Clinical Investigation Report

A MULTICENTER, DOUBLE BLIND, RANDOMIZED, VEHICLE-CONTROLLED CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RELIZEMA™ CREAM IN THE MANAGEMENT OF ATOPIC DERMATITIS IN PAEDIATRIC PATIENTS

Investigational device:	RELIZEMA™ CREAM
Sponsor:	Relife S.r.l. Via dei Sette Santi 3 - 50131 Florence, ITALY
Sponsor's representative:	Silvia Innocenti, MD - Head of Scientific Affairs
CIP identification:	Version no. 1.1 – 31st October 2022
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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.

Table of contents

1. Summary

Title of the clinical investigation - summary information	
Brief Study Title	YOUNG
Full Study Title	A MULTICENTER, DOUBLE BLIND, RANDOMIZED, VEHICLE-CONTROLLED CLINICAL STUD**Y** T**O** EVAL**U**ATE THE EFFICACY A**N**D SAFETY OF RELIZEMA™ CREAM IN THE MANA**G**EMENT OF ATOPIC DERMATITIS IN PAEDIATRIC PATIENTS
Study Code	ReGI/21/Rcr-Dpe/001
Dates of Investigation	First Patient In – 27/10/2022 Last Patient Out - 09/06/2023
Location(s)	The clinical investigation was conducted in Italy: *Site 01* - Dermatology Unit, Santa Maria della Misericordia Hospital, P.le Menghini, 3 - 06129 Perugia. PI Prof. Luca Stingeni *Site 02* – Dermatology Unit, Presidio Ospedaliero Gaspare Rodolico, AOU Policlinico “G. Rodolico-San Marco”, Via S. Sofia, 78 - 95123 Catania. PI Prof. Giuseppe Micali *Site 03* - Dermatology Unit, A.O.U "Federico II" di Napoli, Via Sergio Pansini, 5 - 80131 Napoli. PI Prof. Massimiliano Scalvenzi
If relevant, reason for temporary halt or early termination	No temporary halt or early conclusion occurred. A total of 60 subjects were planned and 50 were enrolled. The enrolment started in October 2022 and its conclusion was planned 3 months after. The deadline was significantly postponed until end of April 2023. After that, no further timing extension was allowed in order to avoid the study conduction during summertime, that could generate bias, being well known that AD spontaneously improves thanks to sun exposition.

Purpose of the clinical investigation
Relizema™ cream is a dermatological cream for topical use indicated for the treatment of itching, and flushing associated with dermatitis, including atopic and contact dermatitis and/or erythema. Thanks to its derma-protective action it helps maintaining and restoring the physiological skin barrier. Relizema™ cream is a CE marked medical device class IIa, manufactured by RELIFE Srl, that was the Sponsor of this pre-market clinical investigation, aimed to test the device in a pediatric population.

Atopic dermatitis (AD) is a long-term (chronic) cutaneous inflammatory disease, very common condition in babies and children, affecting up to 25% of children. Depending on the severity of the disease, symptoms can include erythema, dry, scaly skin, itching, redness and swelling, thickened skin, pale skin on the face, small-raised bumps that may become crusty and leak fluid if scratched, rough bumps on the face, upper arms, and thighs, darkened skin, lichenification etc. Importantly, the disease can cause significant sleep disruption and impact the quality of life of patients and families. Since there is no curative etiological therapy for AD, the aim of all therapeutic interventions is the control and relief of symptoms and prevention of flare-ups.

Currently available pharmacologic treatments for dermatitis management include the topical corticosteroids or immunosuppressants, which have a significant efficacy but are also associated with high incidence of transient skin reactions and, for this reason, are generally not recommended for the young children.

There is strong evidence that the use of topical moisturizers, emollients and protective agents can reduce the need for pharmacologic intervention to treat AD symptoms and are particularly recommended in young patients. 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) are the most popular humectants and are both contained in Relizema™ cream, together with furfuryl palmitate which has antioxidant properties, vitamin E with antioxidant and skin conditioning properties, ethylhexylglycerin with skin conditioning function.

This pre-market clinical investigation was aimed to evaluate the clinical benefit of Relizema™ cream in infants, children and adolescents suffering for AD symptoms. To assess in objective way the effects of Relizema™ cream in the relief of AD symptoms, it was compared to placebo (vehicle) in this double-blind designed study.

Description of the investigational device, clinical investigation, and methods used	
Description of participants	Infants from 6 months of age up to adolescents of 16 years inclusive, of both sexes, affected by mild to moderate atopic dermatitis. <u>Inclusion criteria:</u>

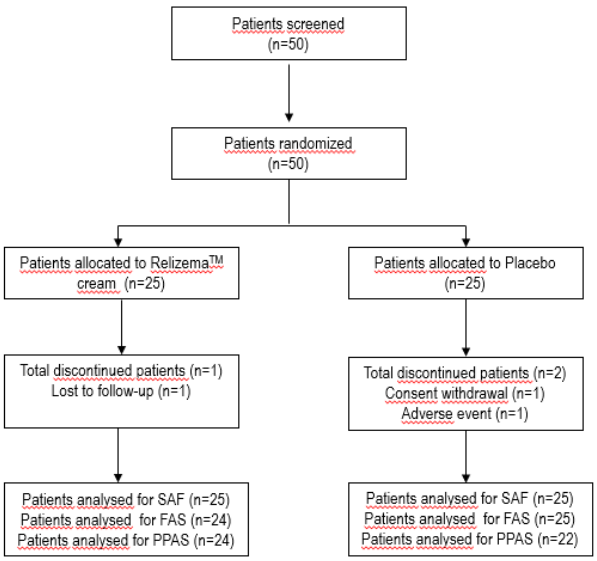
	1. Release of the written informed consent obtained prior to any study-related procedures, by both the parents/the guardian; 2. Male and female infants, children, adolescent aged between 6 months and 16 years, inclusive; 3. Presence of atopic dermatitis (AD) of mild-moderate severity: - IGA score 2 (=mild) or - IGA score 3 (=moderate) 4. Patients with a baseline score for itch at least 4 on the NRS 5. Patients/parents/guardian able to comprehend the full nature and the purpose of the investigation, 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. <u>Exclusion criteria</u>: 1. Severe dermatitis at inclusion; 2. Pregnant and breastfeeding patients; 3. Concomitant other skin disorders including skin infections; 4. Use of antibiotics in the past 7 days; 5. History of congenital or acquired immunodepression; 6. Immunologic or infectious disease (e.g. hepatitis, tuberculosis, HIV or AIDS, any typology of lupus, rheumatoid arthritis) which could place the patient at risk or interfere with study results; 7. Use of any topic or systemic drug for dermatitis in the past 10 days; 8. Use of any topic emollient product for dermatitis in the 2 days before study treatment start; 9. Any systemic treatment or procedure that could influence dermatitis activity within the past 30 days (or 5 half-lives); 10. Use of any corticosteroids, immunosuppressant drugs or immunotherapy within the past 30 days (or 5 half-lives); 11. Use of oral antihistamines and antidepressants in the past 30 days; 12. Patients 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; 13. Allergy, sensitivity or intolerance to the components of the investigational device formulations ingredients; 14. Concomitant or previous participation in other interventional clinical study in the past 3 months; 15. Patients planning sun exposure or tanning booths or UV sources throughout the course of the study.

Description of the device and comparator	Relizema™ cream is a CE marked medical device, class IIa, manufactured by RELIFE Srl. Relizema™ cream is a dermatological cream for topical use indicated for the treatment of itching, and flushing associated with dermatitis, including atopic and contact dermatitis and/or erythema. The mechanism of action of the product is based on the creation of a sheer physical barrier that separates the skin from the surrounding environment, useful for generating favorable conditions for the maintenance and/or recovery of the physiological cutaneous layer in case of dermatitis. It improves dry skin by keeping it hydrated. Its formulation protects and moisturizes the skin with a soothing effect. Its main functional components are: - Hyaluronic acid, with a humectant function, generates a protective film that helps to retain the aqueous content of the skin, keeping it hydrated - Furfuryl palmitate has antioxidant properties - Vitamin E has antioxidant and skin conditioning properties - Glycerin with humectant function - Ethylhexylglycerin with skin conditioning function. As comparator, a placebo was used, constituted by the vehicle alone.
Description of procedures to use the device	Relizema™ cream / vehicle were used two times daily: the first application in the morning and the second in the evening before bedtime, for three cycles of 13 (±2 days). The study treatment started on the day after initial visit (Visit 1) and was suspended for 1 day only on the visit days.
Study design	Multicenter, double blind, randomized, vehicle-controlled, pre-market clinical follow-up study.
Objectives and endpoints	The **primary objective** of this clinical investigation was to evaluate and confirm the performance of the Relizema™ cream in the improvement of the dermatitis severity, assessed through a clinical parameter, the Investigator's Global Assessment (IGA) at baseline and at Visit 3, compared to vehicle. The ***primary endpoint*** was the responder rate in active treatment group and placebo group assessed according to the decrease in the Investigator Global Assessment (IGA) score evaluated at Visit 3, from baseline. Patients were considered responders when the IGA (Investigator Global Assessment) score decreases of at least one point. **Secondary objectives** of this clinical investigation were:

	1. To evaluate the performance of the Relizema™ cream, compared to placebo, in the improvement of dermatitis severity (IGA) at Visit 2 and Visit 4. 2. To evaluate the eczema improvement through the EASI (Eczema Area and Severity Index) score at each time point, in the two treatment groups; 3. To evaluate itching improvement as reported by the patient/parents/guardian at visits by the Numerical Rating Scale (NRS), in the two treatment groups; 4. To evaluate the QoL improvement of the patient related to his/her dermatitis, through the Children Dermatology Life Quality Index (CDLQI) in the two treatment groups; 5. To evaluate the patient's adherence to treatment; 6. To evaluate the need of a rescue treatment (as indicated by the Investigator) to manage AD flare; 7. To evaluate the patient's and Investigator's global evaluation of performance of Relizema™ cream, compared to placebo. ***Secondary endpoints*** were: 1. The percentage of responders, evaluated according to the IGA score decrease as above described, assessed at Visit 2 and 4, compared to baseline (Visit 1); 2. The change in the EASI score (0-72) for the four key signs of AD (erythema, induration/papulation, excoriation and lichenification) assessed at Visit 2, 3 and 4, compared to baseline (Visit 1); 3. The change in NRS scale at Visit 2, 3 and 4, compared to baseline (Visit 1); 4. The change in the CDLQI questionnaire answers at (Visit 2, 3 and 4, compared to baseline (Visit 1); 5. The adherence to treatment, evaluated by counting the applications reported on the patient's diary; 6. The use of a rescue medication, as prescribed by the Investigator; 7. The patient's/parents'/guardian'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). **Safety objectives** was to evaluate the local and general tolerability of Relizema™ cream compared to placebo.

	Safety endpoints were: 1. The number and type of adverse events (AEs) occurring during the study (seriousness, severity, and relation to study treatment). 2. The local tolerability at the site of administration.
Sample size	It was estimated that the percentage of patients improved at Visit 3 was equal to 26% in the placebo arm and 80% in the test medical device arm. With a 0.05 two-sided significance level, a sample size of 48 patients in each arm had 90% power to detect the above estimated difference between groups. Estimating a rate of non-evaluable patients up to 20%, the randomization of 60 patients was thought to allow the replacement of non-evaluable patients for any reason.
Randomisation and blinding	The study treatment was assigned through electronic randomization process (eCRF). The randomization list was generated by the CRO using the PROC PLAN of SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). The blind was maintained during the study using the following methods: - indistinguishable test device and placebo - random treatment assignment - blinded assessments.
Follow up duration	Each patient was followed in the study for 42 (±2) days. The study product application was ended on the evening before last visit.
Concomitant treatments	The following treatments were not permitted during the study: - 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 - sun exposure or tanning booths or UV sources.
Statistical analysis methods	Descriptive statistical analysis of all relevant variables was performed. Continuous variables were summarized by the number of patients (N), mean, standard deviation, median, minimum, maximum. Categorical variables were summarized by number (N) and percentage of patients (%). The significance level of statistical tests was set at 0.05. Parametric tests were used to analyze continuous variables; when continuous variables were not normally distributed, the corresponding non-parametric tests were also performed.

Substantial modifications	No relevant changes were made to the clinical investigation plan during the study. One non substantial amendment dated 31.10.2022 was notified to ECs (Ethics Committees) and CA (Competent Authority), in order to better specify that two different EASI scales were in use, one for children < 8 years and one for children ≥ 8 years of age. One substantial amendment was also issued for the change of the PI at clinical site no.3 (Napoli).

Results of the investigation	
Participant flow	Fifty patients were enrolled and randomized: 25 to Relizema™ cream and 25 to placebo. Three patients withdrew prematurely, 1 in Relizema™ cream group (lost to follow-up after Visit 1) and 2 in placebo group (one for consent withdrawal and one for SAE, both after Visit 2).  Primary and secondary performance endpoints were analyzed on the Full Analysis Set (FAS) population: 49 patients in total, 24 in Relizema™ cream group (patient ID 03-009 was excluded because no data was available after initial visit) and 25 in Placebo group. Additionally, the primary endpoint was analyzed on the Per-Protocol Analysis set (PPAS) made of 46 patients: - patient ID 03-009 randomized to Relizema™ cream was excluded from PPAS because no data was available after initial visit;

	- patients ID 02-004, 02-006 randomized to Placebo were excluded because they drop out from the study after second visit; - patient ID 01-020 randomized to Placebo was excluded because of poor treatment compliance (<80%). Safety endpoints were analyzed on the Safety Analysis Set (SAF) population (i.e 50 patients).
Baseline demographic and clinical characteristics	Of the enrolled patients, 19 were female and 31 were male: in Relizema™ cream group 10 patients (40.0%) were female and 15 patients (60.0%) were male; in Placebo group 9 patients (36.0%) were female and 16 patients (64.0%) were male. Mean age was 6.72 (SD=4.97) years in Relizema™ cream group and 6.62 (SD=4.45) years in Placebo group. Patients were also distributed into three age categories: from 6 months to 2 years, from 3 to 11 years and from 12 to 16 years and the age categories were homogeneous between groups. The body areas most affected by atopic dermatitis were “Face, Legs, Arms, Trunk”: 15 patients (60.0%) in Relizema™ cream group and 16 patients (64.0%) in Placebo group. The remaining 19 patients were evenly distributed among the other body area. Only 2 patients (8.0%) in Placebo group had at least one significant medical condition (food allergy and milk allergy) in the medical history and only 1 patient (4.0%) in Placebo group underwent surgery (orchidopexy) in the past. No statistically significant difference was detected for gender, age, body areas affected by dermatitis and medical/surgical history between groups.
Outcome of the intervention	The proportion of responder (decrease in IGA >= 1) at Visit 3 (i.e. after 28 days of treatment) was the primary performance endpoint. The 70.8% of patients in Relizema™ cream group was responders while only the 60.0% in Placebo group was. The analysis repeated on PPAS showed the same result, with the 70.8% of patients in in Relizema™ cream group and the 59.1% in Placebo group responders. The difference between treatment groups was not statistically significant (Table 2.1.1 and 2.1.2) but the within group analysis showed that Relizema™ cream has a pronounced and statistically significant clinical performance (proportion of responders p value=0.0412*). Also, the proportion of responders analysed at Visit 2 and Visit 4 (i.e. after 2 and 6 weeks of treatment) showed the 50.0% of responders in Relizema™ cream group and the 40.0% in Placebo group at Visit 2 (Table

	2.2.1) and the 75.0% in Relizema™ cream group and 56.0% in Placebo group at Visit 4 (Table 2.2.2). No statistically significant difference between groups was observable but the within groups analysis evidenced the marked and statistically significant clinical performance of Relizema™ cream, at Visit 4 (proportion of responders: p value=0.0143*). EASI score decreased in both treatment groups in similar way and with statistical significance: mean changes from baseline to, respectively 14, 28 and 42 days of treatment were of -3.13 (SD=4.70), -4.30 (SD=5.51) and -5.45 (SD=6.62) in Relizema™ cream group and -3.32 (SD=5.54), -4.64 (6.04) and -4.31 (6.26), in Placebo group. No statistically significant difference between groups was observable (Table 2.2.3). Mean itching rating decreased in both treatment groups from baseline to, respectively 14, 28 and 42 days of treatment: mean changes were -0.96 (SD=1.16), -1.58 (SD=1.21) and -2.42 (SD=1.67) in Relizema™ cream group and -0.50 (SD=1.25), -1.26 (SD=1.66) and -1.83 (SD=1.86), in Placebo group. The Relizema™ cream performance was statistically significant at each time point while the one of Placebo was only at Visit 3 and 4. In any case, no statistically relevant difference was observed between the two groups at each time point of the study (Table 2.2.4). As well, mean worst itching rating decreased in both treatment groups from baseline to, respectively 14, 28 and 42 days of treatment, always with statistical significance within each treatment group: mean changes were -1.21 (SD=1.41), -1.96 (SD=1.49) and -2.63 (SD=2.34) in Relizema™ cream group and -0.63 (SD=1.17), -1.65 (SD=1.40) and -2.00 (SD=1.62) in Placebo group. No statistically significant difference between groups was observable (Table 2.2.4). CDLQI score decreased (meaning an improvement in the QoL) in both treatment from baseline to, respectively 14, 28 and 42 days of treatment, always with statistical significance within each treatment group: mean changes were -2.29 (SD=2.52), -3.86 (SD=4.33) and -5.29 (SD=4.73) in Relizema™ cream group and -1.28 (SD=2.22), -2.56 (SD=2.94) and -3.53 (SD=4.00) in Placebo group. No statistically significant difference between groups was observable (Table 2.2.5). Finally, the Investigators evaluated that at the end of treatment (6 weeks) there was an improvement respect to initial condition in the 79.1% of patients treated with Relizema™ cream and in the 70.8% of patients treated with Placebo.

	The patients (parents/guardian) opinion was more likely to find it Relizema™ cream satisfactory (87.5%) than Placebo (66.6%). In both cases, no statistically significant difference between groups was observable (Table 2.2.8).
Safety outcomes	Only 2 adverse events to 2 patients occurred during the study, none of them was evaluated as related to the study treatment, by the Investigator. One of the two events was serious and leading to study premature discontinuation: patient ID 02-004, randomized to placebo, had a bacterial gastroenteritis requiring hospitalization. The second event was of mild intensity and not related to study treatment: patient ID 01-002, randomized to Relizema™ cream, had a limb injury. The patient continued the study.
Deviations to clinical investigation plan	A total of 60 protocol deviations occurred during the study, 31 in Relizema™ cream group and 29 in Placebo group. All deviations were evaluated as minor (Table 1.2) therefore no protocol deviation caused the exclusion of any subject from the study populations for analyses. The majority of protocol deviations were related to treatment compliance (90.3% and 93.1% respectively in Relizema™ cream and Placebo groups) and a minority were related to delay in scheduled visits (6.5% and 6.9% respectively in Relizema™ cream and Placebo groups).

Conclusions of the clinical investigation
Data analysis showed a consistent improvement of the AD condition and symptoms with the progression of both treatments, Relizema™ cream and Placebo, without statistically significant difference between the two treatments. However, looking to all the performance endpoints, the improvement of the AD condition and symptoms resulted always more relevant within the Relizema™ cream group than within the Placebo group. Also, it must be noticed that the Placebo used in this study was a vehicle with hydrating properties (a real inert placebo could have not been used mainly for ethical reasons), therefore the comparison in this study was between two creams with very close compositions and properties. In light of this it is understandable and justified that no statistically significant difference emerged from data analysis. The relevant result of this clinical investigation is that, from statistical and clinical point of view, the Relizema™ cream has shown to be effective and absolutely safe in the relief of AD symptoms in young patients, from 6 months of age.

2. Introduction

Relizema™ cream is a dermatological cream for topical use indicated for the treatment of itching, and flushing associated with dermatitis, including atopic and contact dermatitis and/or erythema. Thanks to its derma-protective action it helps maintaining and restoring the physiological skin barrier.

Relizema™ cream is a CE marked medical device class IIa, manufactured by RELIFE Srl, that was the Sponsor of this pre-market clinical investigation.

The mechanism of action of the product is based on the creation of a sheer physical barrier that separates the skin from the surrounding environment, useful for generating favorable conditions for the maintenance and/or recovery of the physiological cutaneous layer in case of dermatitis. It improves dry skin by keeping it hydrated. Its formulation protects and moisturizes the skin with a soothing effect.

In this clinical investigation Relizema™ cream was used to treat and alleviate atopic dermatitis symptoms in infants over 6 months of age, children and adolescents. The IFU of the device do not specify the use in children, which was the reason why the study was conceived as pre-market.

2.1 Rationale

Atopic dermatitis is a long-term (chronic) cutaneous inflammatory disease. It causes erythema, dry, itchy skin. It's a very common condition in babies and children, affecting up to 25% of children [1]. It usually first appears during early childhood [2].

The underlying etiopathogenesis is multifaceted with a central role played by the relationship between impaired skin barrier and dysregulated immune response [3,4]. The first step in AD progress seems to be the altered skin barrier where environmental factors irrupt, leading to inflammatory response [5,6,7].

The loss-of-function mutations in the structural protein filaggrin and other skin proteins induce perturbed barrier function, thus resulting in diminished epidermal defense mechanisms to allergens, microbes, and other environmental agents [8,9,10].

Symptoms may come and go or occur most or all of the time. Any area of the body may be affected. In babies, symptoms usually affect the face, neck, scalp, elbows, and knees. In children and adolescents, symptoms usually affect the skin inside the elbows, on the back of the knees, the sides of the neck, around the mouth, and on the wrists, ankles, and hands.

Depending on the severity of the disease, symptoms can include erythema, dry, scaly skin, itching, redness and swelling, thickened skin, pale skin on the face, small raised bumps that

may become crusty and leak fluid if scratched, rough bumps on the face, upper arms, and thighs, darkened skin, lichenification etc.
Importantly, the disease can cause significant sleep disruption and impact the quality of life of patients and families [11].

Since there is no curative etiological therapy for AD, the aim of all therapeutic interventions is the is the control and relief of symptoms and prevention of infections [12].
Some of the currently available treatments for dermatitis management include the topical application of corticosteroids or immunosuppressants, acting at reducing the underlying inflammation and hypersensitization of the epidermis. They have a significant efficacy but are also associated with high incidence of transient skin reactions [13,14,15,16,17] that make them not well accepted by the patient and generally not recommended for the young children.
It is, instead, widely accepted that the application of non-steroidal topical moisturizers, emollients and protective agents should be an integral part of the treatment of young patients with AD, and there is strong evidence that their use can reduce the need for pharmacologic intervention to treat disease flare-ups.
Moisturizers are recommended to improve clinical symptoms and enhance skin barrier function. Moisturizers are generally composed of substances capable to restore the ability of the intercellular lipid bilayers to retain and redistribute water [18,19]. Moisturizers contain three main properties, which are the occlusive, humectant, and emollient effects.
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) are the most popular of all humectants used in personal care products.

Both ingredients are contained in Relizema™ cream, together with furfuryl palmitate which has antioxidant properties, vitamin E with antioxidant and skin conditioning properties, ethylhexylglycerin with skin conditioning function.
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. Evidence is available supporting HA as treatment of AD [20].
On the other hand, studies conducted on glycerol-containing creams [21,22], showed the significant hydration and barrier-improving effect of such products when compared to glycerol-free creams.
In this pre-market clinical investigation Relizema™ cream was tested in infants, children and adolescents to evaluate the effects on AD symptoms relief when compared to placebo (vehicle).

The clinical investigation was regularly submitted to the competent Ethics Committees and to the Italian Ministry of Health (Competent Authority), as for requirements in pre-market clinical investigations.

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 and comparator

The products under investigation were Relizema™ cream and its comparator, the vehicle (or placebo).

Relizema™ cream

Manufacturer:	RELIFE Srl, Via dei Sette Santi 3 - 50131 Firenze (FI) - Italy
Device Name:	DLP011
Trade Name:	Relizema™ cream
Formulation:	cream
Route of administration:	topical application on breached/compromised skin
Composition:	aqua, hydrogenated polydecene, ethylhexyl palmitate, dimethicone, glycerin, glyceryl stearate, peg-100 stearate, cetearyl alcohol, magnesium stearate, ricinus communis seed oil, phenoxyethanol, ascorbyl palmitate, disodium edta, ethylhexylglycerin, furfuryl palmitate, ethyl linoleate, tocopheryl acetate, sodium hyaluronate, ethyl oleate, ethyl linoleate, propyl gallate, tocopherol, ethyl palmitate, ethyl stearate.

It does not contain fragrance and parabens. It is nickel, antimony, arsenic, cadmium, cobalt, chrome, mercury and lead tested.

Vehicle (placebo)

Manufacturer:	RELIFE Srl, Via dei Sette Santi 3 - 50131 Firenze (FI) - Italy
Device Name:	not applicable
Trade Name:	not applicable
Formulation:	cream
Route of administration:	topical application on breached/compromised skin
Composition:	aqua, hydrogenated polydecene, ethylhexyl palmitate, dimethicone, glyceryl stearate, peg-100 stearate, cetearyl

alcohol, magnesium stearate, ricinus communis seed oil, phenoxyethanol, disodium edta, ethylhexylglycerin, ethyl linoleate, sodium hyaluronate, ethyl oleate, ethyl linoleate, propyl gallate, ethyl palmitate, ethyl stearate.

Test device and vehicle were indistinguishable by appearance, smell and possibly other parameters as far as necessary to reach the study objectives (double blind design) and technically feasible.

3.1.2 Intended use of the investigational device

Relizema™ cream is a CE marked, Class IIa medical device, dermatological cream for topical use indicated for symptomatic treatment of dermatitis and erythema. Relizema™ cream is indicated for the treatment of itching and flushing associated with different types of dermatitis, including atopic dermatitis. Thanks to its derma-protective action it helps maintaining and restoring the physiological skin barrier. Its formulation protects and moisturizes the skin with a soothing effect.

Relizema™ cream creates a sheer physical barrier that separates the skin from the surrounding environment, useful for generating favorable conditions for the maintenance and/or recovery of the physiological cutaneous layer in case of dermatitis. It improves dry skin by keeping it hydrated.

3.1.3 Previous intended use or indication for use, if relevant

The medical device Relizema™ cream was intended only for adult population and this clinical investigation was conducted with the aim to extend the indication also to the pediatric population. No other 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

No changes to the medical device nor to the IB occurred during the clinical investigation.

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™ cream in the improvement of the dermatitis severity, assessed through a clinical parameter, the Investigator's Global Assessment (IGA) at baseline (Visit 1) and at Visit 3, compared to vehicle (placebo).

The primary endpoint of this clinical investigation was the responder rate in active and placebo groups assessed according to the decrease in the Investigator Global Assessment (IGA) score evaluated at Visit 3 from baseline.
Patients were considered responders when the IGA (Investigator Global Assessment) score decreased of at least one point.

The secondary performance objectives of the clinical investigation were:

- to evaluate the performance of the Relizema™ cream, compared to placebo, in the improvement of dermatitis severity (IGA) at Visit 3 and 4;
- to evaluate the eczema improvement through the EASI (Eczema Area and Severity Index) score at each time point, in the two treatment groups;
- to evaluate itching improvement as reported by the patient/parents/guardian at visits by the Numerical Rating Scale (NRS), in the two treatment groups;
- to evaluate the QoL improvement of the patient related to his/her dermatitis, through the Children Dermatology Life Quality Index (CDLQI), in the two treatment groups;
- to evaluate the patient's adherence to treatment;
- to evaluate the need of a rescue treatment (as indicated by the Investigator) to manage AD flare;
- to evaluate the patient's and Investigator's global evaluation on the performance of Relizema™ cream, compared to placebo.

Performance secondary endpoints were:

- the percentage of responders, evaluated according to the IGA score decrease as above described, assessed at Visit 2 and 4, compared to baseline (Visit 1);
- the change in the EASI score (0-72) for the four key signs of AD (erythema, induration/papulation, excoriation and lichenification) assessed at Visit 2, 3 and 4, compared to baseline (Visit 1);
- the change in NRS scale at Visit 2, 3 and 4, compared to baseline (Visit 1);
- the change in the CDLQI questionnaire answers at Visit 2, 3 and 4, compared to baseline (Visit 1);
- the adherence to treatment, evaluated by counting the daily applications reported on the patient's diary;
- the use of a rescue medication, as prescribed by the Investigator;
- the patient's/caregiver'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).

Local and general tolerability of Relizema™ cream were assessed by visiting and questioning the patient (or parents/legal guardian) o at visits and were compared to placebo.
Safety endpoints were:

1. the number and type of adverse events (AEs) occurring during the study (seriousness, severity, and relation to study treatment).
2. The local tolerability at the site of administration.

3.2.1.1 Clinical investigation tools description

IGA (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 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 for patients aged ≥ 8 years:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
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)

EASI score calculation for patients aged < 8 years:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	X	X 0.2	
Trunk	(+	+	+	)	X	X 0.3	
Upper extremities	(+	+	+	)	X	X 0.2	
Lower extremities	(+	+	+	)	X	X 0.3	
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 was filled in by the Investigator at each visit.

CDLQI (Children Dermatology Life Quality Index)

CDLQI is a questionnaire used to measure the impact of skin disease on the quality of life of an affected children/person. A specific version for children between 4 and 16 years was compiled while for children below 4 years of age, no questionnaire was to be compiled. However, some questionnaires were compiled by parents also for children below 4 years of age, by mistake. Data from these patients were not entered and not used for the analyses. The questionnaire asks for 10 questions, covering the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, 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 CDQLI was compiled by the patient at each visit. Young children were supported for the questionnaire compilation by the parents/guardian, if necessary.

Patient and Investigator Global Evaluation of Performance

Patients' and Investigator's global evaluation of the performance of the study product 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).

NRS (Numeric Rating Scale) for Itching

The patient/parents/guardian was/were requested to indicate at each visit the average and the worst itching suffered by the patient the same, in the previous 24 hours, by giving a numeric assessment from 0 to 10. Young children were supported for the scale compilation by the

parents/guardian, if necessary. The scale was compiled for youngest children and newborn, by the parents/guardian.

3.2.2 Clinical investigation design

This was a multicenter, double blind, controlled versus placebo, pre-market clinical investigation.

Patients were randomly allocated to one of the following treatment groups:

- Relizema™ cream, topically applied twice a day in all the affected areas for three cycles of 13 (±2) consecutive days.
- Vehicle (placebo), topically applied twice a day in all the affected areas for three cycles of 13 (±2) consecutive days.

Patients started the treatment on the day (Day 1) after the first visit (screening and baseline visit, on Day 0) and continued until the evening before the following visit. On the day of each visit the study product was not applied and it was re-started in the following day. The treatment could have been overall prolonged or shortened of maximum 2 days; in the case intermediate and/or final visits were anticipated or delayed.

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

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

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

Once eligibility of a patient was established, the study treatment was assigned through electronic randomization process based on the eCRF. A computer-generated randomization scheme was provided by the CRO and uploaded into the eCRF. The randomization list was generated using the PROC PLAN of SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Treatments were assigned to patients according to this randomization list.

Patients/parents/guardian, Investigators and site staff persons performing the assessments, the staff of the Sponsor and of the CRO involved in the management of the study and of the data, remained blinded from the time of study start until database lock. The blind was maintained during the study using the following methods:

- indistinguishable test device and placebo
- random treatment assignment

- blinded assessments.

Randomization data, including any documentation identifying the treatment allocation, were kept strictly confidential until the time of the unblinding.

For emergency cases, the treatment assigned to each patient was documented and provided in sealed envelopes, stored for the respective patients at each clinical site in a locked and secure storage facility accessible to the Investigator at all times.

Whenever the code was broken, the patient had to be excluded from the study, the procedures for withdrawals performed, and the fact that the code, including the time, had been opened was to be documented on the eCRF, by the Investigator. However, no code was broken during the clinical investigation.

The blind was broken after all clinical assessments were completed and the database was locked.

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 UNI EN 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 AD are available.

Relizema™ cream is a CE mark medical device already available on the market to treat dermatitis's symptoms such as itching and flushing. In this clinical investigation Relizema™ cream was used in infants from 6 months of age, children and adolescents with mild to moderate atopic dermatitis. The clinical performance of Relizema™ cream in the AD symptoms relief was further confirmed as compared to the vehicle (placebo).

The choice to compare the study product to its vehicle was taken to keep a study design able to evidence the expected beneficial effects of the study product. Placebo was, however, a cream with hydrating properties, without main "active ingredients" of Relizema™ cream.

Relizema™ cream/placebo was recommended twice daily for three cycles of 13 (±2) days each, with treatment suspension only on the visit days. The product's components are known to be safe and well tolerated, therefore no risk seemed to be associated to Relizema™ cream use nor to its placebo.

The only precaution for users was to avoid contact of the study product with eyes and mucous membranes.

Within the clinical investigation the patient/parents/guardian were provided with instructions on the personal hygiene to follow, in order to further improve skin care and safety.

No tests or invasive examinations were foreseen in this study that could increase the risk for participants.

3.2.4 Data quality assurance

During each patient's study visit, the study Investigator or designee collected and reported study data in the relevant patient's chart, documenting all significant observations.
Electronic CRFs (eCRFs) were used to record patient'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 patient, 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 sites and the staff involved and monitored the sites 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. 60 patients were planned to be enrolled in this clinical investigation, selected on the basis of the inclusion/exclusion criteria listed below. Patients were divided into 3 groups: infants from 6 months to 2 years, children from 3 to 11 years and adolescents from 12 to 16 years inclusive. Each site was requested to recruit a minimum of 4 patients in each age group.

Inclusion criteria

1. Release of the written informed consent obtained prior to any study-related procedures, by both the parents/the guardian;
2. Male and female infants, children, adolescent aged between 6 months and 16 years, inclusive;

3. Presence of atopic dermatitis (AD) of mild-moderate severity:
   - IGA score 2 (=mild)

     or
   - IGA score 3 (=moderate)
4. Patients with a baseline score for itch at least 4 on the NRS
5. Patients/parents/guardian able to comprehend the full nature and the purpose of the investigation, 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 patients;
3. Concomitant other skin disorders including skin infections;
4. Use of antibiotics in the past 7 days;
5. History of congenital or acquired immunodepression;
6. Immunologic or infectious disease (e.g. hepatitis, tuberculosis, HIV or AIDS, any typology of lupus, rheumatoid arthritis) which could place the patient at risk or interfere with study results;
7. Use of any topic or systemic drug for dermatitis in the past 10 days;
8. Use of any topic emollient product for dermatitis in the 2 days before study treatment start;
9. Any systemic treatment or procedure that could influence dermatitis activity within the past 30 days (or 5 half-lives);
10. Use of any corticosteroids, immunosuppressant drugs or immunotherapy within the past 30 days (or 5 half-lives);
11. Use of oral antihistamines and antidepressants in the past 30 days;
12. Patients 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;
13. Allergy, sensitivity or intolerance to the components of the investigational device formulations ingredients;
14. Concomitant or previous participation in other interventional clinical study in the past 3 months;
15. Patients planning sun exposure or tanning booths or UV sources throughout the course of the study.

3.2.6 Treatment and treatment allocation schedule

Patients were allocated to Relizema™ cream or to matching placebo (vehicle) according to the randomization system in place. Test device and vehicle were indistinguishable by appearance, smell and other parameters, in order to assure the blinding.

Relizema™ cream and the vehicle were 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 patient received a total of no. 6 tubes containing 100 ml of cream, two per visit, and he/she used a variable amount of cream depending on the extent of the area/s affected by dermatitis to be treated. The quantity of product was enough for the complete treatment as foreseen by the present clinical investigation plan.
Patients were instructed to start using Relizema™ cream / vehicle (placebo) on Day 1, that means the morning after the initial visit. Study product was to be applied on all the affected body areas twice per day, once in the morning and once in the evening before bedtime, for three cycles of 13 (±2 days). The study was to be suspended for 1 day only on the visit days.
No additional creams, moisturizers, lotions or cleansers other than the product provided by the Investigator were permitted. The study product did not have to be applied on the visit days.
In addition to this, throughout the treatment phase, patients 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 patients' 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 the dermatitis
- sun exposure or tanning booths or UV sources.

The patient 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, patients and parents/ guardian received all the information about the study by the Investigator and signed an informed consent form.
All patients/ parents/ guardian were given the opportunity to ask questions and were informed of their right to withdraw from the investigation without prejudice.
At first visit patients were evaluated with regards to the inclusion and exclusion criteria that allowed their participation into the study.

Visit 1 (Day 0): screening, baseline and randomization

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
- NRS for itching
- CDLQI questionnaire
- Randomization
- Study product delivery to patient/ parents/ guardian 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 patient/ parent/ guardian was asked to record, at the end of each day, the study product applications performed with the date and the time of each application.

Visit 2 (Day 14 ± 2) and Visit 3 (Day 28 ± 2) – 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
- Information on any rescue medication for AD used from previous visit
- NRS for itching
- CDLQI questionnaire
- Diary compilation check with the patient for treatment adherence and collection
- New diary delivery
- Study product collection and accountability
- New product delivery
- Adverse events (occurred since previous visit) recording.

The treatment continued from day 1 until the evening before the Visit 2 (hypothetically day 13) and then from day 15 until the evening before the Visit 3 (hypothetically day 27). No treatment was to be applied on the day of the visits.
If Visit 2 was anticipated of one or two days (Day 12 or 13) or postponed of one or two days (Day 15 or 16), within the allowed window, any attempt was to done to plan the following Visit 3 on Day 28.

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
- Information on any rescue medication for AD used from previous visit
- NRS for itching
- CDQLI questionnaire
- Diary compilation check with the patient for treatment adherence and collection
- Study product collection and accountability

- Patient global evaluation of performance
- Investigator global evaluation of performance
- Patient 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 overall treatment days were in the range 40 (as minimum) and 44 (as maximum).

3.2.9 Statistical design, analysis and justifications

The sample size estimation, was based on the primary efficacy endpoint defined as the percentage of patients improved at Visit 3. Improvement to the investigational medical device was defined as an improvement ≥1 point on IGA score in comparison to the baseline visit.
It was estimated that the percentage of patients improved at Visit 3 was equal to 26% in the placebo arm and 80% in the test medical device arm. With a 0.05 two-sided significance level, a sample size of 48 patients in each arm had 90% power to detect the above estimated difference between groups. Estimating a rate of non-evaluable patients up to 20%, the randomization of 60 patients allowed the replacement of non-evaluable patients for any reason.

General Issues

The following populations were defined for this investigation:

- Safety analysis set (SAF): included all patients enrolled who signed informed consent and received at least one administration of the investigational device.
- Full analysis set (FAS): included 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): included all patients of the FAS who also met all inclusion/exclusion criteria and who do not have any major protocol deviation (i.e. wrong inclusion, use of forbidden concomitant medications, etc.). Patients showing a compliance below 80% or over 120% were not considered evaluable to the purpose of clinical performance per-protocol analyses.

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 application, were considered as baseline values. Baseline characteristics of the two groups of patients were compared by Student's t-test or Fisher's Exact test, as appropriate.

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 nor done.

No changes to the planned analysis of the study data were introduced, however the within - group analyses for performance endpoints have been addedd, according to the specifications provided in the relevant SAR v 2.0 of 26/10/2023.The within analyses were done by Wilcoxon signed-rank test.

Descriptive statistics of all relevant variables were performed. Continuous variables were summarized by the number of patients (N), mean, standard deviation, median, minimum, maximum. Categorical variables were summarized by the number (N) and the proportion of patients (%).

The significance level of statistical tests was set at 0.05 for all endpoints.

The normality of distribution of the considered variables was evaluated with Shapiro-Wilks test. In case of normally distributed continuous variables, comparison of the values before-after treatment was evaluated with Student's t-test for paired data and differences were compared between treatment groups with Student's t-test. When appreciable deviation from normality was detected, the non-parametric Wilcoxon signed-rank test and Mann-Whitney U test were used, respectively. In case of categorical variables, differences were compared between treatment groups with Chi-Square test or Fisher's Exact test, as appropriate.

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

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

Pairs of treatment groups were compared to assess if any statistically significant difference was detectable. No adjustment was needed.

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 18th of September 2023).

Demographics and Baseline Characteristics

Demographic and baseline characteristics were analysed by descriptive statistics including number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and number of observations and their percentages for categorical parameters. Fisher's Exact Test was used to compare the distribution of the gender and the age category between groups. Age of the two groups of patients was compared using Student's t-test. Other baseline characteristics of the two groups of patients were compared using Fisher's Exact Test.

Performance Analysis

Primary Endpoint

The primary endpoint was assessed at Visit 3 by comparing, between groups, the proportion of responders (patients with IGA ≥ 1 decrease). Fisher's Exact Test was applied. The percentage of responders was also compared to a referent percentage (50%, taken as the best response possible using vehicle only) using the exact binomial test. Additionally, the distribution of patients within each IGA category was described using descriptive statistics and Mann-Whitney U Test was used to assess a significant change in IGA from baseline to Visit 3.

Secondary Endpoints

1) The proportion of responders (decrease in IGA ≥ 1) in the two groups, assessed at Visit 2, compared to baseline (Visit 1). Fisher's Exact Test was applied. The percentage of responders was also compared to a referent percentage (50%, taken as the best response possible using vehicle only) using the exact binomial test. Additionally, the distribution of patients within each IGA category was described using descriptive statistics and Mann-Whitney U Test was used to assess a significant change in IGA from baseline to Visit 2.
2) The proportion of responders (decrease In IGA ≥ 1) assessed at Visit 4, compared to baseline (Visit 1). Comparison between groups was analyzed using Fisher's Exact Test. The percentage of responders was also compared to a referent percentage (50%, taken

as the best response possible using vehicle only) using the exact binomial test. Additionally, the distribution of patients within each IGA category was described using descriptive statistics and Mann-Whitney U Test was used to assess a significant change in IGA from baseline to Visit 4.

3) The change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in EASI score**.** EASI score was described using descriptive statistics and Mann-Whitney U Test was used to assess a significant change from baseline to each time point. Mann-Whitney U test was used for the comparison between groups instead of Student's t-test, because the variable was not normally distributed**.**
4) The change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in NRS (Numerical Rating Scale) scale. NRS rating (Mean itching rating and Worst itching rating) was described using descriptive statistics and Student's t-test (or Mann-Whitney U Test in case of non-normal distribution) was used to assess a significant change from baseline to each time point.
5) The change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in CDLQI score. CDLQI score was described using descriptive statistics and Student's t-test (or Mann-Whitney U Test in case of non-normal distribution) was used to assess a significant change from baseline to each time point.
6) Patient's adherence to treatment. Treatment compliance was described using descriptive statistics and Student's t-test was used for the comparison between groups. Also, the treatment days were described using descriptive statistics and the same test was used for the comparison between groups.
7) Proportion of patients using rescue medication during investigation. The distribution of patients was described using descriptive statistics and Chi-square test/Fisher's exact test was used for the comparison between groups.
8) Subject's and Investigator's global evaluation on performance of the study product at the end of the study (Visit 4) by means of a 7-items scale. The distribution of patients within each performance category was described using descriptive statistics and Fisher's Exact Test was used to compare treatment groups.

With regard to treatment compliance, it was assessed by counting the number of applications performed, recorded in the patient's diaries. The number of expected applications was estimated based on the treatment duration x 2 times, excluding the day of each visit at the clinical site.

The following formula was used:

$$\frac{Number\ of\ applications\ performed}{Number\ of\ applications\ expected} * 100$$

Treatment compliance was estimated by arithmetic mean of compliances for each period. The patient was considered compliant to the treatment if the arithmetic mean of compliances was between 80% and 120%.

Safety Analysis

Extent of Exposure

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

Adverse Events

The safety analysis included all adverse events occurred during the study.

The number of patients 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 patients withdrawn due to AE was summarized through number (N) and proportion of patients (%).

Adverse events were coded using the version 26.0 of the Medical Dictionary for Regulatory Activities (MedDRA) to give a preferred term (PT) and a system organ class (SOC) for each event and summarized by treatment group.

Local tolerability at the site of administration was carefully considered.

4. Results

4.1 Clinical investigation initiation date

The clinical investigation involved three clinical sites in Italy:

- Site 01 - Dermatology Unit, Santa Maria della Misericordia Hospital, P.le Menghini, 3 - 06129 Perugia. PI Prof. Luca Stingeni
- Site 02 – Dermatology Unit, Presidio Ospedaliero Gaspare Rodolico, AOU Policlinico “G. Rodolico-San Marco”, Via S. Sofia, 78 - 95123 Catania. PI Prof. Giuseppe Micali
- Site 03 - Dermatology Unit, A.O.U "Federico II" di Napoli, Via Sergio Pansini, 5 - 80131 Napoli. PI Prof. Massimiliano Scalvenzi

The first Ethics Committee (EC) favourable opinion was obtained on the 27-Oct-2021 for site 01, the second one on the 10-Dec-2021 for site 03 and the third one on the 20-Dec-2021 for site 02. The National Competent Authority, the Italian Ministry of Health authorized the study conduction on the 27-Jan-2022. Following the completion of authorization process, with sites’ contracts signature, sites were initiated: the site 01 was initiated on the 13-Sept-2022, site 02 on the 11-Oct-2022 and site 03 on 05-Sept-2022.

The first patient (FPI) was enrolled on 27-Oct-2022 and on 03-Nov-2022 the study start was notified to the Ministry of Health.

4.2 Clinical investigation completion/suspension date

The last patient in (LPI) was enrolled on the 27-Apr-2023 and the last patient out (LPO) visit was on 09-Jun-2023. The enrolment period was initially planned of 3 months (end October 2022 – end January 2023) and subsequently it was prolonged of 3 further months (up to end of April 2023). Due to planned enrolment period expiration and due to the summertime incoming (season when AD spontaneously improves) the Sponsor decided not to further extend such deadline. The clinical investigation was regularly closed at the expiration of the timing foreseen for enrolment, also considering that the number of evaluable patients had been reached.

The last clinical site (site 01) was officially closed on 19-Sep-2023.

The clinical investigation conclusion (LPO as for protocol definition) was regularly notified to the National Competent Authority.

4.3 Disposal of subjects and investigational devices

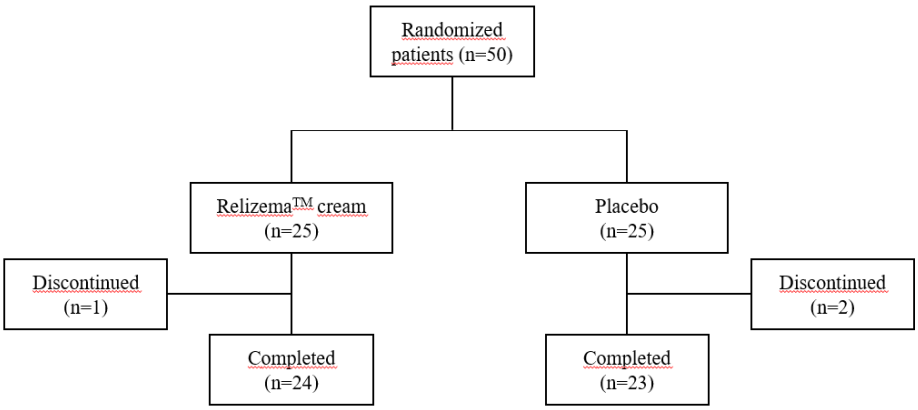
A total of 50 patients were randomized in the study and 47 of them completed the study (24 Relizema™ cream group and 23 Placebo group).

The enrolment phase of the study lasted 6 months: the first patient signed the informed consent and performed the Visit 1 on 27-Oct-2022 and the last patient on 27-Apr-2023.

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

Overall, the study lasted about 7,5 months.

Figure 1. *Patients disposition*



Source: Table 1.1 and Listing 1.

All 50 patients were randomized: 25 patients were treated with Relizema™ cream and 25 patients were treated with Placebo.

Three patients withdrew from the study between V1 and V4:

- Patient ID 03-009, randomized to Relizema™ cream group was lost to follow-up after Visit 1 (no data was available after V1);
- Patient ID 02-004 randomized to Placebo group interrupted the study after Visit 2 because of a Serious Adverse Event;
- Patient ID 02-006, randomized to Placebo group withdrew the consent after Visit 2.

Table 1.1 and Listing 1 show the Subjects' disposition and the list of discontinued subjects. Based on that, 47 subjects, out of 50, regularly completed the study (24 in Relizema™ cream group and 23 in Placebo group).

4.4 Subject demographics

Out of 50 patients enrolled, 19 patients were female and 31 were male: in Relizema™ cream group 10 patients (40.0%) were female and 15 patients (60.0%) were male; in Placebo group 9 patients (36.0%) were female and 16 patients (64.0%) were male. No statistically significant difference was detected for gender between groups.

No statistically significant difference was detected for age between groups: mean age (SD) 6.72 (4.97) years, median 6.33 years in Relizema™ cream group and mean age (SD) 6.62 (4.45) years, median 6.42 years in Placebo group.

Patients were also distributed into three age categories: from 6 months to 2 years, from 3 to 11 years and from 12 to 16 years as shown in Table 1 below. Again, the age categories were homogeneous between groups.

Table 1. *Patients distribution per age category*

	6 months – 2 years	**3 years – 11 years**	**12 years – 16 years**
Relizema™ cream group	n=8 (32.0%)	n=10 (40.0%)	n=7 (28.0%)
Placebo group	n=5 (20.0%)	n=16 (64.0%)	n=4 (16.0%)
Total	n=13 (26.0%)	n=26 (52.0%)	n=11 (22.0%)

Source: Table 1.3 and Listing 4.1

The body areas most affected by atopic dermatitis were "Face, Legs, Arms, Trunk": 15 patients (60.0%) in Relizema™ cream group and 16 patients (64.0%) in Placebo group. The remaining 19 patients were evenly distributed among the other body area. No statistically significant difference was detected between groups. Finally, the analysis of atopic dermatitis year of onset

showed no statistically significant difference between the two groups: patients were evenly distributed among the years, from 2008 to 2023.

Demographic data are reported in Table 1.3 and baseline AD characteristics in Table 1.4. Details are respectively in Listing 4.1 and 4.4

The medical history and the surgical history of the patients are reported in Table 1.5 and Table 1.6, respectively (details are in Listings 4.2 and 4.3). Only 2 patients (8.0%) in Placebo group had at least one significant medical condition (food allergy and milk allergy) and only 1 patient (4.0%) in Placebo group underwent surgery (orchidopexy) in the past. No noteworthy differences between treatment groups were detected.

4.5 CIP compliance

A total of 60 protocol deviations occurred during the study, 31 in Relizema™ cream group and 29 in Placebo group. Overall, 20 patients (40.0%) had at least one protocol deviation: 11 patients (44.0%) in Relizema™ cream group and 9 patients (36.0%) in Placebo group.
All deviations were evaluated as minor (Table 1.2) therefore no protocol deviation caused the exclusion of any subject from the study populations for analyses.
Details about protocol deviations by patient are reported in the Listing 2.
The majority of protocol deviations were related to treatment compliance (90.3% and 93.1% respectively in Relizema™ cream and Placebo groups) and a minority were related to delay in scheduled visits (6.5% and 6.9% respectively in Relizema™ cream and Placebo groups).

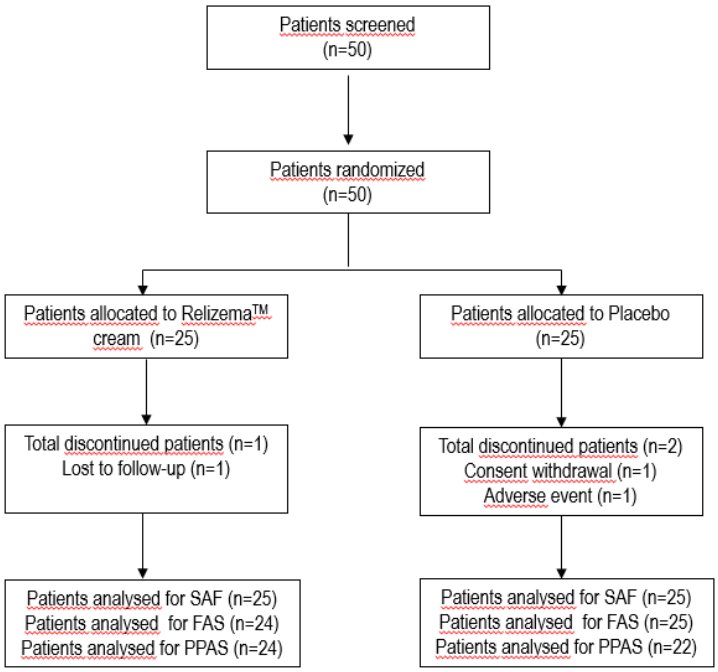
4.6 Analysis

Overall, 50 patients were screened and randomized to treatment: 25 to Relizema™ cream and 25 to Placebo.
Primary and secondary performance endpoints were analyzed on the Full Analysis Set (FAS) population: 49 patients in total, 24 in Relizema™ cream group (patient ID 03-009 was excluded because no data was available after initial visit) and 25 in Placebo group.
Additionally, the primary endpoint was analyzed on the Per-Protocol Analysis set (PPAS) made of 46 patients:

- patient ID 03-009 randomized to Relizema™ cream was excluded from PPAS because no data was available after initial visit;
- patients ID 02-004, 02-006 randomized to Placebo were excluded because they drop out from the study after second visit;
- patient ID 01-020 randomized to Placebo was excluded because of poor treatment compliance (<80%).

Safety endpoints were analyzed on the Safety Analysis Set (SAF) population (i.e 50 patients). The distribution of populations used for the statistical analysis is reported in the Listing 3 and summarized in the Figure 2 below.

Figure 2. *Patients disposition for analysis*



4.6.1 Primary endpoint performance analysis

The primary endpoint was the proportion of responders (decrease in IGA ≥ 1) assessed at Visit 3, compared to baseline (Visit 1).

According to the clinical investigation plan, at Visit 1 the patients were distributed into two categories of IGA: “Mild” and “Moderate”, based on the severity of dermatitis.

In FAS population (Table 2.1.1), at baseline 19 patients (79.2%) in Relizema™ cream group and 17 patients (68.0%) in Placebo group had mild dermatitis, while 5 patients (20.8%) in Relizema™ cream group and 8 patients (32.0%) in Placebo group had moderate dermatitis. No statistically significant difference in baseline AD severity between groups was detected.

At Visit 3 patients were split between the IGA categories:

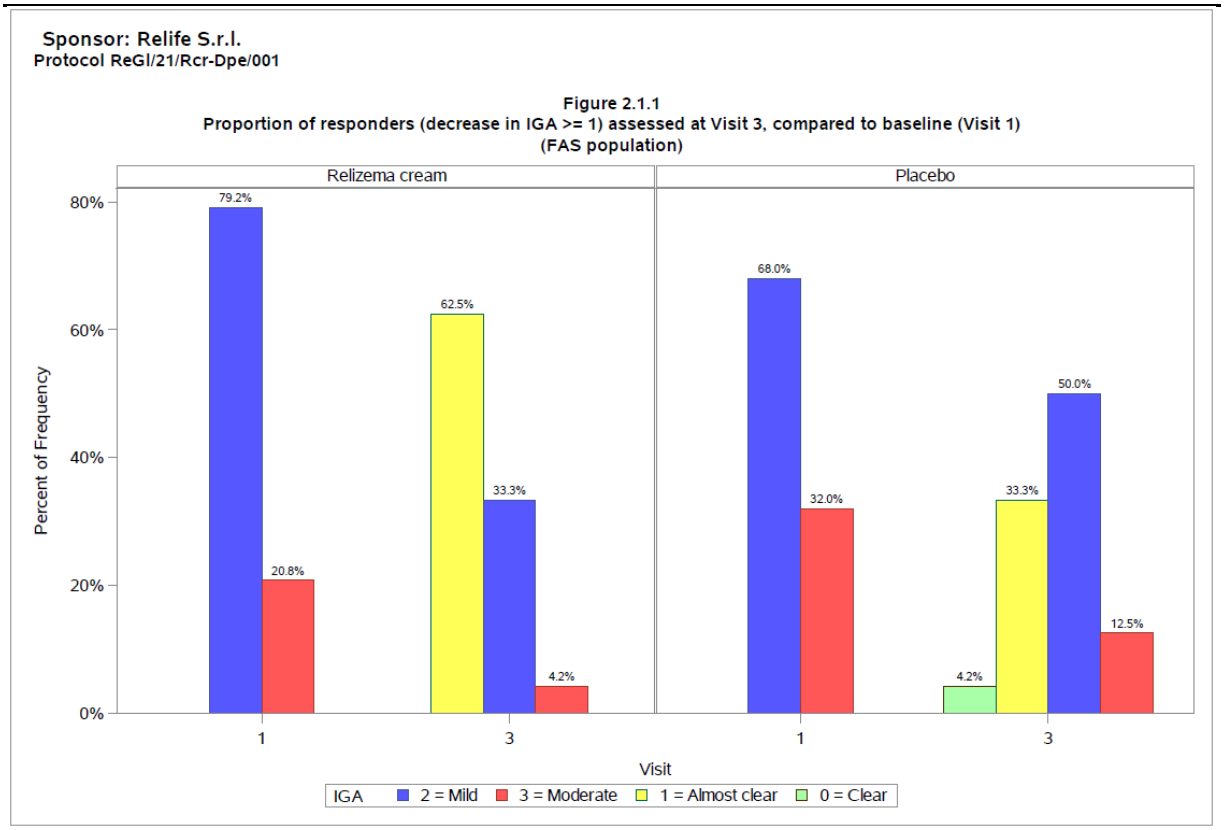
- 15 patients (62.5%) in Relizema™ cream group and 8 patients (33.3%) in Placebo group had “Almost clear” IGA,
- 8 patients (33.3%) in Relizema™ cream group and 12 patients (50.0%) in Placebo group had “Mild” IGA;
- 1 patient (4.2%) in Relizema™ cream group and 3 patients (12.5%) in Placebo group had “Moderate” IGA;

Only 1 patient in Placebo group had “Clear” IGA.

In both groups an improvement was evident, more noticeable with Relizema™ cream treatment, but no statistically significant difference between groups was detected (p value= 0.1855).

The change of IGA between Visit 1 and Visit 3 was compared between groups using Mann-Whitney U Test: mean (SD)= -0.79 (0.59), median= -1.00 in Relizema™ cream group and mean (SD)= -0.63 (0.71), median= -1.00 in Placebo group. Within each group the change of IGA from Visit 1 to Visit 3 was statistically significant (p value<0.0001* in Relizema™ cream treatment and p value=0.0009* in Placebo group) and no statistically significant difference between groups was observed (p value= 0.4021).

The proportion of responders (decrease in IGA >= 1) was described using the number (N) and the percentage of patients (%). The number of responders was 17 (70.8%) in Relizema™ cream group and 15 (60.0%) in Placebo group; consequently 7 patients (29.2%) in Relizema™ cream group and 10 patients (40.0%) in Placebo group were not responder. The proportion of responders was statistically significant only within Relizema™ cream group (p value=0.0412*; p-value from an Exact binomial test with null hypothesis proportion = 50% vs alternative proportion ≠ 50%) while it was not within Placebo group (p value =0.3173). The difference between treatment groups was not statistically significant (p value= 0.5512).
Figure 2.1.1 shows the IGA distribution at Visit 1 and 3 by groups for the FAS population.



The same analysis was performed on the PPAS population and similar conclusions were drawn.

In PPAS population (Table 2.1.2), at baseline 19 patients (79.2%) in Relizema™ cream group and 14 patients (63.6%) in Placebo group had mild dermatitis, while 5 patients (20.8%) in Relizema™ cream group and 8 patients (36.4%) in Placebo group had moderate dermatitis. No statistically significant difference in baseline AD severity between groups was detected.
At Visit 3 patients were split between the IGA categories:

- 15 patients (62.5%) in Relizema™ cream group and 7 patients (31.8%) in Placebo group had “Almost clear” IGA,
- 8 patients (33.3%) in Relizema™ cream group and 11 patients (50.0%) in Placebo group had “Mild” IGA;
- 1 patient (4.2%) in Relizema™ cream group and 3 patients (13.6%) in Placebo group had “Moderate” IGA;

Only 1 patient in Placebo group had “Clear” IGA.

As well as for FAS analysis, in both groups an improvement was evident, more noticeable in Relizema™ cream group, but no statistically significant difference between groups was detected (p value= 0.1346).

The change of IGA between Visit 1 and Visit 3 was compared between groups using Mann-Whitney U Test: mean (SD)= -0.79 (0.59), median= -1.00 in Relizema™ cream group and mean (SD)= -0.64 (0.73), median= -1.00 in Placebo group. The within-groups analysis showed a statistically significant change of IGA from Visit 1 to Visit 3 in both groups (p value<0.0001* within Relizema™ cream treatment and p value=0.0016* in Placebo group) and no statistically significant difference between groups was observable (p value= 0.4564).

The number of responders was 17 (70.8%) in Relizema™ cream group and 13 (59.1%) in Placebo group; consequently 7 patients (29.2%) in Relizema™ cream group and 9 patients (40.9%) in Placebo group were not responder. The proportion of responders was statistically significant only within Relizema™ cream group (p value=0.0412*; p-value from an Exact binomial test with null hypothesis proportion = 50% vs alternative proportion ≠ 50%) while it was not within Placebo group (p value =0.3938). The difference between treatment groups was not statistically significant (p value= 0.5379).
Likewise, figure 2.1.2 shows the IGA distribution at Visit 1 and 3 by groups for the PPAS population.

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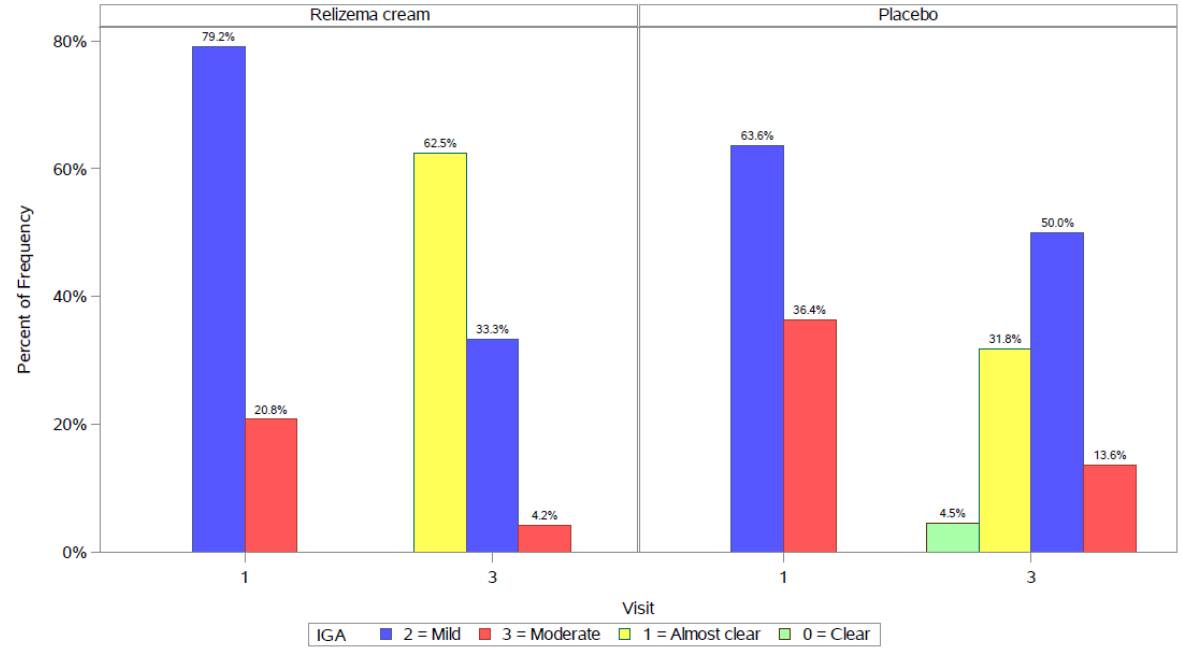
Protocol ReGI/21/Rcr-Dpe/001

Figure 2.1.2
Proportion of responders (decrease in IGA >= 1) assessed at Visit 3, compared to baseline (Visit 1)
(PPAS population)



4.6.2 Secondary endpoints performance analysis

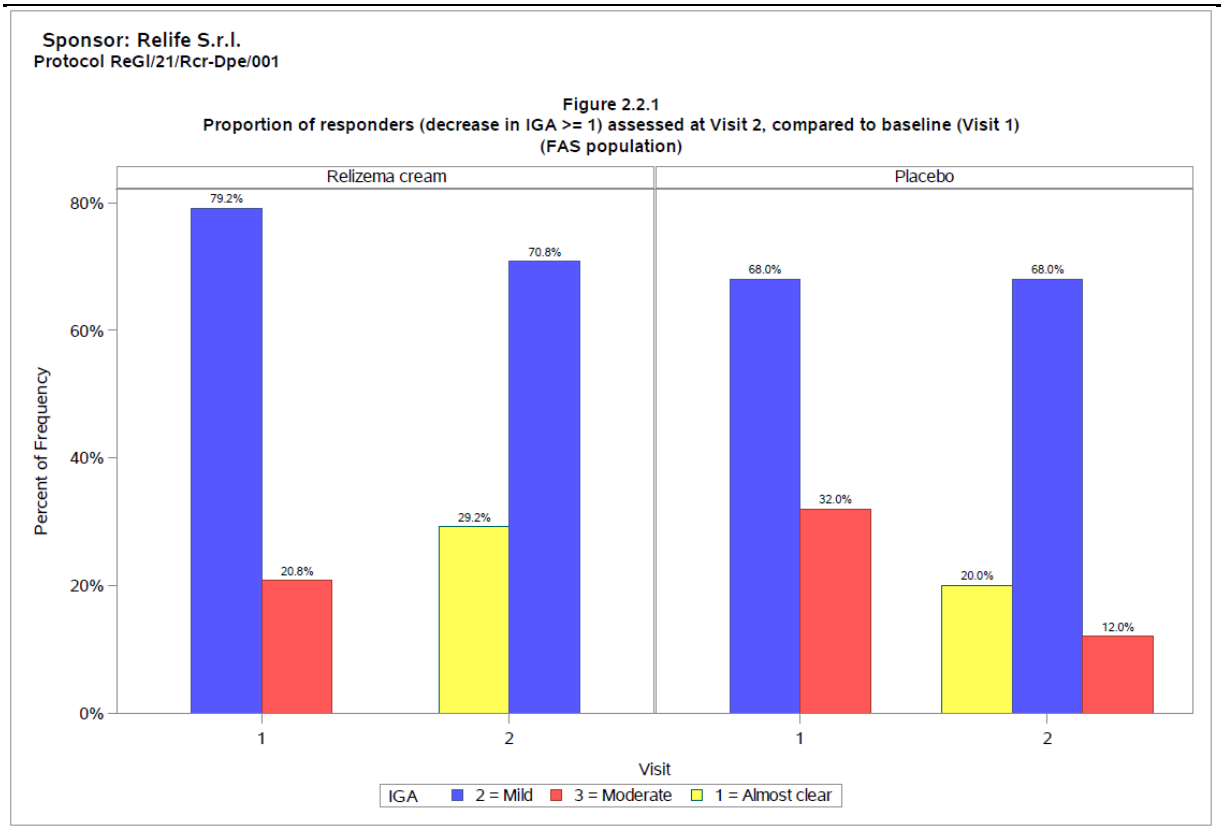
Secondary endpoints analysis was conducted on the FAS population only.

Proportion of responders (decrease in IGA ≥ 1) assessed at Visit 2, compared to baseline (Visit 1)

At Visit 2 patients were split between the IGA categories: 7 (29.2%) patients treated with Relizema™ cream and 5 (20.0%) patients treated with Placebo had “Almost clear” IGA, 17 (70.8%) patients treated with Relizema™ cream and 17 (68.0%) patients treated with Placebo had “Mild” IGA and the remaining 3 patients (12.0%) treated with Placebo had “Moderate” IGA. No statistically significant difference between groups was detected (p value=0.2739).

The change of IGA between Visit 1 and Visit 2 was compared between groups using Mann-Whitney U Test: mean change (SD)= -0.50 (0.51), median= -0.50 in Relizema™ cream group and mean change (SD)= -0.40 (0.65), median= 0.00 in Placebo group. The within-groups analysis showed a statistically significant change of IGA from Visit 1 to Visit 2 in both groups (p value=0.0005* within Relizema™ cream group and p value=0.0107* within Placebo group). No statistically significant difference was detected (p value= 0.5020) between the two groups.

The proportion of responder (decrease in IGA >= 1) was described using the number (N) and the percentage of patients (%). The number of responders was 12 (50.0%) in Relizema™ cream group and 10 (40.0%) in Placebo group; consequently 12 patients (50.0%) in Relizema™ cream group and 15 patients (60.0%) in Placebo group were not responder. The proportion of responders was not statistically significant within each treatment group, at Visit 2. The difference between treatment groups was not statistically significant (p value= 0.5709). Table 2.2.1 and the below Figure 2.2.1 show the IGA distribution at Visit 1 and 2 by groups.



Proportion of responders (decrease in IGA ≥ 1) assessed at Visit 4, compared to baseline (Visit 1)

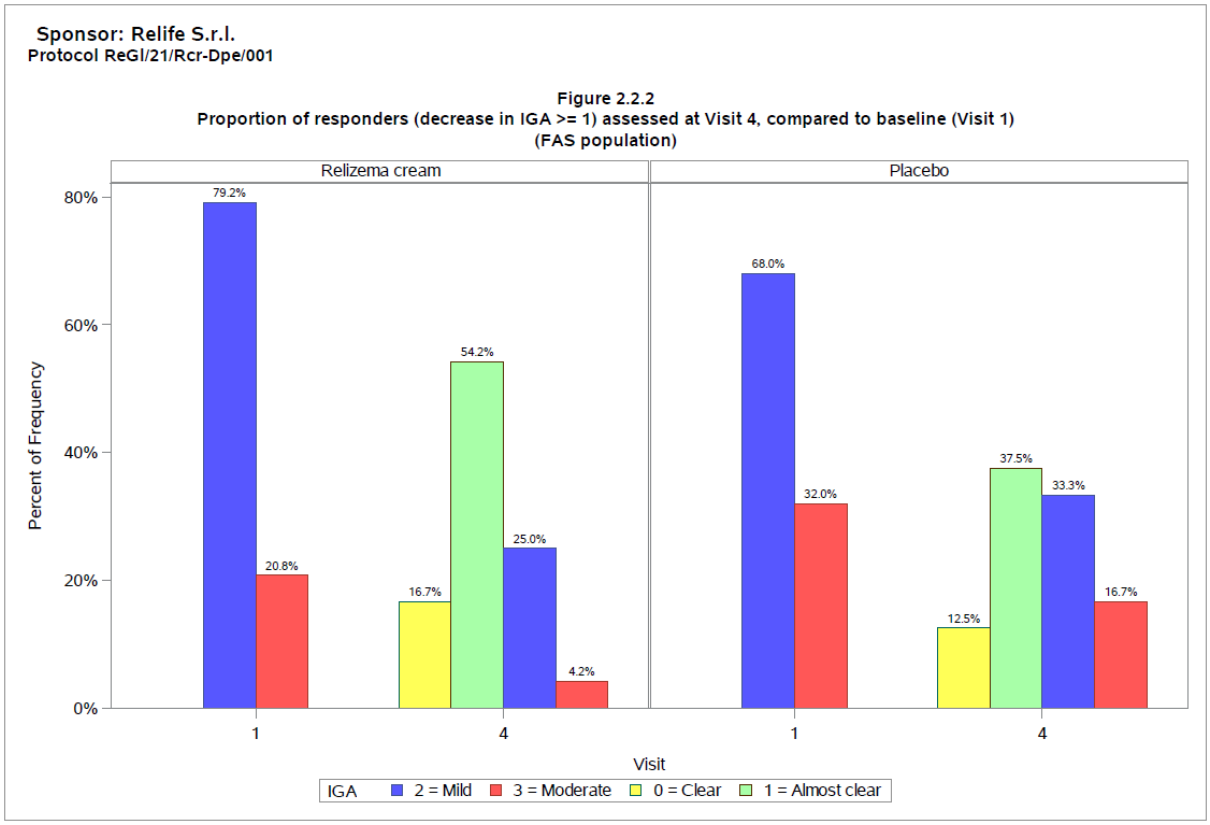
As shown in Table 2.2.2, at Visit 4 patients were split between the IGA categories: 4 (16.7%) patients treated with Relizema™ cream and 3 (12.5%) patients treated with Placebo had "Clear" IGA, 13 (54.2%) patients treated with Relizema™ cream and 9 (37.5%) patients treated with Placebo had "Almost clear" IGA, 6 (25.0%) patients treated with Relizema™ cream and 8 (33.3%) patients treated with Placebo had "Mild" IGA and the remaining 5 patients (1 in Relizema™ cream group and 4 in Placebo group) had "Moderate" IGA. No statistically significant difference between groups was observed (p value=0.4198).

The change of IGA between Visit 1 and Visit 4 was compared between groups using Mann-Whitney U Test: mean change (SD)= -1.04 (0.75), median= -1.00 in Relizema™ cream group and mean change (SD)= -0.79 (0.83), median= -1.00 in Placebo group. The within-groups analysis showed a statistically significant change of IGA from Visit 1 to Visit 4 in both groups (p value<0.0001* in Relizema™ cream group and p value=0.0002* in Placebo group) and no statistically significant difference between groups was observable (p value=0.2632).

The proportion of responder (decrease in IGA >= 1) was described using the number (N) and the percentage of patients (%). The number of responders was 18 (75.0%) in Relizema™ cream group and 14 (56.0%) in Placebo group; consequently 6 patients (25.0%) in Relizema™

cream group and 11 patients (44.0%) in Placebo group were not responder. The proportion of responders was statistically significant only within Relizema™ cream group (p value=0.0143*; p-value from an Exact binomial test with null hypothesis proportion = 50% vs alternative proportion ≠ 50%) while it was not within Placebo group (p value =0.5485). The difference between treatment groups was not statistically significant (p value=0.2321).

Figure 2.2.2 shows the IGA distribution at Visit 1 and 4 by groups.



Change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in EASI (Eczema Area and Severity Index) score

As shown in Table 2.2.3, EASI score decreased in both treatment groups between Visit 1 and Visit 2: mean change (SD)= -3.13 (4.70), median= -1.15 in Relizema™ cream group and mean change (SD)= -3.32 (5.54), median= -1.20 in Placebo group. The change within each treatment group was statistically significant (p value< 0.0001* in both groups) and the difference between treatment groups was not statistically significant (p value=0.8101).

The analysis of EASI score between Visit 1 and Visit 3 provided similar results: mean change (SD)= -4.30 (5.51), median= -2.50 in Relizema™ cream group and mean change (SD)= -4.64 (6.04), median= -2.05 in Placebo group and again the change within each treatment group

was statistically significant (p value<0.0001* in both groups) and the difference between groups was not statistically significant (p value=0.9343).

Similar conclusions can be drawn for the change of EASI score between Visit 1 and Visit 4: mean change (SD)= -5.45 (6.62), median =-2.95 in Relizema™ cream group and mean change (SD)= -4.31 (6.26), median= -2.80 in Placebo group. Again, the change within each treatment group was statistically significant (p value< 0.0001* in Relizema™ cream group and p value=0.0003* in Placebo group) and no difference was observed between groups (p value=0.7259).

Change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in NRS (Numerical Rating Scale)

The itching was evaluated using the Numeric Rating Scale; at each visit the patient indicated the average and the worst itching suffered. The analysis was performed on both indices: mean itching rating and worst itching rating (Table 2.2.4).

Mean itching rating

Mean itching rating decreased in both treatment groups between Visit 1 and Visit 2: mean change (SD)= -0.96 (1.16), median= -1.00 in Relizema™ cream group and mean change (SD)= -0.50 (1.25), median= 0.00 in Placebo group. The change was statistically significant only within Relizema™ cream group (p value=0.0007*; in Placebo group p value was 0.0546) and the difference between the two treatment groups was not statistically significant (p value=0.2404).

The analysis of the mean itching rating between Visit 1 and Visit 3 provided similar results: mean change (SD)= -1.58 (1.21), median= -2.00 in Relizema™ cream group and mean change (SD)= -1.26 (1.66), median= -1.00 in Placebo group. The change was statistically significant within each treatment group (p value<0.0001* in Relizema™ cream group and p value=0.0034* in Placebo group) and again the difference between groups was not statistically significant (p value=0.4579).

Similar conclusions were drawn for the change of itching rating between Visit 1 and Visit 4: mean change (SD)= -2.42 (1.67), median= -2.50 in Relizema™ cream group and mean change (SD)= -1.83 (1.86), median= -2.00 in Placebo group. The change was statistically significant within each treatment group (p value<0.0001* in Relizema™ cream group and p value=0.0001* in Placebo group) and the difference between groups was not statistically significant (p value=0.2580).

Worst itching rating

Worst itching rating decreased in both treatment groups between Visit 1 and Visit 2: mean change (SD)= -1.21 (1.41), median= -1.00 in Relizema™ cream group and mean change (SD)= -0.63 (1.17), median= 0.00 in Placebo group. The change was statistically significant within each treatment group (p value=0.0002* in Relizema™ cream group and p value= 0.0239* in Placebo group) and the difference between treatment groups was not statistically significant (p value=0.1746).

The analysis of the worst itching rating between Visit 1 and Visit 3 provided similar results: mean change (SD)= -1.96 (1.49), median= -2.00 in Relizema™ cream group and mean change (SD)= -1.65 (1.40), median= -2.00 in Placebo group. The change was statistically significant within each treatment group (p value<0.0001* in both groups) and again the difference between groups resulted not statistically significant (p value=0.5032).

Similar conclusions can be drawn for the change of worst itching rating between Visit 1 and Visit 4: mean change (SD)= -2.63 (2.34), median =-2.50 in Relizema™ cream group and mean change (SD)= -2.00 (1.62), median= -2.00 in Placebo group. The change was statistically significant within each treatment group (p value<0.0001* in both groups) and also at Visit 4 the difference between groups was not statistically significant (p value=0.3563).

Change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in CDLQI (Children Dermatology Life Quality Index) score

The analysis of quality of life results is reported in Table 2.2.5.

CDLQI score decreased in both treatment groups between Visit 1 and Visit 2: mean change (SD)= -2.29 (2.52), median= -1.50 in Relizema™ cream group and mean change (SD)= -1.28 (2.22), median= 0.00 in Placebo group. The change was statistically significant within each treatment group (p value=0.0078* in Relizema™ cream group and p value= 0.0273* in Placebo group) and the difference between treatment groups was not statistically significant (p value=0.2612).

The analysis of CDLQI score between Visit 1 and Visit 3 provided similar results: mean change (SD)= -3.86 (4.33), median= -1.50 in Relizema™ cream group and mean change (SD)= -2.56 (2.94), median= -1.50 in Placebo group. The change was statistically significant within each treatment group (p value=0.0010* in Relizema™ cream group and p value= 0.0002* in Placebo group) and again the difference between groups was not statistically significant (p value=0.5360).

Similar conclusions were drawn for the change of CDLQI score between Visit 1 and Visit 4: mean change (SD)= -5.29 (4.73), median= -3.00 in Relizema™ cream group and mean change (SD)= -3.53 (4.00), median= -2.00 in Placebo group. The change was statistically significant

within each treatment group (p value=0.0005* in Relizema™ cream group and Placebo group) and no statistically significant difference was observed between groups (p value=0.2138).

Patient's adherence to treatment

Treatment compliance was summarized by the number of patients (N), mean, standard deviation, median, minimum, maximum. As shown in Table 2.2.6 treatment compliance was generally very high in both treatment groups: mean (SD)= 97.46 (5.13)%, median 100.00% in Relizema™ cream group and mean (SD)= 96.96 (7.32)%, median= 100.00% in Placebo group. The difference between groups was not statistically significant (p value=0.9183).

Also, treatment days were summarized: in Relizema™ cream group the average days of treatment was 39.50 (SD=1.25), with a minimum of 37.00 days and a maximum of 43.00 days, while in Placebo group the average days of treatment is 38.28 (SD=5.99), with a minimum of 13.00 days (mainly due to patient 02-004 who withdrew after Visit 2 due to a SAE), and a maximum of 43.00 days. The difference between groups was not statistically significant (p value=0.6505).

With a high level of certainty, it can be concluded that treatment days approximate the duration of exposure to treatment, as both groups have high compliance.

Proportion of patients using rescue medication during investigation

As shown in Table 2.2.7 no patients in both groups used rescue medication during the investigation.

Subject's and Investigator's Global Evaluation on performance of the study product at the End of the Study (Visit 4)

At the End of Study the clinical performance of the study product was evaluated by means of a 7-items scales by the investigator and by the subject (Table 2.2.8).

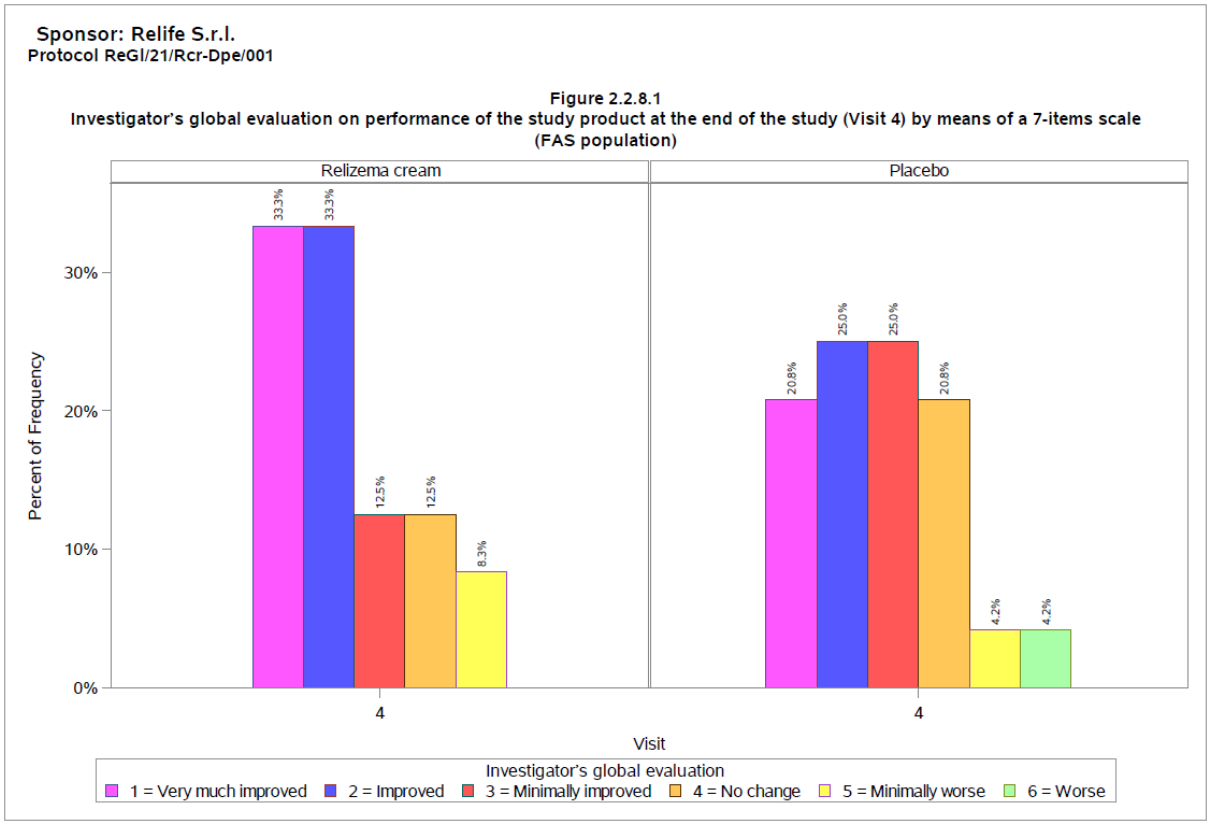
Investigator's Global Evaluation of Performance

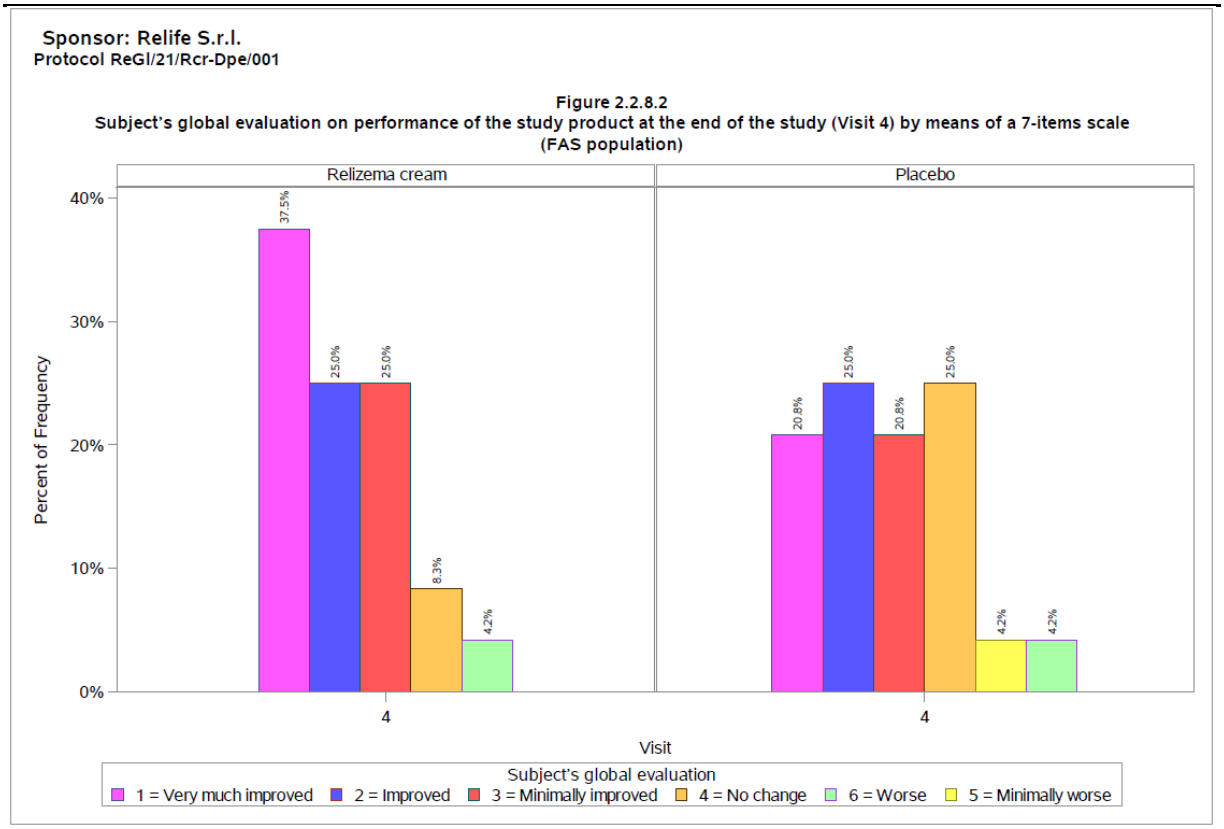
Patients were split between almost all the items on the scale. The investigator evaluated the patients' condition after treatment "Very much improved" / "Improved" / "Minimally improved" for 19 (79.1%) patients treated with Relizema™ cream and for 17 (70.8%) patients treated with Placebo. No change in dermatitis was observed by the investigator in 3 (12.5%) patients treated with Relizema™ cream and in 5 (20.8%) patients treated with Placebo. For the remaining 2 patients in Relizema™ cream group and 2 patients in Placebo group the investigator evaluated their condition "Minimally worsened" / "Worsened" after treatment. No statistically significant difference between groups was observed (p value=0.6476).

Subject's Global Evaluation of Performance

Likewise, the clinical performance of the study product was evaluated by the patient (parents/guardian) and similar conclusions can be drawn. Overall, 21 (87.5%) patients of Relizema™ cream group and 16 (66.6%) patients of Placebo group evaluated their disease "Very much improved" / "Improved" / "Minimally improved" after the treatment received. Two patients (8.3%) treated with Relizema™ cream and 6 (25.0%) of patients treated with Placebo observed no change on the dermatitis severity; finally, 1 patient (4.2%) of Relizema™ cream group and 2 (8.4%) patients of Placebo group evaluated their dermatitis as "Minimally worsened" / "Worsened" after the treatment. Again, no statistically significant difference between groups was detected (p value=0.5172).

Figures 2.2.8.1 and 2.2.8.2 shows the Investigator's and Subject's Global Evaluation on performance of the study product at the End of the Study by groups.





4.6.3 Safety analysis

Safety analysis was conducted on the Safety population (i.e. 50 subjects).

Only 2 adverse events occurred to 2 patients during the study. None of the adverse events occurred was evaluated as related to the study treatment, by the Investigator.

One event was serious, not related to study treatment and leading to study premature discontinuation: patient ID 02-004, randomized to placebo, had a bacterial gastroenteritis requiring hospitalization. The event was resolved but the patient withdrew from the study.

The second event was of mild intensity and not related to study treatment: patient ID 01-002, randomized to Relizema™ cream group, had a limb injury. The patient continued the study and at the time of study conclusion the event was not yet resolved, but stable.

Safety analysis is reported in Tables 3.1 and 3.2 and safety details are in Listing 7.

According to clinical investigation plan, adverse events were coded using the MedDRA dictionary; Table 3.2 shows the two adverse events summarized by body system and preferred terms.

5. Discussion and overall conclusions

Atopic dermatitis (AD) is a long-term (chronic) cutaneous inflammatory disease, very common condition in babies and children. Depending on the severity of the disease, symptoms can

include erythema, dry, scaly skin, itching, redness and swelling, thickened skin, pale skin on the face, small-raised bumps that may become crusty and leak fluid if scratched, rough bumps on the face, upper arms, and thighs, darkened skin, lichenification etc. Importantly, the disease can cause significant sleep disruption and impact the quality of life of patients and families. Since there is no curative etiological therapy for AD, the aim of all therapeutic interventions is the is the control and relief of symptoms and prevention of flare-ups.

Currently available pharmacologic treatments for dermatitis management include the topical corticosteroids or immunosuppressants, which have a significant efficacy but are also associated with high incidence of transient skin reactions and, for this reason, are generally not recommended for the young children.

There is strong evidence that the use of topical moisturizers, emollients and protective agents can reduce the need for pharmacologic intervention to treat AD symptoms and are particularly recommended in young patients. Relizema™ cream is a dermatological cream for topical use indicated for the treatment of itching, and flushing associated with dermatitis, including atopic and contact dermatitis and/or erythema. Thanks to its derma-protective action it helps maintaining and restoring the physiological skin barrier.

This pre-market clinical investigation was aimed to evaluate the clinical benefit of Relizema™ cream in infants, children and adolescents suffering for AD symptoms. To assess in objective way the effects of Relizema™ cream in the relief of AD symptoms, it was compared to placebo (vehicle) in a double-blind designed study.

The proportion of responder (decrease in IGA >= 1) at Visit 3 (i.e. after 28 days of treatment) was the primary performance endpoint. The 70.8% of patients in Relizema™ cream group was responders while only the 60.0% in Placebo group was. The analysis repeated on PPAS showed the same result, with the 70.8% of patients in in Relizema™ cream group and the 59.1% in Placebo group responders. The difference between treatment groups was not statistically significant (Table 2.1.1 and 2.1.2) but the within group analysis showed that Relizema™ cream has a pronounced and statistically significant clinical performance (proportion of responders p value=0.0412*).

Also, the proportion of responders analysed at Visit 2 and Visit 4 (i.e. after 2 and 6 weeks of treatment) showed the 50.0% of responders in Relizema™ cream group and the 40.0% in Placebo group at Visit 2 (Table 2.2.1) and the 75.0% in Relizema™ cream group and 56.0% in Placebo group at Visit 4 (Table 2.2.2). No statistically significant difference between groups was observable but the within groups analysis evidenced the marked and statistically significant clinical performance of Relizema™ cream, at Visit 4 (proportion of responders: p value=0.0143*).

EASI score decreased in both treatment groups in similar and statistically significant way: mean changes from baseline to, respectively 14, 28 and 42 days of treatment were of -3.13 (SD=4.70), -4.30 (SD=5.51) and -5.45 (SD=6.62) in Relizema™ cream group and -3.32 (SD=5.54), -4.64 (6.04) and -4.31 (6.26), in Placebo group (Table 2.2.3). No statistically significant difference was observable between the two groups at each time point.
Mean itching rating decreased in both treatment groups from baseline to, respectively 14, 28 and 42 days of treatment: mean changes were -0.96 (SD=1.16), -1.58 (SD=1.21) and -2.42 (SD=1.67) in Relizema™ cream group and -0.50 (SD=1.25), -1.26 (SD=1.66) and -1.83 (SD=1.86), in Placebo group (Table 2.2.4). The Relizema™ cream performance was statistically significant at each time point while the one of Placebo was only at Visit 3 and 4. In any case, no statistically relevant difference was observed between the two groups at each time point of the study.

As well, mean worst itching rating decreased in both treatment groups from baseline to, respectively 14, 28 and 42 days of treatment, always with statistical significance within each treatment group: mean changes were -1.21 (SD=1.41), -1.96 (SD=1.49) and -2.63 (SD=2.34) in Relizema™ cream group and -0.63 (SD=1.17), 1.65 (SD=1.40) and -2.00 (SD=1.62) in Placebo group (Table 2.2.4). No statistically significant difference was observable between the two groups at each time point.

CDLQI score decreased (meaning an improvement in the QoL) in both treatment from baseline to, respectively 14, 28 and 42 days of treatment, always with statistical significance within each treatment group: mean changes were -2.29 (SD=2.52), -3.86 (SD=4.33) and -5.29 (SD=4.73) in Relizema™ cream group and -1.28 (SD=2.22), -2.56 (SD=2.94) and -3.53 (SD=4.00) in Placebo group (Table 2.2.5). No statistically significant difference was observable between the two groups at each time point.

Finally, the Investigators evaluated that at the end of treatment (6 weeks) there was an improvement respect to initial condition in the 79.1% of patients treated with Relizema™ cream and in the 70.8% of patients treated with Placebo (Table 2.2.8).
The patients (parents/guardian) opinion was more likely to find it Relizema™ cream satisfactory (87.5%) than Placebo (66.6%).
Finally, that treatment compliance was very high in almost all patients and none of them used alternative treatments for the management of AD during the study.

From the safety point of view, no adverse events related to the study treatment were reported: only two AEs occurred to two patients during the study: one event was of mild severity (limb injury) while the other was a Serious Adverse Event (a bacterial gastroenteritis leading to hospitalization and to study discontinuation).

In conclusion, in all performance items analysed the two treatments showed no statistically significant difference, however, looking to all the performance endpoints, the improvement of the AD condition and symptoms resulted always more relevant within the Relizema™ cream group than within the Placebo group.

In this regard, it is necessary to underline that the Placebo used in this study was a vehicle with hydrating properties, both for ethical reasons as it was not acceptable to use a totally inert product in young patients suffering for AD symptoms, and because of technical/manufacturing reasons (a cream inevitably contains substances that give emollient and hydrating properties). In light of this it is understandable and justified that no relevant statistically significant difference between treatments emerges from data analysis. The relevant result of this clinical investigation is that both from statistical and clinical point of view the Relizema™ cream has shown to be effective and safe in the relief of AD symptoms in young patients, from 6 months of age.

6. Abbreviated terms and definitions

ADE	Adverse Device Effect
AE	Adverse Event
AO	Azienda Ospedaliera
CDLQI	Children Dermatology Life Quality Index questionnaire
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
DRM	Data Review Meeting
EASI	Eczema Area and Severity Index
EC	Ethics Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FPI	First Patient In
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
LPI	Last Patient In
LPO	Last patient Out
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Medical Device Regulation
ml	Milliliters
mm	Millimeters
NRS	Numeric Rating Scale
PI	Principal Investigator
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

7. Ethics

The study was conducted in full compliance with the principles of the "Declaration of Helsinki". Before undertaking any study-related procedures with patients, 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 parents/guardian. Specific information sheets were developed for different age groups: 6-11 years and 11-17 years. One information sheet and informed consent form for adults was developed in order to obtain the consent to study participation and data collection and management from parents or guardian.

Three 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 Regionale Umbria), evaluated this clinical investigation in the meeting of the 27-Oct-2021 and expressed a favorable opinion. The two other ECs expressed their favourable opinion on the 10 and 20-Dec-2021 (respectively for site 03 Napoli and site 02 Catania).

The clinical investigation was submitted to the Italian CA (Ministry of Health) on 24-Nov-21 (after coordinating site EC approval) and the validation process completion was notified to the CRO on 27-Jan-2022. The CA was notified about the study start on the 03-Nov-2022, after the first subject was enrolled and about study conclusion on the 13-Sep-2023.

During the study one substantial amendment for the change of the PI at clinical site no.3 (Napoli) and some non-substantial amendments were issued.

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

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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.

21 / 11 / 2023
Date

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

21 / 11 / 2023
Date

Martina Manni
Study Medical Expert
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21 / 11 / 2023
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. Luca Stingeni
Unità Operativa di Dermatologia
Ospedale Santa Maria della Misericordia - Perugia

10. Annexes to the report

A. CLINICAL INVESTIGATION PROTOCOL (including amendments, if any)

B. INSTRUCTIONS FOR USE

C. LIST OF PRINCIPAL INVESTIGATORS AND THEIR AFFILIATED INVESTIGATION SITE, INCLUDING COPY OF THEIR CVs

D. LIST OF NAMES AND ADDRESSES OF ANY THIRD PARTIES

E. LIST OF MONITORS

F. LIST OF ECs

G. TABULATION OF ALL RELEVANT DATASETS

List of Tables

Demographic data

Performance data

Primary endpoints

Secondary endpoints

Table 2.2.3	Change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in EASI (Eczema Area and Severity Index) score (FAS Population
Table 2.2.4	Change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in NRS (Numerical Rating Scale) (FAS Population)
Table 2.2.5	Change from baseline (Visit 1) to each time point (Visit 2, Visit 3 and Visit 4) in CDLQI (Children Dermatology Life Quality Index) score (FAS Population)
Table 2.2.6	Patient's adherence to treatment (FAS Population)
Table 2.2.7	Proportion of patients using rescue medication during investigation (FAS population)
Table 2.2.8	Subject's and Investigator's global evaluation on performance of the study product at the end of the study (Visit 4) by means of a 7-items scale (FAS Population)

Safety data

Table 3.1	Analysis of adverse events observed (Safety population)
Table 3.2	Display of adverse events observed (Safety population)

List of Subject Data Listings

Listing 1	Discontinued Patients
Listing 2	Protocol Deviations
Listing 3	Analysis Populations
Listing 4.1	Demographic Data and Other Baseline Characteristics – Demography
Listing 4.2	Demographic Data and Other Baseline Characteristics – Medical History
Listing 4.3	Demographic Data and Other Baseline Characteristics – Surgical History
Listing 4.4	Demographic Data and Other Baseline Characteristics – Disease Details
Listing 5	Treatment Compliance
Listing 6.1	Individual Efficacy Response Data – Investigator's Global Assessment (IGA)

Listing 6.2	Individual Efficacy Response Data – EASI (Eczema Area and Severity Index) score
Listing 6.3	Individual Efficacy Response Data – NRS (Numerical Rating Scale) for itching
Listing 6.4	Individual Efficacy Response Data – CDLQI (Children Dermatology Life Quality Index) score
Listing 6.5	Individual Efficacy Response Data – Subject's and Investigator's global evaluation of performance
Listing 7	Adverse Events
Listing 8	Concomitant Medications
Listing 9	Physical Examination

H. AUDIT CERTIFICATE, IF APPLICABLE

I. REFERENCES

J. SUPPLEMENTARY TABLES