Clinical Investigation Report

A MULTICENTER, OPEN LABEL, UNCONTROLLED STUDY FOR THE EVALUATION OF EFFICACY AND SAFETY BY CLINICAL PARAMETERS OF RELIZEMA ECOFOAM IN ADULT ATOPIC AND CONTACT DERMATITIS

Investigational device:	RELIZEMA ECOFOAM
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Sponsor's representative:	Silvia Innocenti, MD - Head of Scientific Affairs
CIP identification:	Version no. 2.0 – 26th March 2021
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The clinical investigation was performed in accordance with ISO 14155:2020, MDR, the ethical principles of the current version of the Declaration of Helsinki and GCP and any other applicable guidelines and regulations.

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1. Summary

Title of clinical investigation

A MULTICENTER, OPEN LABEL, UNCONTROLLED STUDY FOR THE EVALUATION OF EFFICACY AND SAFETY BY CLINICAL PARAMETERS OF RELIZEMA ECOFOAM IN ADULT ATOPIC AND CONTACT DERMATITIS

Introduction

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. Dermatitis is a condition that can interfere with social function, sleep and employment. Its persistence and accompanying pruritus may be stressful and frustrating for subjects.

The most common types of dermatitis are contact dermatitis (CD) and atopic dermatitis (AD), also referred as atopic eczema and they both were included in this clinical investigation.

Relizema 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 Relizema 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.

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

Purpose of the clinical investigation

In this clinical investigation Relizema ecofoam was used to treat and alleviate dermatitis severity and symptoms as perceived by the subjects, in compliance with its Instructions for Use (IFU). Different typologies of skin conditions were 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.

Relizema ecofoam 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 Relizema ecofoam in the post-market phase, this post-market clinical follow-

up investigation was designed and conducted in adult males and females affected by mild to moderate dermatoses, like AD, ICD or ACD.

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

The clinical investigation was regularly submitted to the competent Ethics Committees and notified to the Italian Ministry of Health, as for requirements in post market clinical follow-up studies.

Description of the clinical investigation population

A total of 40 subjects were planned for the study but only 13 were enrolled.

Males and females with age ≥ 18 years could be enrolled, having 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).

Written informed consent had to be released by the subject before any study activity start or any data collection for the study. Dermatitis could affect one or more body areas (face, legs, arms, etc.).

The following subjects were excluded from the study: subjects with severe dermatitis, pregnant and breastfeeding women, subjects with other concomitant skin disorders including skin infections, subjects with currently or previously diagnosed or treated (chemotherapy and/or radiotherapy) cancers in the previous 5 years, subjects with history of previous skin cancer (history of non-metastatic squamous or basal cell carcinoma of the skin was allowed), subjects with active infections or use of antibiotics in the past 7 days, diabetic subjects, subjects with history of congenital or acquired immunodepression, with immunologic or infectious disease (e.g. hepatitis, tuberculosis, HIV or AIDS, any typology of lupus, rheumatoid arthritis). The following previous or concomitant therapies were not allowed for eligibility: any topic medication for dermatitis in the past 14 days, any topic product for dermatitis in the 2 days before study treatment start, any corticosteroids, immunosuppressant drugs or immunotherapy within the past 30 days, any oral antihistamines and antidepressants in the past 30 days, any systemic treatment or procedure that could influence dermatitis activity within the past 30 days.

Finally, the following subjects were considered not eligible: subjects with any other clinically significant or unstable concurrent disease or skin condition or general condition that, in the Investigator's opinion, could interfere with the study evaluations; subjects with allergy, sensitivity or intolerance to the ingredients of the investigational device formulations and subjects participating or having participated in other interventional clinical study in the past 3 months.

Sun exposure or tanning booths or UV sources throughout the course of the study was forbidden.

Clinical investigation method used

This was a multicenter (2 clinical sites involved in Italy), open label, single arm, uncontrolled, post-market clinical follow-up study.

All the subjects were allocated to the following treatment group:

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

The subjects started the treatment on the first day of study and continued until 42 days after the first application. The treatment could have been prolonged or shortened of maximum 2 days, in the case intermediate and/or final visits were delayed.

Four visits were planned: initial visit to evaluate the subject eligibility and to train the subject to the correct study product application, then a follow-up visit after 2 weeks (± 1 day), a second follow-up visit after 4 weeks (± 1 day) and a final visit after 6 weeks (± 2 days) of treatment.

Performance evaluations included:

- the disease severity, clinically measured through the vIGA-AD™ (validated Investigator's Global Assessment scale for Atopic Dermatitis). vIGA-AD™ is a five-point scale (0 = clear, 1 = almost clear, 2 = mild, 3= moderate, 4 = severe).
- The extent (area) and severity of eczema, through the EASI score, that considers 4 body regions: head and neck, trunk (including genital area), upper limbs, lower limbs (including buttocks). The scale takes in consideration the percentage of skin affected by eczema in each region, the severity of the eczema in each region, and signs like: redness (erythema, inflammation), thickness (induration, papulation, swelling—acute eczema); scratching (excoriation); lichenification (lined skin, prurigo nodules—chronic eczema).
- The Quality of Life of the subject affected by dermatitis, through the DLQI (Dermatology Life Quality Index) questionnaire. It is a questionnaire with 10 questions, covering topics like 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 subject's life over the previous week.
- VAS for pain, burning and itching.

- Treatment compliance measured through the daily diary where subjects recorded the product applications, every day.
- Subjects' and Investigator's global evaluation of the performance of Relizema ecofoam which takes into account the pleasant or unpleasant feeling with the product and the ease of use, by means of the 7-item scale (1 = very much improved, 2 = improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = worse, 7 = very much worse).
- Subject Overall Acceptability with the study treatment by means of a 5-item scale (1 = very much satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, 5= very much dissatisfied).

Safety evaluations included:

- Number and type of adverse events (AEs) occurring during the study (seriousness, severity, and relation to study treatment).
- Local tolerability at the site of administration.

Results of the clinical investigation

No. 13 subjects signed the informed consent forms, attended the first visit and started the treatment. Seven subjects withdrew from the study between V1 and V4.

In detail:

- Site 01 - subject ID 003 was lost to follow-up after Visit 1 (no data was available after V1 and for that reason the subject was not included in the safety population).
- Site 01 - subjects ID 002 and 008 were lost to follow-up after Visit 2 and Visit 3 respectively.

Site 01 - subjects ID 001, 004, 006, 009 withdrew because of the need to use a not allowed medication to treat dermatitis. The Investigator, in fact, decided to start a pharmacological treatment with topical corticosteroids. In order to start this treatment (not allowed according to study protocol), the subjects' participation in the study was prematurely interrupted. Four subjects were males (33.3%) and eight females (66.7%); mean age of the study population was 49.33 years.

Ten subjects (83.3%) were affected by atopic dermatitis and two subjects (16.7%) by irritant contact dermatitis; body areas mostly affected by dermatitis were arms and legs. Ten subjects (83.3%) had been suffering from the disease for a few years while 2 subjects (16.7%) had been suffering from dermatitis for a long time.

Only 3 subjects out of 12 (25%) had a positive medical history at baseline and one subject only underwent a surgery in the past (hip arthroplasty). No abnormality, except than for skin, was evidenced at physical examination.

Very few concomitant therapies were registered at baseline for two subjects and these therapies did not change during the study.

Primary performance endpoint

The primary performance endpoint was the proportion of responders (decrease in IGA ≥ 1) assessed after 28 days of treatment (Visit 3), compared to baseline (Visit 1).
At baseline 9 subjects (75.0%) had mild dermatitis and 3 subjects (25.0%) had moderate dermatitis; after 28 days of treatment 3 subjects (42.9%) had almost clear dermatitis, 3 subjects (42.9%) had mild dermatitis and only 1 subject (14.3%) had moderate dermatitis.
The proportion of responders was as follows: 3 subjects (42.9%) were considered responder while 4 (57.1%) were considered non-responder.

Secondary performance endpoints

Proportion of responders at IGA score from baseline (V1) to V2 and V4.
Proportion of responders (decrease in IGA ≥ 1) at Visit 2 and Visit 4, compared to baseline (Visit 1) was respectively 41.7% and 33.3% at the two visits.

EASI score change from baseline (V1) to V2, V3 and V4.
Baseline mean of EASI score was 4.05 (SD=3.02).
After 14 days of treatment (Visit 2) the mean of EASI score was 4.36 (SD=4.83), after 28 days of treatment (Visit 3) the mean score was 2.21 (SD=2.34) and after 42 days of treatment (Visit 4) was 1.83 (SD=1.20).

DLQI score change from baseline (V1) to V2, V3 and V4.
At Visit 1 the mean of DLQI score was 5.08 (SD=3.58).
After 14 days of treatment (Visit 2) the mean of DLQI score was 4.33, after 28 days of treatment (Visit 3) the mean score decreased to 2.57 (SD=3.05) and after 42 days of treatment (Visit 4) was 3.50 (SD=2.26).

Change in symptoms like pain, burning and itching were reported by the subject by VAS from baseline (V1) to V2, V3 and V4.
<u>VAS for pain rating</u>
At Visit 1 the mean of VAS for pain rating was 13.42 mm (SD=18.59).

After 14 days of treatment (Visit 2) the mean of VAS rating was 15.33 mm (SD=27.90), after 28 days of treatment (Visit 3) it was 8.71 mm (SD=18.25) and after 42 days of treatment (Visit 4) was 20.83 mm (SD=31.45).

VAS for burning rating

At Visit 1 the mean of VAS for burning rating was 36.83 mm (SD=36.80).

After 14 days of treatment (Visit 2) the mean of VAS rating was 35.00 mm (SD=37.67), after 28 days of treatment (Visit 3) it was 10.57 mm (SD=18.12) and after 42 days of treatment (Visit 4) was 27.17 mm (SD=30.72).

VAS for itching rating

At Visit 1 the mean of VAS for itching rating was 71.50 mm (SD=26.89).

After 14 days of treatment (Visit 2) the mean of VAS rating was 58.58 mm (SD=40.27), after 28 days of treatment (Visit 3) it was 37.43 mm (SD=32.91) and after 42 days of treatment (Visit 4) was 52.17 mm (SD=27.06).

Subject's adherence to treatment

Treatment compliance was generally very high at each time point: the mean of compliance between Visit 1 and Visit 2 was 91.38% (SD=17.10), the mean of compliance between Visit 2 and Visit 3 was 97.14% (SD=6.57), and the mean of compliance between Visit 3 and Visit 4 was 90.67% (SD=15.52).

Subject's and Investigator's global evaluation on performance of the study product

At last Visit, 3 subjects (30.0%) evaluated "Improved" or "Minimally improved" the dermatitis, only 1 subject (10.0%) noticed no changes in its dermatitis status and 6 subjects evaluated "Minimally worse", "Worse" or "Very much worse" the dermatitis.

Similarly, the Investigator evaluated the dermatitis "Improved" or "Minimally improved" in 4 subjects (40.0%), without change in 1 subject (10.0%) and "Minimally worse", "Worse" or "Very much worse" in 5 subjects (50.0%).

Subject's evaluation of overall acceptability with treatment

Six subjects (60.0%) considered "Satisfied" with the acceptability of the product, 1 subject (10.0%) "Neither satisfied nor dissatisfied" and 3 subjects (30.0%) "Dissatisfied".

Safety endpoints

Overall, no.1 adverse event was registered during the study, characterized by mild severity (Subj. ID 012, site 02 – Covid 19 infection). The AE was assessed as not related to the study treatment.

No other AE nor SAE occurred during the study.

Conclusion

Safety data was reassuring, and a small clinical performance seems to be observable at 1 month of treatment, however no clear and robust conclusion on the performance and safety of Relizema ecofoam can be drawn from this clinical investigation, due to the low number of enrolled subjects.

Clinical investigation initiation date: 15-Nov-2021 (first subject in).

Clinical investigation completion date: 31-Dec-2022 (last subject out).

2. Introduction

Relizema ecofoam is a topical compact mousse indicated for treatment of the signs and symptoms associated with atopic and contact dermatitis and erythema. The mechanism of action of Relizema 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.

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

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

In this clinical investigation Relizema ecofoam was used to treat and alleviate dermatitis, including atopic and contact dermatitis (irritant or allergic), symptoms as perceived by the subjects in the full respect of compliance with its Instructions for Use (IFU) rev 02/2020.

Different typologies of skin conditions were 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.

2.1 Rationale

Dermatitis is a common 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 and best characterized type of eczema, atopic dermatitis (AD), appears to be increasing in incidence [1].

AD pathogenesis is not completely known, even though the disease seems to be the result of genetic susceptibility, immune dysfunction and epidermal barrier dysfunction [2]: 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 [3,4]. 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.

Systemic and topical treatments are available for atopic and contact dermatitis.
Among systemic treatments, most common are corticosteroids, immunosuppressant (Tacrolimus or Pimecrolimus) to reduce the inflammation, antihistamines and antidepressant to reduce pruritus, antibiotics to treat secondary infections. Systemic treatments should be reserved to severe and treatment-resistant forms of dermatitis as they are not free from major side effects.
Three main lines of topical treatment have been recognized for the management of these dermatitis: topical steroids, topical immunosuppressant and topical moisturizers.

Topical steroids (corticosteroids, glucocorticosteroids and cortisones, i.e. hydrocortisone) are effective anti-inflammatory preparations. Short courses of topical steroids (fewer than four weeks) are usually safe and cause no problems. Problems may develop when topical steroids are used for long periods, or if short courses of stronger steroids are repeated often. The main concern is if strong steroids are used on a long-term basis.
Side effects from topical steroids can either be local or systemic. Local side effects affect only the damaged skin area; the most serious is the allergy to the contents of the treatment, such as any preservative used. This may irritate the skin being treated and make the inflammation worse. Other minor adverse consequences are a stinging or burning feeling at the first application.
Skin colour may change, and with long-term use of topical steroid the skin may develop permanent stretch marks (striae), bruising, discolouration, or thin spidery blood vessels (telangiectasias), and hair may grow more on the area of skin being treated. Furthermore, topical steroids may trigger or worsen other skin disorders such as acne, rosacea and perioral dermatitis [5] and after their discontinuation the exacerbation of symptoms is not an unusual event [6].
Systemic side effects of topically used steroids affects the whole body. Some topical steroid gets through the skin and into the bloodstream. The amount is usually small and causes no problem unless strong topical steroids are used regularly on large areas of the skin.
For this reason, steroids are prescribed only when the benefit overcomes the risk and possibly for short periods of time [7, 8]. Despite this, today steroidal therapy is still considered one of the most effective pharmacological treatments for dermatitis [1], as confirmed by several clinical trials.

Topical immunosuppressants, mainly represented by two calcineurin inhibitors, Tacrolimus and Pimecrolimus, have a significant efficacy [9] but are also associated with high incidence of transient skin reactions that make them not well accepted by the patient.

To date, the main adverse event reported in clinical trials with topical Tacrolimus is transient burning, irritation and erythema at the site of application [10].

In a long-term safety and efficacy study involving 255 children, subjects applied 0.1% Tacrolimus ointment twice daily for an average of 279 days during a 12-month period. Transient skin burning (25.9% of children), pruritus (23.1%), and skin infection (11.4%) were the most common adverse events associated with the treatment sites [11].

Regarding Pimecrolimus, most patients tolerate the cream well. Initial research indicates that it can be used on large areas of the body and for long periods of time without adverse effects, due to low level of absorption. However, there is no published data reporting its use for more than one year. It is known that the most common side effect that can be experienced around the site of application is a feeling of warmth or a sensation of burning [10,12]. This is usually mild to moderate in severity and goes away within a few days after starting treatment. Also, there is a slightly increased susceptibility to skin infections such as folliculitis, impetigo, herpes simplex and molluscum contagiosum.

The risk for systemic side effects and skin atrophy, problems commonly associated with the use of topical corticosteroids, has not been found with Pimecrolimus use [12]. However, as this is a new drug, the full safety profile is not fully known, and the main concerns relate to its effect on the immune system.

Moisturizers (emollients) increase hydration of the skin and help in maintaining the skin barrier function and reducing skin susceptibility to irritants [13]. A number of clinical trials have shown that they lessen symptoms and signs of dermatitis, including pruritus, erythema and fissuring [5,6]. Most of the time, rash and itching are successfully treated within three weeks [14]. 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 improve disease severity, increase the time of relapse, reduce the time of flares [15, 16, 17] and lastly reduce the need for pharmacologic steroids intervention to treat disease flare-ups [13].

Emollients used for eczema tend to be bland and non-perfumed. In general, they are recognized to be safe products, even for long-term treatments. However, some creams contain preservatives, fragrances and other additives. Occasionally, some people become allergic (sensitized) to an ingredient. Moreover, thick emollient ointments sometimes block the hair

follicles in the skin. This may cause a mild inflammation or infection of the affected hair follicles (folliculitis).

Among moisturizers, humectants are substances that attract water when applied to the skin and improve hydration of the stratum corneum with a physical mode of action. Glycerin, together with hyaluronic acid (HA), is the most popular of all humectants used in personal care products. Moreover, today, it is recognized that products enriched in antioxidant such as furfuryl derivatives can represent a valid aid in the treatment of atopic dermatitis and other skin disorders [13].

HA is a well-known component of the extracellular matrix of most connective tissue. It is especially abundant in the skin, where it has a protective, structure-stabilizing and shock-absorbing role. Evidences are available supporting HA as treatment of AD [18].

On the other hand, studies conducted on glycerol-containing creams [19], showed the significant hydration and barrier-improving effect of such products when compared to glycerol-free creams.

All these ingredients are contained in Relizema ecofoam, the device under investigation.

The device was developed for the treatment of the signs and symptoms of all types of dermatitis and erythema. Its CE mark was supported by literature research, therefore, in order to allow the Manufacturer to review and confirm the clinical performance and safety of the medical device Relizema ecofoam (DLP012) in the post-market phase, the present post-marketing clinical follow-up study was designed and conducted in adult males and females affected by mild-to-moderate atopic and contact (irritant or allergic) dermatitis.

The clinical investigation was regularly submitted to the competent Ethics Committees and notified to the Italian Ministry of Health, as for requirements in post market clinical follow-up studies.

The study was conducted in the full respect of the Helsinki Declaration, of the ISO 14155 and GDPR (General Data Protection Regulation 679/2016) prescriptions.

3. Investigational device and methods

3.1 Investigational device description

3.1.1 Description of the investigational device

The product under investigation was Relizema ecofoam. It is a class IIa, CE marked medical device for topical use. The primary package was a 70 ml labelled canister with pump.

Manufacturer: Relife Srl, Via dei Sette Santi 3 - 50131 Firenze (FI) - Italy

Device Name:	DLP012
Trade Name:	Relizema ecofoam
Formulation:	ecofoam
Route of administration:	topical application on breached/compromised skin

Table 1: Relizema ecofoam ingredients and their functions

INGREDIENT	INGREDIENT FUNTION
aqua	solvent
peg-40 hydrogenated castor oil	emulsifying/surfactant
glycerin	humectant/solvent
pullulan	film forming
capryloyl/caproyl methyl glucamide	emulsifying/skin conditioning/surfactant
ethylhexylglycerin	skin conditioning
lauroyl/myristoyl methyl glucamide	emollient/skin conditioning/surfactant/viscosity controlling
tocopheryl acetate	antioxidant/skin conditioning
sodium cocoyl glycinate	cleansing/skin conditioning
furfuryl palmitate	antioxidant
hexamidine diisethionate	preservative
sodium hyaluronate	humectant/skin conditioning
citric acid	buffering

3.1.2 Intended use of the investigational device

Relizema ecofoam is indicated for the treatment of the signs and symptoms associated with all types of dermatitis (including atopic dermatitis and contact dermatitis) 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.

3.1.3 Previous intended use or indication for use, if relevant

No previous intended use nor indication for use.

3.1.4 Changes to the investigational device during the clinical investigation or any change from the IB

Being the present study a post-market clinical follow-up study, no IB was issued.

3.2 Clinical investigation plan (CIP)

3.2.1 Clinical investigation objectives

The primary objective of this clinical investigation was to evaluate and confirm the performance of the Relizema ecofoam in the improvement of the dermatitis severity, assessed through a

clinical parameter, the Investigator's Global Assessment (vIGA-AD™, subsequently named in this report as "IGA") at baseline and after 28 days of treatment.

The secondary objectives of this clinical investigation were:

- to evaluate the performance of the Relizema 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 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 Relizema ecofoam;
- to evaluate the subject's overall acceptability of the treatment.

Safety and local tolerability of the study treatment were assessed by visiting and questioning the subject at visits.

3.2.1.1 Clinical investigation tools description

vIGA-AD™ (validated Investigator's Global Assessment scale for Atopic Dermatitis)

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

0 = clear
1 = almost clear
2 = mild
3= moderate
4 = severe

The IGA was filled in by the Investigator at each visit.

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 were considered: head and neck, trunk (including genital area), upper limbs, lower limbs (including buttocks). The percentage of skin affected by eczema in each region

was 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) was 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 was as follows:

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 were 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 was filled in by the Investigator at each visit.

DLQI (Dermatology Life Quality Index)

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 subject's life over the previous week.

Each question was 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 was compiled by the subject at each visit.

Subject and Investigator Global Evaluation of Performance

Subjects' and Investigator's global evaluation of the performance of Relizema ecofoam was 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).

Subject Overall Acceptability

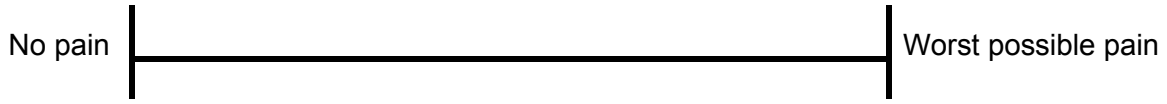
Subjects' evaluation of overall acceptability with the study treatment, which took into account the pleasant or unpleasant feeling with the product and the ease of use, was performed by means of a 5-item scale, where 1 = very much satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 =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

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

VAS for itching, burning and pain

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

Example:



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

A VAS scale for each of the 3 symptoms was completed by the subject at each visit.

3.2.2 Clinical investigation design

This was a multicenter, open label, uncontrolled, post-market clinical follow-up study.

All the subjects were allocated to the following treatment group:

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

The subject started the treatment on the first day of study and continued 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 were delayed.

Each subject for whom written consent was obtained was identified during the study by a "Subject Code", automatically generated and assigned by the electronic CRF (e-CRF).

All screened subjects received the Code regardless of whether they received the treatment or not. If a subject discontinued from the study at any time, the Code was not re-used.

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

3.2.3 Ethical considerations

The study was conducted in compliance with the current version of the Declaration of Helsinki, with the clinical investigation plan, the ISO 14155 current version, the MDR, the GDPR, the Italian laws in force and the principles of the Good Clinical Practice.

The clinical investigation started at clinical sites only after obtaining the approval of the relevant Ethics Committees.

To date a large variety of products for the treatment of eczematous dermatoses are available. Relizema 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 Relizema ecofoam was used in adult subjects with mild to moderate dermatitis, of any origin, and erythema, according to its authorized indications.

Relizema ecofoam was recommended twice daily for 42 days (±2). The product's components are known to be safe and well tolerated, therefore no risk was envisioned associated to Relizema ecofoam use.
The only precaution for users was to avoid contact of the product with eyes and mucous membranes (rinse immediately with plenty of water, in such an eventuality).
Within the clinical investigation the subject was provided with instructions on the personal hygiene to follow, in order to further improve skin care and safety.
Finally, no placebo group was used and no tests or invasive examinations were foreseen that could increase the risk for participants.

3.2.4 Data quality assurance

During each subject's study visit, the study Investigator or designee collected and reported study data in the relevant subject's chart, documenting all significant observations.
Electronic CRFs (eCRFs) were used to record subject's study data. The Investigator ensured that the eCRFs were properly and completely filled in. The Investigator reviewed all eCRFs and signed and dated them for each subject, verifying that the information was complete, accurate and correct.
Any data correction was entered, and registered in the audit trail system of the eCRF: date, time and the person making the correction were recorded. Previous data and new data, after correction, and the reason for correction, were recorded too by the e-system. Only the Principal Investigator or personnel authorized by the Principal Investigator entered corrections on the original eCRFs.
The access to the eCRF was controlled by user-specific account and password combinations. Queries were generated through the eCRF by the CRO Data Management staff. The Investigator was responsible for the review and approval of all queries.

The study was monitored by the CRO Latis S.r.l.. The CRA assessed the adequacy of the study site and the staff involved and monitored the site on a regular basis throughout the study period to ensure the proper conduct of the clinical study.
The CRO implemented and maintained quality control and quality assurance procedures with written standard operating procedures to ensure that the study was conducted and data was generated, documented and reported in compliance with the protocol, ISO14155, GCP and applicable regulatory requirements.

3.2.5 Subject population for the clinical investigation

No. 40 subjects were planned to be enrolled in this clinical investigation, selected on the basis of the following inclusion/exclusion 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 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.

3.2.6 Treatment and treatment allocation schedule

All the subjects were allocated to the same active treatment, in open label design.
The investigational device was used according to its Instructions for Use.

The study device was provided for the study by the Sponsor of this clinical investigation and shipped to the clinical sites only after the completion of all Ethics and Administrative procedures. The product was labeled as experimental treatment in accordance with applicable Good Manufacturing Practice (GMP, Annex 13).

Each subject received a total of no. 3 canisters and he/she used a variable amount of cream depending on the extent of the area/s affected by dermatitis to be treated. Occasionally, if the subject needed further treatment (beyond the 3 canisters received), the Investigator was allowed to provide further amount of treatment. Any additional canister provided to the subject was recorded in the eCRF.
Subjects were instructed to use Relizema 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 subject should be instructed to press the valve two or three times to activate the pump mechanism. After this, the subject had to press the valve gently to obtain one or more doses of the product to apply on the selected area and massage.
In addition to this, throughout the treatment phase, subjects were required to avoid soap and use only the product DermoRelizema detergente liporestitutivo, a 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).

3.2.7 Concomitant medications/treatments

Any medications that were considered necessary for the subjects' well-being and did not interfere with the study product could be given at the Investigator's discretion.

According to exclusion criteria, the following prior and concomitant medications were 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 was recommended not to use any other product for the personal hygiene than the one provided by the Investigator.
Any concomitant medication/treatment was recorded in the appropriate section of the eCRF.

3.2.8 Duration of follow-up

Before any study specific evaluation and data collection carried out, subjects received all the information about the study by the Investigator and signed an informed consent form.
Between verbal information and written informed consent the subjects were given sufficient time. All subjects were given the opportunity to ask questions and were informed of their right to withdraw from the investigation without prejudice.
Subjects were evaluated with regards to the inclusion and exclusion criteria that allowed their participation into the study.

Visit 1: screening, baseline and treatment start (Day 1)
The following activities were performed at Visit 1, after informed consent release:

- 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 itching, burning, pain
- 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.

On the diary each subject was asked to record, at the end of each day, the study product applications performed.

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

The following activities were performed 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
- 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 was anticipated of one day (Day 13) or postponed of 1 day (Day 15), any attempt was done to fix the following Visit 3 so that 28 days of study and treatment were respected (i.e. if Visit 2 was on Day 13, then Visit 3 was scheduled 15 days after Visit 2).

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

The following activities were 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
- 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 was done to fix the Visit 4 so that the study and treatment days were as minimum 40 and as maximum 42.

3.2.9 Statistical design, analysis and justifications

The sample size estimation, was based on a conservative hypothesis of spontaneous improvement of the pathology in the 50% of cases. This hypothesis derived from the review of the literature data, which shows a percentage of responders to IGA, among subjects treated with only the vehicle (placebo), between 14.6% [21] and 49.3% [22].

Regarding the efficacy of the product, the Sponsor conducted and concluded a clinical study [20] similar to the one proposed, with a similar product (Relizema cream), which showed an improvement in IGA in the 87.5% of treated subjects (responders).

For this study, it was hypothesized to have at least 75% of the subject responders at Day 28. This percentage was compared to a referent percentage of 50% (taken as the best response possible using vehicle only according to the literature data previously cited). Under this hypothesis, an exact binomial test with a nominal 5% two-sided significance level had 80% power to detect the difference between the two hypothesized percentages when the sample size was 30 subjects. Assuming a possible 25% dropout rate, 40 subjects were to be enrolled.

<u>General Issues</u>

The following populations were defined for this investigation:

- Safety analysis set (SAF): all subjects enrolled who sign informed consent and receive at least one administration of the investigational device.
- Full analysis set (FAS): all subjects 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 subjects 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 was performed in the Safety population (SAF). Analysis of performance endpoints was performed on the FAS population. The analysis of primary endpoint was repeated in the PPAS.

Data and measures collected at Visit 1, before any study treatment administration, were considered as baseline values.
Descriptive statistical analysis of all relevant variables was performed. Continuous variables were summarized by the number of subjects (N), mean, standard deviation, median, minimum, maximum. Categorical variables were summarized by the number (N) and the proportion of subjects (%). Where appropriate, 95% confidence intervals for the target variables were estimated.
No interim analysis was foreseen.
No changes to the planned analysis of the study data were introduced.
The statistical analysis was carried out using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA), as planned.

Methods for Withdrawals and Missing Data

Missing data was not replaced in any statistical analysis.

Multicenter Studies Considerations

No covariates or interaction analysis was planned nor performed.

Multiple Comparisons and Multiplicity

This was single-arm clinical investigation and no adjustment for multiplicity was used.

Protocol Deviations

Protocol deviations were detected during monitoring activities and during data management activities. They were fully reviewed and discussed with the Sponsor before the database lock during Data Review Meeting (on the 8th of May 2023).

Demographics and Baseline Characteristics

Demographic (gender, age) and baseline characteristics (number and distribution of warts and target warts) were summarized using mean, median, standard deviation, minimum and maximum for continuous variables and frequencies and percentages for categorical variables.

Efficacy Analysis

Primary Efficacy Endpoints

The primary endpoint was the proportion of responders, i.e. the number of subjects with a decrease of at least one point in IGA, between baseline and day 28. A responder rate of at least 75% was expected. According to study protocol the number (N) and the percentage of responders (%) was to be described and the percentage of treatment successes was to be compared to a referent percentage (50%, taken as the best response possible using vehicle only) using the exact binomial test. However, since when the enrolment period expired only 13 subjects were enrolled, the primary endpoint outcome was described by descriptive statistics only and no inferential analysis was made.

Secondary Efficacy Endpoints

Secondary endpoints were:

1. The number (N) and percentage (%) of responders (decrease in IGA ≥ 1), to be analyzed also between baseline and both days 14 (Visit 2) and 42 (Visit 4).
2. Changes in EASI score after 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4) of treatment, compared to baseline.
3. Changes in DLQI questionnaire after 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4) of treatment, compared to baseline.
4. Changes in VAS for itching, burning and pain after 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4) of treatment, compared to baseline.
5. The subject's adherence to treatment (number of applications reported on the subject's diary).
6. The subject's and Investigator's global evaluation of performance of Relizema ecofoam, by means of a 7-items scale.
7. The subject's overall acceptability of Relizema ecofoam, by means of a 5-item scale.

Treatment compliance was assessed through the counting of the number of applications performed, recorded in the subject's diaries. The number of expected applications was estimated based on the treatment duration x 2 times.

The following formula was used:

*(Number of applications performed) / (Number of applications expected) * 100*

Due to the low number of subjects enrolled, all the secondary endpoints outcomes were only described by descriptive statistics and no inferential analysis was made.

Safety Analysis

Extent of Exposure

The extent of exposure was 1,5 month (42 days ±2).

Adverse Events

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

Adverse events (AEs) and Adverse Device Effects (ADEs) were coded using the 26.0 version of the Medical Dictionary for Regulatory Activities (MedDRA) 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 were summarized through number (N) and proportion of subjects (%).

Local tolerability at the site of administration (e.g., skin increased itching or redness or irritation) was carefully considered.

4. Results

4.1 Clinical investigation initiation date

The clinical investigation involved two clinical sites in Italy:

- Unità Operativa Complessa di Dermatologia - A.O.U. Policlinico “G. Rodolico-San Marco”, Via S. Sofia 78, 95123 Catania, Italy – P.I. Prof. Giuseppe Micali - Coordinating site (site 01);
- Unità Operativa di Dermatologia - Azienda Ospedaliero Universitaria Pisana - Stabilimento di Santa Chiara, Via Roma, 67, 56126 Pisa, Italy – P.I. Prof. Marco Romanelli (site 02).

The first Ethics Committee (EC) favourable opinion was obtained on the 19-Apr-2021 for site 01 and the second one on the 10-Feb-2022. Following the completion of authorization process, with sites’ contracts signature, sites were initiated: the first site (site 01) was initiated on the 11-Oct-2021 and the last one (site 02) on the 06-Sept-2022.

The first subject was enrolled at site 01 on 15-Nov-2021 and on 01-Dec-2022 the study start was notified to the National Competent Authority, the Italian Ministero della Salute.

4.2 Clinical investigation completion/suspension date

The last subject in (LSI) was enrolled on the 16-Nov-2022 and the last subject out (LSO) visit was on 31-Dec-2022.

The last clinical site (site 02) was officially closed on 29-Mar-2023 and the conclusion was notified to the National Competent Authority on 04-Apr-2023. The clinical investigation was regularly completed.

4.3 Disposal of subjects and investigational devices

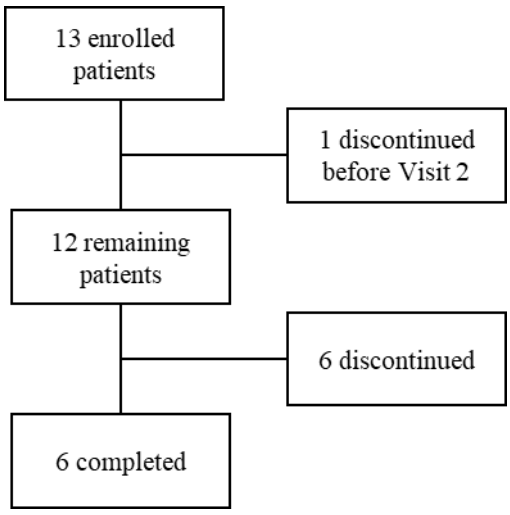
A total of 40 subjects were planned but only 13 were enrolled in the study and all of them started the treatment. Even if the Sponsor noticeably prolonged the recruitment period (up to one year) the study target was not reached.

The enrolment phase of the study lasted about 12 months: the first subject signed the informed consent and performed the Visit 1 on 15-Nov-2021 and the last subject on 16-Nov-2022.

At the Visit 1, after eligibility confirmation, subjects received the treatment to be started on the same day (the time of the first application depending on the time of the visit). After that, three visits were performed: one follow-up visit after 2 weeks (± 1 day) of treatment, one follow-up visit after 4 weeks (± 1 day) of treatment and a conclusive visit (end of treatment/end of study) after 6 weeks (± 2 days) of treatment.

The last subject completed the study on 31-Dec-2022. Overall, the study lasted about 13,5 months.

Figure 1. *Subject disposition*



Source: Table 1.1

Seven subjects withdrew from the study between V1 and V4.

In detail:

- Site 01 - subject ID 003 was lost to follow-up after Visit 1 (no data was available after V1 and for that reason the subject was not included in the safety population).
- Site 01 - subjects ID 002 and 008 were lost to follow-up after Visit 2 and Visit 3 respectively.

Site 01 - subjects ID 001, 004, 006, 009 withdrew because of the need to use a not allowed medication to treat dermatitis. The Investigator, in fact, decided to start a pharmacological treatment with topical corticosteroids. In order to start this treatment (not allowed according to study protocol), the subjects' participation in the study was prematurely interrupted. Table 1.1 and Listing 1 show the Subjects' disposition and the list of discontinued subjects.

Based on this, 6 subjects, out of 13, regularly completed the study.

4.4 Subject demographics

Thirteen subjects were enrolled in the study and twelve entered in the Safety population.

The demographic characteristics were analysed on Safety population (subjects ID 003 from site 01 was excluded as no further information after V1 was available) made of 12 subjects:

- 4 subjects were males (33.3%) and 8 females (66.7%);
- mean age of the study population was 49.33 years (min. 21 - max. 84 years old). Most of the population was 49 years old (median 49.00).

Baseline characteristic of age and sex are reported in Table 1.3 and Listing 4.1.

With regards to other baseline characteristics, 10 subjects (83.3%) were affected by atopic dermatitis and 2 subjects (16.7%) by irritant contact dermatitis; body areas mostly affected by dermatitis were arms and legs. Ten subjects (83.3%) had been suffering from the disease for a few years (2018-2022) while 2 subjects (16.7%) had been suffering from dermatitis for a long time (1982 and 2014) (Table 1.4 and Listing 4.4).

Three subjects (25%) had a positive medical history at baseline while 9 subjects (75%) had negative medical history at baseline (Table 1.5 and Listing 4.2). Only one subject underwent a surgery in the past (hip arthroplasty) (Table 1.6 and Listing 4.3). At baseline the physical examination showed no relevant condition, except than skin abnormality in all subjects (Table 1.7 and Listing 9).

Very few concomitant therapies were registered at baseline for two subjects (Listing 8) and these therapies did not change during the study.

4.5 CIP compliance

Overall, 10 protocol deviations (Listing 2) were registered during the study, no. 6 deviations involving 4 subjects at clinical site 01 and no. 4 deviations involving 1 subject at site 02. Nine deviations were assessed as “minor” and only one was evaluated as “major”: subject ID no. 005 (from site 01) performed all visits with big delay. No protocol deviation caused the exclusion of any subject from the study populations for analyses.

Overall, 7 deviations regarded in fact the execution on delay of some visits, 2 deviations were due to the study product compliance and 1 deviation regarded the missed return of the diary of Visit 1.

4.6 Analysis

Due to the small size of the data sets, all endpoints were performed on the Safety Analysis Set (SAF) and were described by descriptive statistics.

4.6.1 Primary endpoint performance analysis

The primary performance endpoint was the proportion of responders (decrease in IGA ≥ 1) assessed after 28 days of treatment (Visit 3), compared to baseline (Visit 1).

IGA was described using the number (N) and the proportion of subjects (%) at Visit 1 and Visit 3. At baseline 9 subjects (75.0%) had mild dermatitis and 3 subjects (25.0%) had moderate dermatitis; after 28 days of treatment 3 subjects (42.9%) had almost clear dermatitis, 3 subjects (42.9%) had mild dermatitis and only 1 subject (14.3%) had moderate dermatitis.

The proportion of responders was as follows: 3 subjects (42.9%) were considered responder while 4 (57.1%) were considered non-responder (Table 2.1.1).

4.6.2 Secondary endpoints performance analysis

Secondary endpoints analysis was conducted on the SAF population as well.

Proportion of responders (decrease in IGA ≥ 1) assessed after 14 days (Visit 2) and 42 days (Visit 4) of treatment, compared to baseline (Visit 1)

IGA was described using the number (N) and the proportion of subjects (%) at Visit 1, Visit 2 and Visit 4.

As stated for primary endpoint, at baseline 9 subjects (75.0%) had mild dermatitis and 3 subjects (25.0%) had moderate dermatitis.
After 14 days of treatment 3 subjects (25.0%) had almost clear dermatitis, 3 subjects (25.0%) had mild dermatitis and 6 subjects (50.0%) had moderate dermatitis.
The proportion of responders was: 5 subjects (41.7%) were considered responder while 7 (58.3%) were considered non-responder (Table 2.2.1).
After 42 days of treatment 1 subject (16.7%) had almost clear dermatitis, 4 subjects (66.7%) had mild dermatitis and only 1 subject (16.7%) had moderate dermatitis.
The proportion of responders was: 2 subjects (33.3%) were considered responder while 4 (66.7%) were considered non-responder (Table 2.2.2).

EASI score after 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4), compared to baseline (Visit 1)

EASI score was described using the number of subjects (N), mean, standard deviation, median, minimum, maximum at Visit 1, Visit 2, Visit 3 and Visit 4.
At Visit 1 the mean of EASI score was 4.05 (SD=3.02), with a minimum of 0.90 and a maximum of 10.80.
After 14 days of treatment (Visit 2) the mean of EASI score was 4.36 (SD=4.83) with a minimum of 0.40 and a maximum of 16.20 (Table 2.2.3).
After 28 days of treatment (Visit 3) the mean of EASI score decreased to 2.21 (SD=2.34) with a minimum of 0.20 and a maximum of 6.20 (Table 2.2.4).
After 42 days of treatment (Visit 4) the mean of EASI score decreased to 1.83 (SD=1.20) with a minimum of 0.60 and a maximum of 4.10 (Table 2.2.5).

DLQI questionnaire after 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4), compared to baseline (Visit 1)

DLQI score was described using the number of patients (N), mean, standard deviation, median, minimum, maximum at Visit 1, Visit 2, Visit 3 and Visit 4.
At Visit 1 the mean of DLQI score was 5.08 (SD=3.58), with a minimum of 2.00 and a maximum of 15.00.
After 14 days of treatment (Visit 2) the mean of DLQI score was 4.33 (SD=3.50) with a minimum of 0.00 and a maximum of 11.00 (Table 2.2.6).
After 28 days of treatment (Visit 3) the mean of DLQI score decreased to 2.57 (SD=3.05) with a minimum of 0.00 and a maximum of 8.00 (Table 2.2.7).
After 42 days of treatment (Visit 4) the mean of DLQI score was 3.50 (SD=2.26) with a minimum of 1.00 and a maximum of 6.00 (Table 2.2.8).

VAS after 14 days (Visit 2), 28 days (Visit 3) and 42 days (Visit 4), compared to baseline (Visit 1)

VAS was described using the number of subjects (N), mean, standard deviation, median, minimum, maximum at Visit 1 and Visit 2. VAS was used to evaluate pain, burning and itching improvement.

VAS for pain rating

At Visit 1 the mean of VAS for pain rating was 13.42 mm (SD=18.59), with a minimum of 0.00 mm and a maximum of 50.00 mm.

After 14 days of treatment (Visit 2) the mean of VAS for pain rating was 15.33 mm (SD=27.90) with a minimum of 0.00 mm and a maximum of 81.00 mm (Table 2.2.9).

After 28 days of treatment (Visit 3) the mean of VAS for pain rating was 8.71 mm (SD=18.25) with a minimum of 0.00 mm and a maximum of 50.00 mm (Table 2.2.10).

After 42 days of treatment (Visit 4) the mean of VAS for pain rating was 20.83 mm (SD=31.45) with a minimum of 0.00 mm and a maximum of 77.00 mm (Table 2.2.11).

VAS for burning rating

At Visit 1 the mean of VAS for burning rating was 36.83 mm (SD=36.80), with a minimum of 0.00 mm and a maximum of 88.00 mm.

After 14 days of treatment (Visit 2) the mean of VAS for burning rating was 35.00 mm (SD=37.67) with a minimum of 0.00 mm and a maximum of 98.00 mm (Table 2.2.9).

After 28 days of treatment (Visit 3) the mean of VAS for burning rating was 10.57 mm (SD=18.12) with a minimum of 0.00 mm and a maximum of 50.00 mm (Table 2.2.10).

After 42 days of treatment (Visit 4) the mean of VAS for burning rating was 27.17 mm (SD=30.72) with a minimum of 0.00 mm and a maximum of 77.00 mm (Table 2.2.11).

VAS for itching rating

At Visit 1 the mean of VAS for itching rating was 71.50 mm (SD=26.89), with a minimum of 8.00 mm and a maximum of 100.00 mm.

After 14 days of treatment (Visit 2) the mean of VAS for itching rating was 58.58 mm (SD=40.27) with a minimum of 3.00 mm and a maximum of 100.00 mm (Table 2.2.9).

After 28 days of treatment (Visit 3) the mean of VAS for itching rating was 37.43 mm (SD=32.91) with a minimum of 3.00 mm and a maximum of 81.00 mm (Table 2.2.10).

After 42 days of treatment (Visit 4) the mean of VAS for itching rating was 52.17 mm (SD=27.06) with a minimum of 15.00 mm and a maximum of 85.00 mm (Table 2.2.11).

Subject's adherence to treatment

Treatment compliance was summarized by the number of subjects (N), mean, standard deviation, median, minimum, maximum. As shown in Table 2.2.12 treatment compliance was generally very high at each time point: the mean of compliance between Visit 1 and Visit 2 was 91.38% (SD=17.10), the mean of compliance between Visit 2 and Visit 3 was 97.14% (SD=6.57), and the mean of compliance between Visit 3 and Visit 4 was 90.67% (SD=15.52). Accordingly, also the average compliance, calculated by averaging the compliances of each period, was very high: 89.64% (SD=14.73) with a minimum of 54.00% and a maximum of 105.00%.

Subject's and Investigator's global evaluation on performance of the study product

The Subject's and Investigator's global evaluation on performance of the study product was assessed at Visit 4. The evaluation was obtained by means of a 7-items Likert scale; it was described using the number (N) and the proportion of subjects (%) (Table 2.2.13).

Three subjects (30.0%) evaluated "Improved" or "Minimally improved" the dermatitis, only 1 subject (10.0%) noticed no changes in its dermatitis status and 6 subjects evaluated "Minimally worse", "Worse" or "Very much worse" the dermatitis.

Similarly, the Investigator evaluated the performance of study product: for 4 subjects (40.0%) the dermatitis was evaluated as "Improved" or "Minimally improved", for 1 subject (10.0%) no changes were noticed and for 5 subjects (50.0%) the dermatitis was evaluated as "Minimally worse", "Worse" or "Very much worse".

Subject's evaluation of overall acceptability with treatment

The Subject's evaluation of overall acceptability with treatment was assessed at Visit 4. The evaluation was obtained by means of a 5-items Likert scale; it was described using the number (N) and the proportion of subjects (%) (Table 2.2.14).
Six subjects (60.0%) considered "Satisfied" with the acceptability of the product, 1 subject (10.0%) "Neither satisfied nor dissatisfied" and 3 subjects (30.0%) "Dissatisfied".

4.6.3 Safety analysis

Safety analysis was conducted on the Safety population (i.e., 12 subjects).
Only 1 adverse event (Covid-19 infection) was registered during the study, involving subject ID 012 from site 02. It was not serious, mild severity and not related to the study treatment (Table 3.1 and Listing 7).
No adverse events related to the study treatment occurred during the study.

5. Discussion and overall conclusions

Dermatitis is a skin inflammatory disease characterized by reddening, itching and skin dryness of the affected epidermis. Dermatitis is a condition that can interfere with social function, sleep and employment. Its persistence and accompanying pruritus may be stressful and frustrating for subjects.

The most common types of dermatitis are contact dermatitis (CD) - particularly allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) - and atopic dermatitis (AD), also referred as atopic eczema.

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.

Relizema ecofoam is a topical compact mousse indicated for treatment of the signs and symptoms associated with all types of dermatitis and erythema. Its mechanism of action is based on the creation of a 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.

This clinical investigation was planned and conducted to the purpose of collecting clinical evidence of the document the activity and safety of Relizema ecofoam in the management of dermatitis symptoms in adults affected by mild to moderate dermatitis, including atopic dermatitis and contact dermatitis.
The study unfortunately had a very low enrolment and when timings for enrolment expired only 12 subjects were enrolled and treated (one more subject was enrolled but immediately after resulted lost to follow-up and no post-baseline information nor data were available). Due to the low recruitment, no firm conclusions on clinical performance and safety can be drawn, from this study.
All the analyses were only descriptive and done on the Safety Population set (i.e. 12 subjects).
With regard to the primary endpoint (decrease in Investigator Global Assessment ≥ 1 assessed after 28 days of treatment), the 42.9% of the subjects were considered responder while the 57.1% were considered non-responder.
Considering IGA at other study time-points (secondary performance endpoint), after 14 days of treatment the 41.7% of subjects was considered responder while the 58.3% was non-responder; after 42 days of treatment the 33.3% of subjects was considered responder while the 66.7%) was non-responder.

Mean EASI score at baseline was 4.05 (SD=3.02) and respectively 4.36 (SD=4.83), 2.21 (SD=2.34) and 1.83 (SD=1.20) after 14, 28 and 42 days of treatment.

Mean of DLQI score at baseline was 5.08 (SD=3.58) and respectively 4.33 (SD=3.50), 2.57 (SD=3.05) and 3.50 (SD=2.26) after 14, 28 and 42 days of treatment.

Mean pain measured by VAS resulted 13.42 mm (SD=18.59) at baseline and respectively 15.33 mm (SD=27.90), 8.71 mm (SD=18.25) and 20.83 mm (SD=31.45) after 14, 28 and 42 days of treatment.
Mean burning measured by VAS resulted 36.83 mm (SD=36.80) at baseline and respectively 35.00 mm (SD=37.67), 10.57 mm (SD=18.12) and 27.17 mm (SD=30.72) after 14, 28 and 42 days of treatment.
Mean itching measured by VAS resulted 71.50 mm (SD=26.89) at baseline and respectively 58.58 mm (SD=40.27), 37.43 mm (SD=32.91) and 52.17 mm (SD=27.06) after 14, 28 and 42 days of treatment.

With regard to the Subject's global evaluation on performance of the study product the 30.0% of the subjects evaluated their dermatitis "Improved" or "Minimally improved", the 10.0% noticed no changes the 60% evaluated "Minimally worse", "Worse" or "Very much worse" the dermatitis.

Similarly, the Investigator evaluated the dermatitis “Improved” or “Minimally improved” in the 40.0% of subjects, not changed in the 10.0% and “Minimally worse”, “Worse” or “Very much worse” in the 50.0% of subjects.

With regard to the overall treatment acceptability, the subjects were "Satisfied" in the 60.0% of cases, “Neither satisfied nor dissatisfied” in the 10.0% of cases and “Dissatisfied” in the 30.0% of cases.

Globally, some positive effects on signs and symptoms of dermatitis were observed during this study, especially after one month of treatment. However, the improvements seem to be not very marked and not stable: after 4 weeks of treatment it was noticed an improvement in several endpoints but the gain seems to be getting lost at 6 weeks of treatment. In addition to this, 3 out of 13 subjects were lost to follow-up and 4 subjects prematurely interrupted the study as the Investigator decided to start a pharmacological treatment with topical corticosteroids. These 4 cases of study interruption to start a not allowed pharmacologic treatment were duly analysed with the Principal Investigator. His opinion was that, despite the severity of the dermatitis was assessed as “mild” at baseline, these subjects suffered of a condition that rapidly and spontaneously worsened and, as such, had to be immediately directed to a pharmacological treatment eventually integrated with emollients, but emollient treatment alone could not be sufficient.

From the safety point of view, no adverse events related to the study treatment were reported: only one AE occurred during the study, not related, of mild severity and resolved: Covid-19 infection.

Based on all the above considerations and on the fact that the number of subjects enrolled was too small, this PMCF study does not allow to draw strong and clear conclusion nor a statistical analysis on the clinical performance and safety of Relizema ecofoam.

6. Abbreviated terms and definitions

ADE	Adverse Device Effect
AE	Adverse Event
AO	Azienda Ospedaliera
CE	Conformité Européenne (European Conformity)
CI	Interval of Confidence
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index questionnaire
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
EC	Ethics Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation 679/2016
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IFU	Instructions For Use
IGA	Investigator Global Assessment
LSI	Last Subject In
LSO	Last Subject Out
MDD	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Medical Device Regulation
ml	Milliliters
mm	Millimeters
OTC	Over the Counter
PI	Principal Investigator

PMCFS	Post Market Clinical Follow-up Study
PT	Preferred Term
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAF	Safety Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
vIGA-AD™	Validated Investigator's Global Assessment Scale for Atopic Dermatitis

7. Ethics

The study was conducted in full compliance with the principles of the "Declaration of Helsinki". Before undertaking any study-related procedures with subjects, the purpose and nature of the study as well as possible adverse effects were explained to them in understandable terms and written informed consent was obtained from everyone.

- Unità Operativa Complessa di Dermatologia - A.O.U. Policlinico “G. Rodolico-San Marco”, Via S. Sofia 78, 95123 Catania, Italy – P.I. Prof. Giuseppe Micali - Coordinating site (site 01);
- Unità Operativa di Dermatologia - Azienda Ospedaliero Universitaria Pisana - Stabilimento di Santa Chiara, Via Roma, 67, 56126 Pisa, Italy – P.I. Prof. Marco Romanelli (site 02).

Two clinical sites were involved and for each of them the competent EC approval was requested and obtained. The EC of the coordinating site (Comitato Etico Catania 1), evaluated this clinical investigation in the meeting of the 19-Apr-2021 and expressed a favorable opinion. The second EC favourable opinion was obtained on the 10-Feb-2022.
The Italian CA (Ministry of Health) was notified about the study start on the 01-Dec-2022, after the first subject was enrolled (15-Nov-2021).
During the study no substantial amendment was issued.
The clinical investigation was definitely terminated with the last closure visit on the 29-Mar-2023 and promptly notified to ECs and CA on the 04-Apr-2023.
The study essential documents were archived according to the CRO SOPs (in line with ISO 14155 guideline) and will be kept by the investigational sites and the Sponsor according to MDR 2017/45 requirements. It will be responsibility of the Principal Investigators to assure that the study essential documents are duly filed in the Trial Centre File and that the Trial Centre File is correctly stored and preserved after the study closure.

8. Investigators and administrative structure of clinical investigation

Study Site 01 – Coordinating Site Unità Operativa Complessa di Dermatologia A.O.U. Policlinico "G. Rodolico-San Marco", Via S. Sofia 78, 95123 Catania	**Principal Investigator** Giuseppe Micali
Study Site 02 Unità Operativa di Dermatologia Azienda Ospedaliero Universitaria Pisana - Stabilimento di Santa Chiara, Via Roma, 67, 56126 Pisa	**Principal Investigator** Marco Romanelli
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9. Signature page

Sponsor

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and the results of the clinical investigation.

28 / 07 / 2023

Date

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

28 / 07 / 2023

Date

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

_____ ____/____/____

Date

Camilla Palermiti
Head of Statistics & Data Management
Latis S.r.l.

Principal Investigator

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and the results of the clinical investigation.

_____ ____/____/____

Date

Prof. Giuseppe Micali
Unità Operativa Complessa di Dermatologia
A.O.U. Policlinico “G. Rodolico-San Marco”, Catania

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