visit 2, 3, 4) of treatment in the DLQI questionnaire 5. Adherence to treatment, evaluated by counting the applications reported on the subject's diary and the product accountability 6. Subject's and Investigator's global evaluation on performance of the study product performed by means of a 7-items scale (where 1 = very much improved, 2 = improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = worse, 7 = very much worse) at the end of the study (Visit 4) 7. Subject's evaluation of overall acceptability with treatment (which takes into account pleasant or unpleasant feeling with the product and the ease of use), performed by means of a 5-item scale (where 1 = very much satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, 5 = very much dissatisfied) at the end of the study (Visit 4).

	Safety endpoints 1. Number and type of adverse events (AEs) occurring during the study (seriousness, severity, and relation to study treatment). 2. Local tolerability at the site of administration.
Sample size determination	An exact binomial test with a nominal 5% two-sided significance level will have 80% power to detect the difference between the Null hypothesis proportion, π_o of 0.5 (i.e., 50% of patients with treatment success) and the Alternative proportion, π_1, of 0.75 (i.e., 75% of patients with treatment success) when the sample size is 30 subjects. Assuming a possible 25% dropout rate, 40 subjects will be enrolled.
Statistical Analysis	Descriptive statistical analysis of all relevant variables will be performed. Continuous variables will be summarized by the number of patients (N), mean, standard deviation, median, minimum, maximum. Categorical variables will be summarized by number (N) and proportion of patients (%). The significance level of statistical tests will be set at 0.05. Parametric tests will be used to analyze continuous variables; when continuous variables are not normally distributed, the corresponding non-parametric tests will also be performed.
Statistical Analysis – Primary performance endpoint	Wilcoxon signed rank-sum test will be used to assess a significant change in IGA from baseline to day 28. IGA will be also dichotomized in terms of treatment success (decrease in IGA ≥ 1) or treatment failure (no decrease in IGA). The proportion of treatment successes will be compared to a referent proportion (50%, Null hypothesis proportion) using the exact binomial test.
Statistical Analysis – Secondary performance endpoints	Wilcoxon signed rank-sum test will be used to assess significant changes in IGA from baseline to day 14 and 42. IGA will be also dichotomized in terms of treatment success (decrease in IGA ≥ 1) or treatment failure (no decrease in IGA) and described using number (N) and the proportion of patients (%). Changes from baseline (Visit 1) to 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4) of treatment in EASI score, DLQI questionnaire and pruritus, itching, burning and pain severity will be analyzed using paired t-test. The number of applications reported on the subject's diary and the product accountability will be summarized to evaluate adherence to treatment. Subject's and Investigator's global evaluation on performance of the

	study product performed at the end of the study (Visit 4) will be summarized through number (N) and proportion of patients (%) for each item. The variable will be also dichotomized in terms of improved/not improved. Subject's evaluation of overall acceptability with treatment, performed by means of a 5-item scale will be summarized through number (N) and proportion of patients (%) for each item.
Statistical Analysis – Safety endpoints	AEs and ADEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) after medical coding using the Medical Dictionary for Regulatory Activities (MedDRA). An overview of AEs and ADEs will be prepared showing the number of AEs and ADEs and the number of patients with any AEs or ADEs, serious AEs or ADEs, severity of AEs or ADEs and AEs or ADEs leading to withdrawal. Summary tables showing the number of patients with at least one AE or ADE and event counts by SOC and PT (Preferred Term) will be prepared. Local tolerability at the site of administration will be summarized.
Population	The following populations are defined for this investigation: •Safety analysis set (SAF): all patients enrolled who sign informed consent and receive at least one administration of the investigational device. •Full analysis set (FAS): all patients of the SAF who have performed the baseline assessments and have at least one post-baseline assessment of any performance endpoint. •Per-Protocol analysis set (PPAS): all patients of the FAS who meet all inclusion/exclusion criteria and who do not have any major protocol deviation. The analysis of safety endpoints will be performed in the Safety population (SAF). Analysis of performance endpoints will be performed on the FAS population. The analysis of primary endpoint will be repeated in the PPAS.

Table 1: *Study Flow-Chart*

	Visit 1	Visit 2	Visit 3	Visit 4*
	Day 1	Day 14 ± 1	Day 28 ± 1	Day 42 ± 2
	Screening Baseline Treatment start	Follow-up visit	Follow-up visit	End of treatment End of study
Written informed consent	✓			
Demographic data	✓			
Medical and surgical history	✓			
Physical examination (focused on skin examination)	✓	✓	✓	✓
IGA	✓	✓	✓	✓
EASI	✓	✓	✓	✓
Concomitant medications/treatments	✓	✓	✓	✓
Inclusion and exclusion criteria	✓			
Study product dispensed	✓	✓	✓	
Study product administration	→ (twice daily)			
Study product returned		✓	✓	✓
Diary dispensed	✓	✓	✓	
Study treatment recording on the diary	→ (daily)			
VAS administration for pain, itching, burning, pruritus	✓	✓	✓	✓
Diary returned		✓	✓	✓
DLQI questionnaire	✓	✓	✓	✓
Global evaluation of performance[1]				✓
Global evaluation of product acceptability[2]				✓
Treatment compliance		✓	✓	✓
Local and general adverse events		✓	✓	✓

*Or Early termination Visit
[1]To be evaluated by both the subject and the Investigator
[2]To be evaluated by the subject

2. Identification and Description of the Investigational Device

DermoRelizema ecofoam is a topical compact mousse indicated for treatment of the signs and symptoms associated with all types of dermatitis (including atopic, contact dermatitis, dermatitis caused by radiotherapy and by sun radiations) and erythema. The mechanism of action of DermoRelizema ecofoam is based on the creation of a protective thin layer on the skin, which protects the skin against external irritants without hindering normal transpiration. It helps reducing skin redness and its derma-protective action it helps maintaining and restoring the physiological skin barrier.

Thanks to its light texture, it can be easily applied on wide areas.

DermoRelizema ecofoam is a CE marked medical device class IIa, manufactured by Relife Srl, that is the Sponsor of this post-market clinical follow-up investigation.

In this clinical investigation DermoRelizema ecofoam will be used to treat and alleviate dermatitis severity and symptoms as perceived by the patients, in compliance with its Instructions for Use (IFU). Different typologies of skin conditions will be treated like atopic dermatitis, irritant dermatitis, contact dermatitis, as they have common symptomatology and they all could benefit from the treatment with the topic product under investigation.

3. Justification for the Design of the Clinical Investigation

Dermatitis is a skin inflammatory disease commonly spreading in a limited area of the body and characterized by reddening, itching and skin dryness of the affected epidermis [1]. Dermatitis is a condition that can interfere with social function, sleep and employment. Its persistence and accompanying pruritus may be stressful and frustrating for patients.

The most common types of dermatitis are contact dermatitis (CD) and atopic dermatitis (AD), also referred as atopic eczema, but also dermatitis caused by radiotherapy or solar radiations can occur. Only atopic dermatitis and contact dermatitis will be included in this clinical investigation.

The most common and best characterized type of eczema, **atopic dermatitis (AD)**, appears to be increasing in incidence [2]. AD pathogenesis is not completely known, even though the disease seems to be the result of genetic susceptibility, immune dysfunction and epidermal barrier dysfunction [3]: it has been hypothesized that patients with eczema have defects in the skin barrier that allows antigens to enter and trigger the stimulation of inflammatory cytokines [4,5]. AD is characterized by a red and

itchy rash most commonly located where the skin flexes (e.g. inside the elbows, behind the knees and the front of the neck).
Other common eczematous dermatoses are contact dermatitis (CD), particularly allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD).

Contact dermatitis (CD) is a rash that occurs on areas of the body that have come into contact with substances that either irritate the skin or cause an allergic reaction. CD can be irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD). ICD is provoked by handling water, detergents, solvents or harsh chemicals and by friction, while ACD is due to skin contact with substances that most people don't react to (most commonly nickel, perfume, rubber, hair dye or preservatives). CD is commonly characterized by skin becoming red, blistered, dry, scaly and cracked.
The first precaution in ICD and ACD is to avoid or limit the contact with substances that are irritant or generate the allergic reaction.

Although the above-mentioned types of dermatitis are characterized by different etiological factors, a key issue of the clinical condition is the dysfunction of the epidermal barrier. An altered skin barrier is the initial step that starts the so-called “vicious circle” of atopic dermatitis, characterized by dryness, tendency to itching and scratching, risk of superinfections, inflammation, pain and sleep disturbances.

In order to support the resolution of epidermis damage in the case of any dermatitis, the principal approach is the induction and enhancement of skin barrier repair.
Some of the currently available treatments for dermatitis management forecast the topical application of drugs - such as corticosteroids or immunosuppressants - acting at reducing the underlying inflammation and hypersensitization of the epidermis, though they are related to some side effects resulting from the topical application [7,8,9,10, 11].
On the other hand, to effectively heal the skin barrier, TEWL (Trans Epidermal Water Loss) must be minimized and the skin must be protected from further contact with irritants, allergens and infectious organisms [12].
A number of clinical trials have shown that moisturizers lessen symptoms and signs of dermatitis, including pruritus, erythema and fissuring [13-15]. Most of the time, rash and itching are successfully treated within three weeks [16]. It is now widely accepted that the application of topical moisturizers, emollients and protective agents should be an integral part of the treatment of patients with atopic and contact dermatitis, and there is strong evidence that their use can reduce the need for pharmacologic intervention to treat disease flare-ups.

Moisturizers - including petrolatum, physiological lipid mixtures, and ceramide-dominant triple-physiolosic lipid (ceramide:cholesterol:free fatty acids at a 3:1:1 molar ratio) - play critical roles in dermatitis management [17]. Their daily use is now universally recommended to improve clinical symptoms and enhance skin barrier function. Moreover, the barrier improvement deriving from the prolonged use of these products is particularly relevant, given that the long-term topical application of corticosteroids is not well-tolerated and also reduces skin barrier function and increases TEWL [18].

Moisturizers are generally composed of substances capable to restore the ability of the intercellular lipid bilayers to retain and redistribute water [19, 20]. Moisturizers contain three main properties, which are the occlusive, humectant, and emollient effects.

The occlusive ingredients physically block TEWL by forming a hydrophobic film on the skin surface and within the superficial interstitium between corneocytes [21].

The second property of moisturizers is the emollient effect, which smoothes skin by filling space between skin flakes with a droplet of oil [22].

The other property of moisturizers is to be also humectant. Humectants are substances that attract water from the external environment when applied to the skin and theoretically improve hydration of the stratum corneum with a physical mode of action [23]. Glycerin, together with panthenol and hyaluronic acid, is the most popular of all humectants used in personal care products. All these three ingredients are contained in DermoRelizema ecofoam.

Hyaluronic acid (HA) is a widely available, biocompatible, polysaccharide with distinguishing physiochemical properties, which inspire its application throughout several fields of medicine. HA is also a naturally-occurring molecule, one of the major components of the extracellular matrix of the skin. It is produced by fibroblasts and keratinocytes, and is present in all layers of the epidermis and the dermis. HA binds a large number of water molecules, improving tissue hydration and resistance to mechanical damage, especially in aesthetic dermatology. Moreover, HA is used in the treatment of skin damage that manifests during radiation therapy for the treatment of solid tumors, in particular breast, head and neck, thorax and abdomen cancers; since 1997, it has demonstrated to be effective and safe when applied topically for the prevention of radioepithelitis [24]. In addition, DermoRelizema ecofoam contains Sodium Butyroyl Formoyl Hyaluronate (sodium hyaluronate butyrate and formate). Sodium Butyroyl Formoyl Hyaluronate is a hyaluronan derivative in which hydroxylic functions of the polysaccharide are substituted by butyric acid. The substitution positively affects the stability of the molecule, because esterification of sodium hyaluronate with butyric acid reduces the rate of enzymatic degradation.

DermoRelizema ecofoam also contains glycerol, which is a well-known cosmetic ingredient and acts as humectant [25]. Glycerol-containing moisturizers produce long-lasting moisturization by binding and holding water, thus minimizing water loss.

DermoRelizema ecofoam (DLP034) CE mark was supported by literature research. In order to allow the Manufacturer, Relife Srl, to review and confirm the clinical performance and safety of the medical device DermoRelizema ecofoam in the post-market phase, this post-market clinical follow-up investigation was designed and is going to be conducted in adult males and females affected by mild to moderate dermatoses, like AD, ICD or ACD.

4. Risk and Benefits of the Investigational Device and Clinical Investigation

To date a large variety of products for the treatment of eczematous dermatoses are available.
DermoRelizema ecofoam is a medical device that is CE marked and already in use to treat dermatitis symptoms such as itching, flushing and erythema. In this clinical investigation DermoRelizema ecofoam will be used in adult subjects with mild to moderate dermatitis, of any origin, and erythema, according its IFU.
DermoRelizema ecofoam will be recommended twice daily for 42 days (±2). The product's components are known to be safe and well tolerated, therefore no risk seems to be associated to DermoRelizema ecofoam use.
The only precaution for users is to avoid contact of the product with eyes and mucous membranes (if contact does occur rinse immediately with plenty of water).
Within the clinical investigation the subject will be provided with instructions on the personal hygiene to follow, in order to further improve skin care and safety.
No tests or invasive examinations are foreseen in this study that can increase the risk for participants.
In the light of the above, no additional risk arising from the participation to this clinical investigation can be envisioned.

5. Objectives and Hypotheses of the Clinical Investigation

5.1 Primary Objective

The primary objective of this clinical investigation is to evaluate and confirm the performance of the DermoRelizema ecofoam medical device in the improvement of the dermatitis severity, by alleviating the symptomatology.

The disease severity will be clinically measured through the Investigator Global Assessment (IGA) for dermatitis after 28 days of treatment.

5.2 Secondary Objectives

The secondary objectives of this clinical investigation are:

- to evaluate the performance of the DermoRelizema ecofoam in the improvement of dermatitis severity (IGA) after 14 and 42 days of treatment;
- to evaluate the eczema improvement through the EASI (Eczema Area and Severity Index) score;
- to evaluate the improvement in itching, burning, pain and pruritus at visits, as reported by the subject at visits by VAS;
- to evaluate improvement in the Quality of Life (QoL) of the subject related to his/her dermatitis, through the DLQI (Dermatology Life Quality Index) questionnaire;
- to evaluate the subject's adherence to treatment.
- to evaluate the subject's and Investigator's global evaluation of performance of DermoRelizema ecofoam;
- to evaluate the subject's overall acceptability of the treatment.

5.3 Tolerability and Safety Objectives

To evaluate the local and general tolerability of DermoRelizema ecofoam.

6. Design of the Clinical Investigation

6.1 General

This is a multicenter, open label, uncontrolled, post-market clinical follow-up investigation.

All the subjects will be allocated to the following treatment group:

- DermoRelizema ecofoam, topically applied twice a day in all the affected areas for 42 consecutive days.

The subject will start treatment on the first day of study and will go on until 42 days after the first application. The treatment could be prolonged or shortened of maximum 2 days, in the case intermediate and/or final visits are delayed.

Each subject for whom written consent is obtained will be identified during the study by a "Subject Code", automatically generated and assigned by the e-CRF.

All screened subjects will receive the Code regardless of whether they receive the treatment or not. If a subject discontinues from the study at any time, the Code will not be re-used.

All subjects who will sign the informed consent and receive the Subject Code will be entered into a Subject's Register, containing the name and surname of the patients and their Subject Codes. The Subject's Register will be accessible for source data verification but will be preserved only at clinical site.

Once eligibility of a patient is established (see Inclusion/Exclusion Criteria) the study treatment will be assigned.

The Investigator will keep record of all enrolled patients in the Subject's Screening/Enrolment Log: the Subject Code, the date of consent, the treatment assigned to the patient, if applicable, or the reason for not actively entering the study will be recorded.

6.2 Investigational device

6.2.1 DermoRelizema ecofoam

The product under investigation is DermoRelizema ecofoam.

Manufacturer:	Relife Srl, Via dei Sette Santi 3 - 50131 Firenze (FI) - Italy
Device Name:	DLP034
Trade Name:	DermoRelizema ecofoam
Formulation:	ecofoam
Route of administration:	topical application on breached/compromised skin
Composition:	aqua, peg-40 hydrogenated castor oil, glycerin, betaine, pullulan, capryloyl/ caproyl methyl glucamide, sodium cocoyl glycinate, ethylhexylglycerin, panthenol, propylene glycol, tocopheryl acetate, lauroyl/ myristoyl methyl glucamide, glyceryl caprylate, chondrus crispus powder, sodium butyroyl/formoyl hyaluronate, sodium

hyaluronate, hexamidine diisethionate, biotin, caprylhydroxamic acid, citric acid.
It is formulated without fragrances, paraben, alcohol and gas. Nickel, antimony, arsenic, cadmium, cobalt, chrome, mercury and lead tested.

DermoRelizema ecofoam is a CE marked, Class IIa medical device, dermatological compact mousse for topical use indicated for symptomatic treatment of all types of dermatitis (including atopic dermatitis, contact dermatitis, or dermatitis caused by radiotherapy and solar radiation) and erythema. It forms a thin protective layer on the skin which protects against external irritants, without hindering normal perspiration, and helps reduce redness. Additionally, due to its light texture, it can also be easily applied to large areas.

6.2.1.1 Packaging and labelling

DermoRelizema ecofoam will be provided for the study by the Sponsor of this clinical investigation.
The study product shipment to the study sites will be done only after the completion of all Ethics and Administrative procedures.
The product will be labeled as experimental treatment in accordance with applicable Good Manufacturing Practice (GMP, Annex 13).
The primary package is a 70 ml labelled canister with pump. Each subject will receive a total of no. 3 canisters and he/she will use a variable amount of cream depending on the extent of the area/s affected by dermatitis to be treated. Occasionally, if the subject needs further treatment (beyond the 3 canisters received), the Investigator will be able to provide further amount of treatment. Additional canisters provided to the subject will be recorded in the CRF.

6.2.1.2 Study device instructions for use

Patients will be instructed to use DermoRelizema ecofoam two times daily: the first application in the morning and the second in the evening before bedtime, for 42 consecutive days.
At the first use of the product the patient should be instructed to press the valve two or three times to activate the pump mechanism. After this, the subject should press the valve gently to obtain one or more doses of the product to apply on the selected area and massage.

6.2.1.3 Handling and storage

It is the Investigator/Institution's responsibility to set up a system for handling the clinical investigation treatment, so as to ensure that:

- deliveries of product supply from the Sponsor are correctly received
- products are handled and stored safely and properly in a secured area
- treatments are only dispensed to study subjects in accordance with the clinical investigation plan
- any unused, used, partially used product is returned to the Investigator (including empty canisters).

The study product shall be carefully stored at the study site, in a safe area and separately from other devices/drugs/products. It shall be stored in a dry and cool place, away from direct sunlight or heat.

The pharmacist and/or the Investigator shall maintain records of the study products receipt by the study site and an updated inventory of the study product.

Treatments will be dispensed to the subjects enrolled in this clinical investigation only by authorized personnel.

After study conclusion, all unused study product shall be returned to the Sponsor or destroyed at site after written Sponsor approval.

6.2.1.4 Study product accountability and compliance

The Investigator is responsible for ensuring the accountability of the study product.

Accountability records will include:

- confirmation of product delivery and receipt to/at the clinical site
- records concerning the product delivery to each subject and the return from each subject
- the return to the Sponsor or alternative disposition of unused products.

The Investigator should maintain records that adequately document:

- that the subjects were provided with the quantities specified by the clinical investigation plan/amendment(s)
- that all study products provided by the Sponsor were fully reconciled.

Unused products must not be discarded or used for any purpose other than the present clinical investigation.

Products that have been allocated to one subject must not be re-dispensed to a different patient.

Subjects will be reminded of the importance of strictly complying with the instructions received from the Investigator and to return all unused treatment or empty canisters to the Investigator.

The Investigator will check and register when subjects are bringing back to the site the used/unused products. Compliance to the treatment will be done with subject's diary information.

6.2.2 Concomitant Medications/Treatments

Any medications (other than those excluded by the clinical investigation plan) that were considered necessary for the patients' well-being and do not interfere with the study product can be given at the Investigator's discretion.

According to exclusion criteria, the following prior and concomitant medications are prohibited:

- any topic product for dermatitis
- oral antihistamines and antidepressants
- corticosteroids (by any route)
- antibiotics
- immunosuppressant drugs and immunotherapies
- any systemic treatment or procedure that could influence dermatitis
- chemo and radiotherapies
- sun exposure or tanning booths or UV sources.

The subject will be recommended not to use any other product for the personal hygiene than the one provided by the Investigator.

Any concomitant medication/treatment shall be recorded in the appropriate section of the CRF.

6.3 Subjects

In this clinical investigation 40 subjects will be enrolled fulfilling the following eligibility criteria.

6.3.1 Inclusion criteria

1. Subject's written informed consent obtained prior to any study-related procedures;
2. Generally healthy male and female aged ≥ 18 years;
3. Presence of dermatitis of any typology, including atopic dermatitis (AD), irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD), of mild-moderate severity:
   - IGA score 2 (=mild) or 3 (=moderate)
4. Dermatitis affecting one or more body areas (face, legs, arms, etc.);
5. Subjects with cooperative attitude, able to comprehend the full nature and the purpose of the investigation, including possible risks and side effects, and able to comply with the requirements of the entire investigation (including ability to attend the planned visits according to the time limits), based on Investigator's judgement.

6.3.2 Exclusion criteria

1. Severe dermatitis at inclusion;
2. Pregnant and breastfeeding women;
3. Concomitant other skin disorders including skin infections;
4. Currently or previously diagnosed or treated (chemotherapy and/or radiotherapy) for cancer in the past 5 years;
5. History of previous skin cancer (history of non-metastatic squamous or basal cell carcinoma of the skin is allowed);
6. Active infections or use of antibiotics in the past 7 days;
7. Diabetic subjects;
8. History of congenital or acquired immunodepression;
9. Immunologic or infectious disease (e.g. hepatitis, tuberculosis, HIV or AIDS, any typology of lupus, rheumatoid arthritis) which could place the subject at risk or interfere with study results;
10. Use of any topic medication for dermatitis in the past 14 days;
11. Use of any topic product for dermatitis in the 2 days before study treatment start;
12. Any systemic treatment or procedure that could influence dermatitis activity within the past 30 days (or 5 half-lives);
13. Use of any corticosteroids, immunosuppressant drugs or immunotherapy within the past 30 days (or 5 half-lives);
14. Use of oral antihistamines and antidepressants in the past 30 days;
15. Subjects with any other clinically significant or unstable concurrent disease or skin condition or general condition that, in the Investigator's opinion, might interfere with the study evaluations;
16. Allergy, sensitivity or intolerance to the components of the investigational device formulations ingredients;
17. Concomitant or previous participation in other interventional clinical study in the past 3 months;
18. Subjects planning sun exposure or tanning booths or UV sources throughout the course of the study.

6.4 Procedures

6.4.1 Study Visits and Assessments

Visit 1 screening – baseline- treatment start (day 1):

Subjects will be evaluated with regard to the inclusion and exclusion criteria that will allow their participation into the study.

Before any study specific evaluation is carried out, subjects will receive all the information about the study by the Investigators and will sign an informed consent form.

The following activities will be performed:

- Collection of information about demography
- Medical and surgical history
- Physical examination, focused on skin examination
- IGA on dermatitis
- EASI Score
- Previous (in the 30 days before) and concomitant medications/treatments recording
- Inclusion/exclusion criteria assessment
- VAS for pain, itching, burning, pruritus
- DLQI questionnaire
- Study product delivery to subject and instructions on how to use it
- Recommendations for personal hygiene to follow
- Diary dispensation and explanations on how to fill it in.

Diary: on the diary each subject will record, at the end of each day, the study product applications performed.

***Recommendations for personal hygiene to follow*:** throughout the treatment phase subjects will be required to avoid soap and use only the product DermoRelizema liporestitutive cleanser, particularly indicated for dry and sensitive skin, provided by the Investigator for bathing and showering (bathing should be once a daily, with warm water, for approximately 5 to 10 minutes).

DermoRelizema ecofoam application: to apply the study product on the affected body areas twice per day, once in the morning and once in the evening before bedtime. No additional creams, moisturizers, lotions or cleansers other than the product provided by the Investigator will be permitted.

Visit 2 (Day 14 ± 1) and Visit 3 (Day 28 ± 1) – follow-up visits:

The following activities will be done at Visit 2 and Visit 3:

- Physical examination, focused on skin examination
- IGA on dermatitis
- EASI Score
- Change in concomitant medications/treatments recording
- VAS for itching, burning, pain, pruritus
- DQLI questionnaire
- Diary compilation check with the subject for treatment adherence and collection
- New diary delivery
- Study product collection and accountability
- New product delivery
- Adverse events (occurred since previous visit) recording.

If Visit 2 is anticipated of one day (Day 13) or postponed of 1 day (Day 15), any attempt will be done to fix the following Visit 3 so that 28 days of study and treatment are respected (i.e. if Visit 2 is on Day 13, then Visit 3 will be 15 days after Visit 2).

Visit 4 – End of treatment and end of study (Day 42 ±2):

The following activities will be done at Visit 4:

- Physical examination, focused on skin examination
- IGA on dermatitis
- EASI Score
- Change in concomitant medications/treatments recording
- VAS for itching, burning, pain, pruritus
- DQLI questionnaire
- Diary compilation check with the subject for treatment adherence and collection
- Study product collection and accountability
- Subject global evaluation of performance
- Investigator global evaluation of performance
- Subject global acceptability evaluation on the study product
- Adverse events (occurred since previous visit) recording.

Any attempt will be done to fix the Visit 4 so that the study and treatment days are as minimum 40 and as maximum 42.

6.4.2 IGA (Investigator's Global Assessment)

IGA is a tool used in the clinical routine to define the dermatitis severity. The Investigator's Global Assessment is based on a six-point scale:

0 = clear

1 = almost clear

2 = mild

3= moderate

4 = severe

5 = very severe.

The IGA will be filled in by the Investigator at each visit.

6.4.3 EASI (Eczema Area and Severity Index)

The EASI score is a tool used to measure the extent (area) and severity of eczema.

Four body regions are considered: head and neck, trunk (including genital area), upper limbs, lower limbs (including buttocks). The percentage of skin affected by eczema in each region is correlated to an area score (0 = 0: no eczema in this region; 1 = 1-9%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; 6 = 90-100%: the entire region is affected by eczema).

A severity score (0 =none, 1 = mild), 2 =moderate or 3 = severe) is then recorded for each of the four regions identified for the following four signs:

1. Redness (erythema, inflammation);
2. Thickness (induration, papulation, swelling—acute eczema);
3. Scratching (excoriation);
4. Lichenification (lined skin, prurigo nodules—chronic eczema).

EASI score calculation:

Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	X	x 0.1	
Trunk	(+	+	+	)	X	x 0.3	
Upper extremities	(+	+	+	)	X	x 0.2	
Lower extremities	(+	+	+	)	X	x 0.4	
The final EASI score is the sum of the 4 region scores							____ (0-72)

Severity strata for the EASI are as follows: 0 = clear; 01-1.0 = almost clear; 1.1-7.0 = mild; 7.1-21.0 = moderate; 21.1-50.0 = severe; 50.1-72.0 = very severe.

The EASI score will be filled in by the Investigator at each visit.

6.4.4 DLQI (Dermatology Life Quality Index) – Appendix 2

DLQI is a questionnaire used to measure the impact of skin disease on the quality of life of an affected person. There are 10 questions, covering the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, treatment. Each question refers to the impact of the skin disease on the patient's life over the previous week.

Each question is scored from 0 to 3, giving a possible score range from 0 (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life).

Global score:

0-1 = No effect on patient's life

2-5 = Small effect

6-10 = Moderate effect

11-20 = Very large effect

21-30 = Extremely large effect.

The DQLI will be compiled by the subject at each visit.

6.4.5 Subject and Investigator Global Evaluation of Performance – Appendices 3 and 4

Subjects' and Investigator's global evaluation of the performance of DermoRelizema ecofoam will be performed by means of the 7-item scale, where 1 = very much improved, 2 = improved, 3 = minimally

improved, 4 = no change, 5 = minimally worse, 6 = worse, 7 = very much worse at the end of the study (Visit 4).

6.4.6 Subject Overall Acceptability – Appendix 5

Subjects' evaluation of overall acceptability with the study treatment, which takes into account the pleasant or unpleasant feeling with the product and the ease of use, will be performed by means of a 5-item scale, where 1 = very much satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, 5= very much dissatisfied.

Global acceptability evaluation by the subject will be assessed at the end of the treatment (Visit 4).

6.4.7 VAS for pruritus, itching, pain and burning

The subject will be requested to indicate at each visit his/her pruritus, itching, burning and pain by placing a vertical mark along a 100 mm VAS (Visual Analogue Scale). The rating will be recorded as a distance from the left side of the scale (0 mm) to the mark made by the patient.

Example:

Rating (mm): |__|__|__|

A VAS scale for each of the 4 symptoms will be completed by the subject at each visit.

6.5 Monitoring Plan

The study will be monitored on a regular basis by the CRO's adequately qualified and trained clinical Monitors throughout the study period to ensure the proper conduct of the clinical Investigation.

The purposes of study monitoring are to verify that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete and verifiable against the source documents, and that the study is conducted in accordance with the current clinical investigation plan, Good Clinical Practice guideline (UNI EN ISO 14155) and applicable regulatory requirements.

During the monitoring visits, Monitors will verify the following, including but not limited to: subject informed consent, subject's eligibility, safety data and reporting, quality of source documents and CRF data against subject's medical records. If inconsistencies are found, the corresponding corrections to the CRF data will have to be made by the Investigator or designated person. Monitors will also check subject compliance, accrual, study product handling, including dispensing procedures and

accountability logs, delegation of responsibilities within the Investigator's team, relevant communications with family doctors, if any, ancillary equipment and facilities, etc. The Investigator and other site staff involved in the study must allocate enough time to the Monitor at these visits.

Given the current COVID-19 pandemic situation also proper approaches will be implemented remotely to allow the performance of the monitoring activities, in line with applicable guidelines of competent authorities and best practices.

Upon request by the Sponsor, on-site study audits may be conducted in order to ensure the study is in compliance with GCP, applicable regulatory requirements, and the clinical investigation plan. The auditing activities may also be conducted after study completion.

The Investigator agrees to allow Sponsor/auditors/CRO monitors to have direct access to his/her study records for review, being understood that they are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

Regulatory Authorities may wish to conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator must inform the Sponsor and CRO immediately. The Investigator will make all efforts to facilitate the conduct of the audits and inspections giving access to all necessary facilities, data and documents.

Any result or information arising from the inspection will be immediately communicated by the Investigator to the Sponsor. The Investigator will take all appropriate measures required by the Sponsor to implement corrective actions for all problems found during audits or inspections.

7. Statistical Considerations

This section summarizes the statistical principles and methods planned to analyze the data for this clinical investigation.

7.1 Sample Size Determination

An exact binomial test with a nominal 5% two-sided significance level will have 80% power to detect the difference between the Null hypothesis proportion, π_0 of 0.5 (i.e., 50% of patients with treatment success) and the alternative proportion, π_1, of 0.75 (i.e., 75% of patients with treatment success) when the sample size is 30 subjects. Assuming a possible 25% dropout rate, 40 subjects will be enrolled.

7.2 Definition of Study Populations for Analysis

The following populations are defined for this investigation:

- Safety analysis set (SAF): all patients enrolled who sign informed consent and receive at least one administration of the investigational device.
- Full analysis set (FAS): all patients of the SAF who have performed the baseline assessments and have at least one post-baseline assessment of any performance endpoint (primary or secondary).
- Per-Protocol analysis set (PPAS): all patients of the FAS who also meet all inclusion/exclusion criteria and who do not have any major protocol deviation (i.e. wrong inclusion, use of forbidden concomitant medications, etc.).

The analysis of safety endpoints will be performed in the Safety population (SAF). Analysis of performance endpoints will be performed on the FAS population. The analysis of primary endpoint will be repeated in the PPAS

7.3 Statistical Analysis

Descriptive statistical analysis of all relevant variables will be performed. Continuous variables will be summarized by the number of patients (N), mean, standard deviation, median, minimum, maximum. Categorical variables will be summarized by the number (N) and the proportion of patients (%). Where appropriate, 95% confidence intervals for the target variables will be estimated.

The significance level of statistical tests will be set at 0.05. Parametric tests (e.g., paired t-test) will be used to analyze continuous variables; when continuous variables are not normally distributed, the corresponding non-parametric tests (e.g. Wilcoxon signed-sum rank test) will also be performed. Details of statistical analysis are provided in the following paragraphs.

The statistical analysis will be performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

7.3.1 Missing Data

Missing data will not be replaced in any statistical analysis.

7.3.2 Multiplicity

This is a single-arm clinical investigation and no adjustment for multiplicity will be used.

7.3.3 Covariates, Interactions and Subgroups

This is a single-arm clinical investigation. No covariates or interaction analysis will be performed. Subgroup analyses could be performed to better describe the performance and safety of the study device.

7.3.4 Analysis of Demographics and Baseline Variables

Demographic (gender, age) and baseline characteristics will be summarized using mean, median, standard deviation, minimum and maximum for continuous variables and frequencies and percentages for categorical variables.

7.3.5 Efficacy analysis

7.3.5.1 Primary endpoint

Wilcoxon signed rank-sum test will be used to assess a significant change in IGA from baseline to day 28.

The assessment will be also dichotomized in terms of treatment success (decrease in IGA between baseline and day 28 ≥ 1) or treatment failure (no decrease in IGA, i.e. IGA at day 28 equal to or higher than IGA at baseline) and described using number (N) and the proportion of patients (%). The proportion of treatment successes will be compared to a referent proportion (50%, Null hypothesis proportion) using the exact binomial test.

7.3.5.2 Secondary endpoints

Wilcoxon signed rank-sum test will be used to assess significant changes in IGA from baseline to day 14 and 42. IGA will be also dichotomized in terms of treatment success (score decrease ≥ 1) or treatment failure (no score decrease) and described using number (N) and the proportion of patients (%).

Changes from baseline (Visit 1) to 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4) of treatment in EASI score, DLQI questionnaire and VAS for pruritus, itching, burning and pain severity will be analyzed using paired t-test.

The number of applications reported on the subject's diary will be summarized to evaluate adherence to treatment.

Subject's and Investigator's global evaluation on performance of the study product performed at the end of the study (Visit 4), by means of a 7-items scale, will be summarized through number (N) and proportion of patients (%) for each item. The variable will be also dichotomized in terms of improved/not improved.

Subject's evaluation of overall acceptability with treatment, performed by means of a 5-item scale will be summarized through number (N) and proportion of patients (%) for each item.

7.3.6 Safety Analysis

All enrolled subjects receiving at least one treatment application will be included in the safety analysis.

Adverse events (AEs) and Adverse Device Events (ADEs) will be coded using the last updated version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary to give a preferred term (PT) and a system/organ class term (SOC) for each event. The number of subjects who experienced at least one AE or ADE, study product-related AE or ADE, serious AE or ADE, severe AE or ADE and the number of subjects withdrawn due to AE will be summarized.

For each SOC and preferred term, summaries will be made with respect to the proportion of subjects having at least one occurrence of that event during the study and the total number of events. The incidence of AEs and ADEs will be presented overall, by SOC and preferred term, and additional grouping by severity and relationship to the study treatment.

Local tolerability at the site of administration (e.g. skin increased itching or redness or irritation) will be reported and summarized.

7.4 Planned Interim Analysis

No interim analysis is planned.

8. Data Management

During each study visit, the study Investigator (or designee) will collect and report study data in the relevant patient's chart, documenting all significant observations.

Any contact with the patient via telephone or other means that provides significant clinical information shall be documented in the source data.

An Electronic Case Report Form (e-CRF) will be used to record subject's study data.

All data relating to the study will be documented in the electronic CRF (e-CRF). This CRF is developed to record the data requested by the protocol.

The Investigator will maintain a list of all persons authorized to make entries and/or corrections on the e-CRFs. Each authorized person will be provided with a user-specific ID protected by a renewable password. Data entries and corrections will be made only by the authorized persons. The e-CRF system will record date and time of any entry and /or correction and the user ID of the person making the

entry/correction. The system will keep track of all old and new values (audit trail). It is the responsibility of the Investigator to ensure that the CRFs are properly and completely filled in. The CRFs must be completed for all subjects who have been included in the study. The Investigator will review all CRFs and electronically sign and date them for each subject, verifying that the information is complete, true and correct. All fields on the CRF must be completed as applicable.

Checks to assist during the data entry and to assess the appropriateness and consistency of data will be developed on the e-CRF system. E-CRF pages will be reviewed both on site by the monitor of the center and remotely, by the data management staff of the CRO. Data Clarification Sheets (DCS) will be generated through the e-CRF system, both automatically, through edit checks, and manually, by CRAs and/or data managers, and the Investigator will have to check and solve them. The Investigator is responsible for the review and approval of all query resolutions.

Subject's diaries will be dispensed at each Visit; the diary will have to be filled daily by the subject during treatment period. It is responsibility of the Investigator's to instruct the participants on how to fill in the diaries in a clear way and preferably in black ball-point pen. The diary is anonymous, the subject is identified through the Subject Code. Diaries data will be reported on the e-CRF by the Investigator (or designee). Diaries will be considered source data.

Subjects will be provided with paper questionnaires. Such documents will be filled by the subjects during the study visits, to record data concerning their QoL with respect to dermatitis condition and to report the symptoms severity.

It is responsibility of the Investigators to instruct the study participants on how to fill in questionnaires in a clear way and preferably in black ball-point pen. The questionnaires will be anonymous, each subject is identified through the Subject Code. Questionnaires data will be reported on the e-CRF by the Investigator (or designee). Questionnaires will be considered source data, too.

At the beginning of the trial, a Study Master File will be established according to Sponsor or Latis SOPs, in order to maintain the trial documents as specified in the UNI EN ISO 14155 Guideline and as required by the applicable regulatory requirements. Latis will take measures to prevent accidental or premature destruction of these documents.

Clinical sites will permit trial-related monitoring, audits, and regulatory inspection providing direct access to source data / documents.

Essential documents of the clinical investigation, including the subject identification list, source data and case report forms will be retained for 10 years after the completion or discontinuation of the trial

at clinical sites. The sponsor will retain the trial master file for 10 years after the Marketing Authorisation for the study product has been discontinued in all countries.

9. Amendments to the CIP

Changes to the clinical investigation plan may only be made by means of a written amendment, which has to be approved and signed by the authorized representatives of the Sponsor, and by the Investigator.

Exhaustive justifications that motivate the amendment to the clinical investigation plan should clearly be addressed in the document.

All substantial Clinical Investigation Plan amendments must be submitted for approval to IEC and notified to the Regulatory Authority. In case of non-substantial amendment the IEC and the Regulatory Authority (when applicable) will be only notified of the amendment without the request to review and approve it.

The Investigator, the Sponsor and IEC, separately or together, should decide whether the subject's informed consent form needs to be changed.

10. Deviations from Clinical Investigation Plan

The Investigator is to conduct the study in accordance with the relevant, current clinical investigation plan and will only deviate when necessary to protect the safety, rights and welfare of the subjects. In the event that an isolated, unforeseen instance occurs resulting in a clinical investigation plan deviation, the Investigator is to document this deviation and notify the CRO or the Sponsor as soon as possible. In no instance should this increase the subject's risk or affect the validity of the study.

11. Device Accountability

The Investigator is responsible of ensuring accountability of the study product, including reconciliation of study product and maintenance of records.

Upon receipt of the study product, the Investigator (or designee) will check the contents and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained in the Investigator File.

The dispensing of the study product will be carefully recorded on the appropriate accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Study Monitor at each monitoring visit.

Study product accountability records will include:

- Confirmation of study product receipt at the clinical site.
- The inventory at the site of study product provided by the Sponsor.
- The tubes delivery to each subject.
- The tubes return from each subject.
- The return to the Sponsor or alternative disposition of unused study product.

The Investigator should maintain records that adequately document:

- That the subjects were provided with the quantities specified by the Clinical Investigation Plan/amendment(s), and
- That all study products provided by the Sponsor were fully reconciled.

Unused study product must not be discarded or used for any purpose other than the present study. Study product that has been dispensed to a subject must not be re-dispensed to a different subject.

The Study Monitor will periodically collect the study product accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the clinical site.

12. Statement of Compliance

The study will be conducted in compliance with the current version of the Declaration of Helsinki (Appendix 6), with the clinical investigation plan, the UNI EN ISO 14155, the Italian laws in force and the principles of the Good Clinical Practice.

The clinical investigation will start at clinical site only after obtaining the approval of the relevant Ethics Committee.

13. Informed Consent Process

The Investigator is responsible for and will obtain informed consent from each subject in the study, in accordance with the UNI EN ISO 14155, and the current version of the Declaration of Helsinki.

All subjects invited to participate in the study are entitled to make their voluntary decision based on all current available information provided to them by the Investigator/designee. In addition, they will be given a document in native language written in clear concise lay language for review and consideration. The document will previously have been approved by the relevant independent Ethics Committee (IEC) and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the study.

The subject must be made aware that he/she may refuse to join the study or may withdraw his/her consent at any time without prejudicing further medical care and that he/she is covered by the Sponsor's indemnity insurance in the event of a study related injury. Subjects must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by Regulatory Authority and IEC and that personal information will be collected and retained in a confidential database. Consent will always be given in writing after the subject has had adequate time to review the information and ask questions, if need be.

14. Adverse Events, Adverse Device Effects and Devices Deficiencies

14.1 Definitions

Adverse Event (AE)

Any undesirable experience occurring to a subject, whether or not it is considered causally related to the investigational medical device. An AE may be a clinical finding, a clinical laboratory abnormality or a symptomatic complaint which is considered by the Investigator to be outside the normal variation for that parameter.

Adverse Device Effect (ADE)

Any untoward and unintended response to a medical device. This includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of a user error.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, safety or performance (included malfunctions, use errors and inadequate labelling).

Serious Adverse Event (SAE)

A serious adverse event (SAE) could be any event that suggests a significant hazard, contraindication, side effect, or precaution. The seriousness of an AE relates to its clinical significance and its potential impact on health.

An AE will be considered as serious when:

Lead to death

Lead to serious deterioration in the health of the subject, that either results in:

a. a life-threatening illness or injury, or
b. a permanent impairment of a body structure or a body function, or
c. in-patient or prolonged hospitalization, or
d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function

Lead to foetal distress, foetal death or a congenital abnormality or birth defect.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

Incident

Any malfunction or deterioration in the characteristics and/or performance of a device,
as well as any lack of labelling or instructions for use which, directly or indirectly, may cause or have caused death or serious deterioration in the health of the patient or of a user or of other persons.

14.2 Adverse Event Intensity/Causality

The Investigator, based on his direct observation or on subjects' report, will record the event according to the current version of CTCAE:

Description	**Definition**
Grade 1 (Mild):	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 (Moderate):	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental daily life activities.
Grade 3 (**Severe):**	medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self -care daily life activities.
Grade 4 (Life-threatening consequences):	urgent intervention indicated.
Grade 5:	death related to AE

The relationship of any AE to the product will be classified by the Investigator as follows:

Description	**Definition**
Certain	The AE is clearly related to the study product
Probable	The AE is likely related to the study product
Possible	The AE may be related to the study product
Doubtful	The AE is unlikely related to the study product
None	The AE is clearly not related to the study product
Unknown	Causality is not assessable, for one reason or another, e.g. because of insufficient evidence, conflicting data or poor documentation

14.3 Adverse Event, Device Deficiency, Adverse Device Effect, reporting

The Investigator will record any AEs, Device Deficiency and ADEs occurring during the study. He/She will also co-operate with the Sponsor in connection with the reporting of any SAE/SADE, Serious Incident to the Competent Authority and to the Independent EC, if applicable.

All AEs regardless of severity occurring between recruitment and completion of the study by a subject must be recorded on the AE form provided with the e-CRF.

If there is a significant worsening of a medical condition that was present before starting the study, this should be considered as a new AE and a complete evaluation recorded.

Signs and symptoms considered as lack of efficacy and occurring during the study will not be recorded on the AEs Section of the e-CRF except on the condition that, in the Investigator's opinion, these signs and symptoms are caused by any reason different from lack of efficacy of the study product or meet the definition of serious AE.

In the event of a SADE/SAE, Serious Incident the Investigator has to:

- Complete the relevant CRF pages and a reporting form with all the available initial information,
- Immediately inform the Sponsor or the CRO by telephone,
- Fax the completed report form to the contact person at the Sponsor or the CRO as soon as possible.

SAE/SADE, Serious Incidents reporting contacts are on page 5 of this Clinical Investigation Plan.

The Investigator is responsible for ensuring the follow-up of any subject who experiences an SAE/SADE/ Serious Incident during the study. The investigator must re-examine the subject at regular intervals until the symptoms have completely disappeared or stabilized.

The Sponsor or its delegate will be responsible for reporting the SAE/SADE/Serious Incident to the appropriate Authorities and EC, according to the local regulations.

15. Vulnerable Population

This section is not applicable, since no subject belonging to any vulnerable population will be recruited for participating in this study.

16. Suspension or Premature Termination of the Clinical Investigation

Unless premature interruption occurs, the end of the study will be the last closure visit at clinical sites.

16.1 Study Discontinuation

Subjects may be discontinued at any time from the study for any of the following reasons:

- An AE occurs that, in the opinion of the Investigator, makes it unsafe for the subject to continue in the study
- Lack of compliance of the subject to the study treatment or assessments
- The subject needs to use a medication/treatment not allowed for a disease or for a flare of the dermatitis
- The subject is lost to follow-up
- The subject dies
- The subject withdraws consent
- The Investigator, for any reason, terminates the entire study, or terminates the study for that subject or the attending physician requests that the subject be withdrawn for any medical reason

- The Sponsor or the Regulatory Authority or the Ethics Committee, for any reason, terminates the entire study or terminates the study for this site or for a particular subject.

If a subject is discontinued from the study, the Investigator will, as far as possible, complete the end of study visit (Visit 4) e-CRF fields. The Investigator should try to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights.

16.2 Study Interruption

The Sponsor may consider study closure at the clinical site if the following occurs:

- serious and/or persistent non-compliance with the Clinical Investigation Plan
- inadequate collaboration of site personnel with CRO/Sponsor
- administrative reasons
- non-compliance with GCP, SOPs or regulatory requirements
- lack of confidentiality and/or non-compliance with the contract spread with the Sponsor.

17. Publication Policy

All information obtained as a result of the study will be regarded as confidential.

The results of the clinical study will be documented in an integrated clinical study report according to UNI EN ISO 14155.

The Sponsor and the Investigator(s) agree that no publications presenting or discussing data and/or results from this clinical study sponsored by Relife Srl will take place until the participating centers have completed the study, the data have been interpreted, and the final report has been issued.

As a rule, the Sponsor is free to use the data collected in the sponsored study for world-wide scientific product documentation, and for publication.

In general, the Sponsor has no objections if the Investigators publish the results of the study. However, the Investigators are requested to provide the Sponsor with a copy of the manuscript for review before submitting it to the publisher with a cover letter informing the Sponsor about the intention to publish the study results. When permission for presentation or for publication is granted, Investigators, prior to submission of a manuscript or abstract to the publisher, shall forward a copy of said manuscript or abstract to the Sponsor who shall have 90 days to request any reasonable amendment thereto, which shall be taken into due account and consideration by the Investigators.

The Sponsor is entitled to include as authors of the publication all Sponsor's personnel who contributed substantially to the theoretical or experimental work and also to take part in the decision

that establishes the order in which the authors' names will be given. Costs for publication must be regulated by written agreement between the parties.

If publication of the results of the study, either in part or in full, is prepared by the Sponsor, the Investigators will be provided with a copy of the manuscript before the submission to the publisher and asked to give approval of the document. The Investigators will be asked in writing if they accept to be included as author of the publication. Answers should be sent in writing to the Sponsor within a reasonable time limit (30 days). If no answer is received, it is assumed that the Investigators agree to the Sponsor's proposal.

18. Study Protocol Personal Data Protection Section

18.1 General Principles on Personal Data Compliance

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the patients shall remain protected in accordance with the applicable law on personal data protection such as the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medical device product 745/2017.

This section defines the appropriate technical and organisational measures that shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of patients' privacy rights.

18.2 Acknowledgment

The Sites, the Principal investigator, the CRO as well as their appointed staff and service providers acknowledge that:

(a) the performance of the study will imply processing of sensitive personal data;

(b) personal data processing is regulated by the applicable European (i.e. the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medical device product 745/2017) and local laws (i.e. the laws of the country where the study is conducted) as well as by the Sponsor's national legislation. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore the Sites, the Principal investigator, the CRO shall cooperate with the Sponsor to allow the fulfillment of such obligations;

(c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the Sites, the Principal investigator, the CRO.

18.3 Data Controllers and Data Processors

The Sponsor, the Sites, the Principal investigator and the CRO acknowledge that according to the applicable privacy laws, Sponsor and Sites will act as independent data controllers while CRO and the Principal investigator will act as data processors respectively of the Sponsor and of Sites. Before the beginning of the study, the Sites will instruct in writing Principal Investigator as its data processor[1]. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the Sites, the Principal investigator and the CRO will implement the relevant legal instruments (e.g. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalised; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalised).

18.4 Duties of the Parties Involved in the Performance of the Study

Collection and use of patients' personal data (i.e. subjects' data), will be carried out in full respect of the provisions of the information notices submitted to patients, as well as the privacy rights, the fundamental freedoms and the dignity of data subjects. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws.

The Sites, the Principal investigator, the Sponsor, the CRO as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study-, shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the study. In particular:

(i) DATA SAFETY. The Sites and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimise the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorised access to patient's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the study, the Sites and/or the Principal

[1] For clinical trials where the Principal Investigators are the owners of the Site, this provision may not apply. In such cases, the Principal Investigator might be considered as a Data Controller.

Investigator shall ensure that the actual measures they have implemented are fit-for-purpose and law-compliant, and in particular:

- in order to minimise the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every two months and feature at least 8 characters, with upper-case and lower-case recognition, containing "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her , such as name and year of birth (e.g. "johnbrown80") or easily predictable strings of characters (e.g. "qwerty", "12345", "admin", "user", etc.);
- adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorised to access them);
- high level security measures shall be implemented also on the files or databases which contain the "key" to match the patients' personal data (i.e. name, surname, etc.) with their respective "Patient IDs" (as defined at point (iv) below);
- Backup processes and other measures that ensure rapid restoration of business critical systems shall be implemented;
- Updated Antivirus and firewall programs shall be installed on the IT devices.

The Sites shall, regularly test and update the measures listed above.

The Sites shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.

The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralised database(s) used to process study's data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.

(iii) SECURITY OF THE CENTRALISED DATA BASE. The centralised database held by the Sponsor shall have the following safeguards in place:

- appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study;
- appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

(iv) PSEUDONYMIZATION. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudonymisation" process). The Principal investigator shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to a an alphanumerical code ["Patient ID"], whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the Sponsor, and /or the CRO. Sites/Principal Investigator shall securely store a separate list (e.g: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.

(v) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues.

All actions related to the implementation of the afore mentioned measures shall be provided by the Sponsor, the Sites and/or the CRO to the competent authorities (including data protection authorities) and Ethics Committees if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, The Sites, the Principal investigator, the CRO undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

18.5 Archiving of the Clinical Trial Master File and Code Pairing List

Unless other EU laws require archiving for a longer period, the Sponsor the Sites and the Principal Investigator shall archive the content of the clinical trial master file, including the relevant patients' personal data, for at least 25 years after the end of the clinical trial. However, medical records shall be archived in accordance with the national laws of the country where the study is performed. The

patient code pairing list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived care of the Principal Investigator.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall undertake the responsibilities set out in this protocol.

Once mandatory data retention time for the clinical trial master file has elapsed, the Centre/Principal Investigator shall seek the authorisation of the Sponsor to destroy the clinical trial master file.

18.6 Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Sites, sponsor, CRO, Principal Investigator etc.; data loss is when the data may still exist, but the Sites, sponsor, CRO, Principal Investigator etc. has lost control or access to it, or no longer has it in its possession; damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or man-made disaster, etc.), personal data become temporarily inaccessible to the Sites, sponsor, CRO, Principal Investigator etc.

Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g. an unauthorised access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g. cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data.

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the SME, the sponsor's Data Protection Officer, who may be contacted at DPO contact details: dpo@menarini.com, the Sites and the CRO responsible persons for data breach incidents management at dpo@latiscro.it and shall provide the following information:

(i) Anomalous Event / Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.);

(ii) Person or source that first reported the Anomalous Event/ Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event / Data Breach became aware of it;

(iv) Anomalous Event / Data Breach Date and Time (actual or presumed);

(v) Place (specify if actual or alleged) where the Anomalous Event / Data Breach occurred;

(vi) Anomalous Event / Data Breach Description;

(vii) Indicate the source of the Anomalous Event / Data Breach (e.g. I.P. source) - (if relevant);

(viii) Indicate the affected infrastructure / system / application / cloud/ software / hardware / database and their location;

(ix) List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant);

(x) Number of data subjects involved (if known);

(xi) Amount of allegedly breached data

(xii) Other relevant information

Once all the above information has been provided, the Sponsor and/or the Sites should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, Sponsor and Sites, each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of patients enrolled within the European Union, Sponsor and Sites autonomously or jointly-depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. Collect the necessary evidence and information;
2. Categorise the breach;
3. Determine the risk probability and level to the rights and freedom of the concerned patients;
4. Identify and put in place appropriate remedies to minimise the impact of the Data Breach
5. Determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

18.7 Information Notice on Personal Data Protection and Pseudonymisation

Prior to patients' enrolment in the study, the Principal Investigator and/or the Sites (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above.

Among other things, the ICF (or the separate form) shall inform patients about:

(i) the applicable data protection legislation

(ii) the kind of data that shall be collected during the study listing them in detail or by category;

(iii) the purpose of data processing (eg. vigilance, post market surveillance data) and the legal basis;

(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study (if the processing relies on consent as a legal basis);

(v) the pseudonymisation procedure and scope;

(vi) who can access patients' data and under what circumstances eg. Principal Investigator, Site, Sponsor, regulatory authorities, CRO;

(vii) the period of data retention/storage as defined in paragraph 8;

(viii) patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016.

(ix) Data Controllers / Data Processors and the relevant contact details

(x) Sponsor's Data Protection Officer contacts (DPO).

18.8 Transfer of Patients' Data Outside the European Union

The study performance does not entail transferring patients' personal data (coded data) outside the EU.

18.9 Exercise of patients' data privacy rights

Each study patient has the right to contact the Sponsor, the Sites, the Principal investigator, the CRO to exercise the rights afforded to the patient by the law, including those afforded under articles 15 to 22 of Regulation (EU) 2016/679, namely: knowing whether or not any data referring to his/her is being processed in the context of the study; access his/her data; verify the data's content, origin, exactness, location (including, where applicable, the non EU countries where the data might be); obtain a copy of

the data including their transmission to another entity indicated by the patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/her data for legitimate reasons. Each patient has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the Data Protection Officer any use of his/her personal data the patient regards as inappropriate.

Each study patient is free to withdraw at any time from the study. In such case, each study patient may ask the Sponsor, the Sites, the Principal investigator, the CRO to destroy/delete his/her personal data thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study.

If the Sites, the Principal investigator, the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by email at DPO contact details: dpo@menarini.com.

The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Sites, the Principal investigator, the CRO shall implement adequate organisational measures to reply to patients within the above mentioned deadline.

19. Bibliography

1. Smith SM, Nedorost ST. "Dermatitis" defined. Dermatitis. 2010 Sep-Oct;21(5):248-50.

2. Zug KA, McKay M. Eczematous dermatitis: a practical review. Am Fam Physician. 1996 Sep 15;54(4):1243-50, 1253-4. Review. Erratum in: Am Fam Physician 1997 Feb 1;55(2):448.

3. http://www.aafp.org/afp/1999/0915/p1191.html

4. http://www.dermnetnz.org/topics/causes-of-atopic-dermatitis/

5. http://www.skindermatologists.com/eczema.html

6. Lamb JH, Shelmire B, Cooper Z, Morgan RJ, Keaty C. Solar dermatitis. Arch Derm Syphilol. 1950 Jul;62(1):1-27.

7. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014; 71:116-132.

8. Werfel T. Topical use of pimecrolimus in atopic dermatitis: update on the safety and efficacy. J Dtsch Dermatol Ges. 2009;7:739-742.

9. Takahashi-Ando N, Jones MA, Fujisawa S, et al. Patient-reported outcomes after discontinuation of long-term topical corticosteroid treatment for atopic dermatitis: a targeted cross-sectional survey. Drug Healthc Patient Saf. 2015;7:57-62.

10. Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. Indian Dermatol Online J. 2014 Oct;5(4):416-25.

11. Kempers S, Boguniewicz M, Carter E, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. J Am Acad Dermatol 2004; 51: 515–25.

12. Chamlin SL, Kao J, Frieden IJ, Sheu MY, Fowler AJ, Fluhr JW, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. J Am Acad Dermatol 2002;47:198-208.

13. Ex 8 Rawlings AV, Canestrari DA, Dobkowski B. Moisturizer technology versus clinical performance. Dermatol Ther 2004;17(Suppl):49-56.

14. Breternitz M, Kowatzki D, Langenauer M, Elsner P, Fluhr JW. Placebo-controlled, double-blind, randomized, prospective study of a glycerol-based emollient on eczematous skin in atopic dermatitis: biophysical and clinical evaluation. Skin Pharmacol Physiol 2008; 21:39-45.

15. Peris K, Valeri P, Altobelli E, Fargnoli MC, Carrozzo AM, Chimenti S. Efficacy evaluation of an oil-in-water emulsion (Dermoflan) in atopic dermatitis. Acta Derm Venereol 2002; 82:465-6.

16. http://www.webmd.com/skin-problems-and-treatments/eczema/tc/atopic-dermatitis treatment-overview

17. Kim BE, Leung DYM. Significance of Skin Barrier Dysfunction in Atopic Dermatitis. Allergy Asthma Immunol Res. 2018 May;10(3):207-215.

18. Kao JS, Fluhr JW, Man MQ, Fowler AJ, Hachem JP, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. J Invest Dermatol 2003; 120: 456-464.

19. Moncrieff G, Cork M, Lawton S, Kokiet S, Daly C, Clark C. Use of emollients in dry-skin conditions: consensus statement. Clin Exp Dermatol. 2013;38:231–238.

20. Kraft JN, Lynde CW. Moisturizers: what they are and a practical approach to product selection. Skin Therapy Lett. 2005;10:1–8.

21. Del Rosso JQ. Moisturizers: Function, formulation and clinical applications. In: Draelos Z, Dover JS, Alam M, editors. Cosmeceuticals. 2nd ed. China: Saunders Elsevier; 2009. pp. 97–102.

22. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. Lancet. 2012 Jan 28; 379(9813):361-72.

23. Verdier-Sévrain S, Bonté F. Skin hydration: a review on its molecular mechanisms. J Cosmet Dermatol. 2007 Jun;6(2):75-82.

24. Liguori V, Guillemin C, Pesce GF, Mirimanoff RO, Bernier J. Double-blind, randomized clinical study comparing hyaluronic acid cream to placebo in patients treated with radiotherapy. Radiother Oncol 1997;42:155-61.

25. Rawlings AV, Canestrari DA, Dobkowski B. Moisturizer technology versus clinical performance. Dermatol Ther. 2004;17 Suppl 1:49-56.

26. Chren MM, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. J Cutan Med Surg. 2001;5:105-110.

Appendix 1

List of Abbreviations

ACD	Allergic Contact Dermatitis
AD	Atopic Dermatitis
ADE	Adverse Device Effect
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
CD	Contact Dermatitis
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index questionnaire
EASI	Eczema Area and Severity Index
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICD	Irritant Contact Dermatitis
ICH	International Conference on Harmonization
IFU	Instructions For Use
IGA	Investigator Global Assessment
IEC	Indipendent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PPAS	Per-Protocol Analysis Set
PT	Preferred Term
ml	Milliliters
N	Number
SADE	Serious Adverse Device Effect
SAF	Safety Analysis Set
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
TEWL	Trans Epidermal Water Loss
USADE	Unanticipated Serious Adverse Device Effect
UV	Ultraviolet
VAS	Visual Analogue Scale

Appendix 2

QUESTIONARIO SULLA QUALITA' DELLA VITA IN DERMATOLOGIA*

N° Centro: |_|_|_| Data: |_|_|_|
N° Paziente: |_|_|_| gg/mm/aa
Iniziali: |_|_|_| Diagnosi: _____

DLQI
Punteggio ☐

Lo scopo del questionario è di misurare quanto i suoi problemi alla pelle hanno influito sulla sua vita NEGLI ULTIMI 7 GIORNI. La preghiamo di fare una crocetta ☒ su una sola casella per ogni domanda.

1.	Negli ultimi 7 giorni, ha avuto **prurito, dolore,** o **sensazioni di bruciore** alla pelle?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	
2.	Negli ultimi 7 giorni, si è sentito/a **imbarazzato/a** o **a disagio** a causa dei suoi problemi alla pelle?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	
3.	Negli ultimi 7 giorni, i suoi problemi alla pelle le hanno creato fastidi per **fare la spesa,** occuparsi della **casa** (o del **giardino**)?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	Non riguarda il mio caso ☐
4.	Negli ultimi 7 giorni, i suoi problemi alla pelle hanno influenzato la scelta dei **vestiti** da indossare?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	Non riguarda il mio caso ☐
5.	Negli ultimi 7 giorni, i suoi problemi alla pelle hanno influito sulle sue **attività con gli altri,** o **di tempo libero**?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	Non riguarda il mio caso ☐
6.	Negli ultimi 7 giorni, i suoi problemi alla pelle le hanno reso difficile praticare **sport**?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	Non riguarda il mio caso ☐

7.	Negli ultimi 7 giorni, i suoi problemi alla pelle le hanno impedito completamente di **lavorare** o di **studiare**?	Si' No	☐ ☐	Non riguarda il mio caso ☐
	Se ha risposto "no": negli ultimi 7 giorni, i suoi problemi alla pelle le hanno creato difficoltà nel **lavoro** o nello **studio**?	Molto Un po' Per niente	☐ ☐ ☐	
8.	Negli ultimi 7 giorni, i suoi problemi alla pelle le hanno creato difficoltà con il/la suo/a **compagno/a**, con gli **amici intimi** o con i **parenti**?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	Non riguarda il mio caso ☐
9.	Negli ultimi 7 giorni, i suoi problemi alla pelle le hanno creato **difficoltà di carattere sessuale**?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	Non riguarda il mio caso ☐
10.	Negli ultimi 7 giorni, la **cura** per la pelle le ha dato problemi, per esempio portandole via del tempo o sporcando in casa?	Moltissimo Molto Un po' Per niente	☐ ☐ ☐ ☐	Non riguarda il mio caso ☐

La preghiamo di controllare di aver risposto ad OGNI domanda. Grazie.

* Finlay A.Y., Khan G.K. Dermatology Life Quality Index (DLQI) - A simple practical measure for routine clinical use. Clinical and Experimental Derm 1994; 19:210-16.

Appendix 3

Questionario per la valutazione, da parte del Paziente, della prestazione

Codice Soggetto: |___|___|

Data di compilazione del questionario: |___|___| |___|___| |___|___|___|___|

giorno mese anno

Come valuta complessivamente la Sua dermatite rispetto a prima del trattamento con il prodotto DermoRelizema ecofoam?

☐ Molto migliorata/o

☐ Migliorata/o

☐ Solo leggermente migliorata/o

☐ Nessuna variazione rispetto a prima

☐ Leggermente peggiorata/o

☐ Peggiorata/o

☐ Molto peggiorata/o

Appendix 4

Questionario per la valutazione, da parte dello Sperimentatore, della prestazione

Codice Soggetto: |___|___|

Data di compilazione del questionario: |___|___| |___|___| |___|___|___|___|

giorno mese anno

Come valuta complessivamente la dermatite del Suo/della Sua paziente, rispetto a prima del trattamento con DermoRelizema ecofoam?

☐ Molto migliorata

☐ Migliorata

☐ Solo leggermente migliorata

☐ Nessuna variazione rispetto a prima

☐ Leggermente peggiorata

☐ Peggiorata

☐ Molto peggiorata

Appendix 5

Questionario per la valutazione della accettabilità da parte del paziente

Codice Soggetto: |___|___|

Data del questionario: |___|___| |___|___| |___|___|___|___|

giorno mese anno

Relativamente alla sensazione di gradevolezza sulla pelle del prodotto DermoRelizema ecofoam, Le chiediamo di esprimere il suo grado di soddisfazione

☐ Molto soddisfatto

☐ Soddisfatto

☐ Né soddisfatto né insoddisfatto

☐ Non soddisfatto

☐ Decisamente non soddisfatto

Relativamente alla facilità di utilizzo (spalmabilità) del prodotto DermoRelizema ecofoam, Le chiediamo di esprimere il suo grado di soddisfazione

☐ Molto soddisfatto

☐ Soddisfatto

☐ Né soddisfatto né insoddisfatto

☐ Non soddisfatto

☐ Decisamente non soddisfatto

Appendix 6

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include

information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant

aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the

completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.