Clinical Investigation Report

EFFICACY AND TOLERABILITY EVALUATION OF A TOPICAL MEDICAL DEVICE BASED ON SHBF IN MANAGEMENT OF RADIODERMATITIS. AN OBSERVER-MASKED, CONTROLLED STUDY

Investigational device:	DERMORELIZEMA™ CREAM
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CIP identification:	Version no. 02 - 10th Feb 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.

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1. Summary

Title of clinical investigation

EFFICACY AND TOLERABILITY EVALUATION OF A TOPICAL MEDICAL DEVICE BASED ON SHBF IN MANAGEMENT OF RADIODERMATITIS. AN OBSERVER-MASKED, CONTROLLED STUDY

Introduction

Approximately 50 percent of all cancer patients can benefit from radiation therapy (RT) in the management of their disease. However, RT is not free from toxicity. Acute and chronic radiation-induced skin reactions (RISR) represent an inevitable consequence for up to 95% of people receiving RT.

The development of RISR usually occurs within few weeks after the initiation of the RT and persists up one month. RISR are usually characterized by swelling, redness, pigmentation, followed dry and then mostly desquamation, epilation, fibrosis, and ulceration of the skin and subjective symptoms including pain, warmth, burning, itching, psychological distress, leading even to discontinuation of the RT.

Currently there are no unanimously recognised guidelines for the management of RISRs and so far there is no treatment considered gold standard.

Based on DermoRelizema™ cream ingredients properties and based on pre-clinical and clinical evidence, it can constitute a safe and effective treatment for dermatitis and erythema.

Purpose of the clinical investigation

DermoRelizema™ cream topical formulation (cream) based on Sodium Hyaluronate Butyrate Formiate (SHBF). According to the current European regulation, DermoRelizema™ cream is a CE marked Class IIa Medical Device commercialized by Relife Italia Srl (Menarini Group) and is indicated for the symptomatic treatment of dermatitis and erythema.

In this study, DermoRelizema™ cream was tested in the management of RISRs in patients with breast cancer who started the treatment with the study product about one week before the start of RT, to prevent, delay and reduce the radiodermatitis signs and symptoms onset and severity.

This was a monocenter, randomized, comparative vs Dexeryl® cream, observer-masked, post-market clinical follow-up investigation.

The clinical investigation was regularly submitted to the competent Ethics Committee and

notified to the Italian Ministry of Health, as for requirements in post market clinical follow-up studies.

Description of the clinical investigation population

This study enrolled women with breast cancer at any stage who had undergone quadrantectomy, for whom hypofractionated adjuvant RT of the thoracic region was indicated and with good cutaneous trophism, in the region to be treated, according to investigator's judgement.

A minimum of 68 evaluable patients were planned (34 in each treatment group).

Women with the following characteristics were considered eligible:

- Giving their written consent.
- Aged ≥18 years.
- With breast cancer at any stage who have undergone quadrantectomy, for whom hypofractionated adjuvant RT of the thoracic region is indicated.
- RTOG/ EORTC radiodermatitis grade equal to 0 (zero) and good cutaneous trophism, in the region to be treated, according to investigator's judgement.
- Cooperative with regard to compliance with study-related constraints.

The following patients were excluded from the study:

- Pregnant or lactating women (as not eligible to RT), and fertile women not following, at the investigators' judgement, an adequate contraceptive method.
- Subjects incapable of giving consent.
- Concomitant inflammatory skin diseases in acute phase such as: atopic dermatitis, contact dermatitis, psoriasis, lichen planus, pityriasis rosea.
- Collagen vascular disease, vasculitis, scleroderma, dermatomyositis, or systemic lupus erythematosus.
- Unhealed surgical sites, breast infections.
- Bilateral breast cancer or multiple neoplasia needing other independent RT treatments.
- Prior breast reconstructions, implants, and/or expanders.
- Known radio-sensitivity syndromes (e.g. ataxia-telangiectasia).
- Known history of intolerance or hypersensitivity to any ingredient of the study products.
- Previous RT in the same or different location.
- Topical pharmacological and medical device treatments on the skin region affected by the RT, in the last 2 weeks.
- Systemic or topical (including inhaled or intranasal) treatments containing corticosteroids of any class in the 2 days preceding the enrolment.
- Photo-therapy (PUVA, UVB) in the 2 weeks preceding the enrolment and/or planned to be administered during the course of the study.
- Participation in another clinical trial at the time of the randomization or within 28 days before randomization.
- Patient's difficulties or problems, in the judgment of the investigator, in being compliant with study procedures and requirements, including social or mental constrains.

Clinical investigation method used

This was a monocenter (1 clinical site involved in Italy), randomized, comparative, observer-masked, post-market clinical follow-up study.

All the subjects were allocated (1:1) to the following treatment groups:

- DermoRelizema™ cream. Fingertip units (FTU) depending on the extent of the affected skin to treat, two times per day. The treatment was applied since about 7 (±3) days prior to RT start and continued until 14 days post RT end. After that the study product applications could go on for further 2 weeks, according to the investigator's decision. sessions.
- Dexeryl® cream. FTUs depending on the extent of the affected skin to treat, two times per day. The treatment wase applied since 7 (±3) days prior to RT start and continued until 14 days post RT end. After that the study product applications could go on for further 2 weeks, according to the investigator's decision.

The products were not applied within four hours before the RT.

Four visits were planned: initial visit to evaluate the subject eligibility and to train the subject to the correct study product application, then a Visit 2 at RT completion, Visit 3 at 2 weeks after RT completion and Visit 4 at 4 weeks after RT completion.

Performance evaluations included:

- the portion of patients with Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG / EORTC) radiodermatitis grade ≤ 1 and >1, at V3 (end of study treatment at V3, 2 weeks after RT conclusion, as primary endpoint) and at V2 (end RT, as secondary endpoint) and V4 (4 weeks after RT conclusion, as secondary endpoint);
- the patient's reported daily pain, itch, burning, and tenderness severity at application site by VAS, time to onset and time to peak;
- the radiodermatitis grade (investigator) by the RTOG / EORTC at V2, V3 and V4;
- the radiation dermatitis severity by Radiation Dermatitis Severity (RDS) scoring scale (investigator) at V2, V3 and V4;
- the size of the affected area at visit 2, 3 and 4, by measuring major and minor diameters;
- the instrumental descriptive assessment of tissue vascularization and integrity and structural parameters change from baseline, by OCT and D-OCT, at V2, V3 and V4;
- the patient's evaluation on the product pleasantness for odor, consistency, spreadability, satisfaction by a 5-points Likert scale, at V3;
- the patient's adherence to treatment (assessed by patient's diary).

Safety evaluations included:

- number, type and severity of adverse events (AEs) related to study treatment occurring during the study.
- .

Results of the clinical investigation

No. 70 patients signed the informed consent forms, attended the first visit and were randomized to start the treatment: 35 were randomized to DermoRelizema™ cream and 35 to Dexeryl®.

In the DermoRelizema™ cream group four patients interrupted prematurely the study (pts. ID 01-024, 01-029, 01-050 and 01-058).

In the Dexeryl® group three patients ((pts. ID 01-005, 01-025 and 01-038) withdrew before V2 and since no data was available after V1, they were excluded from all the populations for analysis. Two further patients interrupted prematurely the study (pts. ID 01-030 and 01-063).

Protocol deviations analysis defined the populations for Safety, Intention to treat (ITT) and per protocol (PP) analyses, as follows:

Safety population included all patients enrolled except the 3 patients without follow-up data after V1: overall 67 patients, 35 in DermoRelizema™ cream group and 32 patients in Dexeryl® group.

ITT population included overall 60 patients, 31 in DermoRelizema™ cream group and 29 patients in Dexeryl® group.

PP population included overall 50 patients, 27 in DermoRelizema™ cream group and 23 patients in Dexeryl® group.

All patients were female and of Caucasian origin. No statically significant difference (p value = 0.8580) was detected between groups for age (mean age 59.11 (SD=10.86) years in DermoRelizema™ cream group; mean age 59.56 (SD=9.43) years in Dexeryl® group).

The two groups were homogeneous also for vital signs and patient's habits (drinking, smoking, and sport). The only differences between groups observed at baseline were in systolic blood pressure (p value=0.0383, mean value 125.77 (SD=14.58) in DermoRelizema™ cream group and 133.59 (SD=15.70) in Dexeryl® group) and in the number of smoked cigarettes (p value= 0.0358, mean value 4.80 (SD=2.49) in DermoRelizema™ cream group and 13.71 (SD=7.85) in Dexeryl® group).

All the patients had at least one medical history and the most frequent (apart from breast cancer) involved the cardiovascular, endocrine/metabolic, gastrointestinal and

musculoskeletal systems. No noteworthy differences between treatment groups were detected.

Primary performance endpoint

The primary performance endpoint was the treatment success measured as the proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and > 1 at V3. In the ITT population, the 96.8% of patients treated with DermoRelizema™ cream and the 96.6% of patients treated with Dexeryl® cream had radiodermatitis grade ≤ 1 (Table 14.2.1.1). In the PP population, success was observed in 100.0% of patients treated with DermoRelizema™ cream and in 95.7% of patients treated with Dexeryl® cream (Table 14.2.1.2). The difference between treatment groups was not statistically significant (ITT p value= 0.737, PP p value= 0.460).

Secondary performance endpoints

Proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1 at V2 and V4

At V2, 27 patients (87.1%) had radiodermatitis grade ≤ 1 in DermoRelizema™ cream group and 26 (92.9%) in Dexeryl® group. No difference between groups was detected (p value= 0.8781).

At V4, 30 patients (100.0%) had radiodermatitis grade ≤ 1 in DermoRelizema™ cream group and 28 (100.0%) in Dexeryl® group (Table 14.2.2.15).

Time to onset and time to peak of RISR symptoms

Four symptoms were evaluated through VAS compiled every day by the patient: pain, itch, burning and tenderness at application site. At first visit all symptoms were = 0 (baseline value).

Pain mean time to onset was 15.56 days (SD=15.58, with median 12.5 days) in DermoRelizema™ cream group and 17.90 days (SD=14.05, median 17.0 days) in Dexeryl® group (Table 14.2.2.1). No difference between groups resulted (p value= 0.5482). Mean time to peak was 25.22 days (SD=14.11, with median 27.0 days) and 30.80 days (SD=12.37, with median 28.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups. No difference between groups resulted (p value= 0.2059).

Itch mean time to onset was 14.42 days (SD=10.29, with median 16.0 days) in DermoRelizema™ cream group and 15.79 days (SD=10.81, with median 18.0 days) in Dexeryl® group. No difference between groups resulted (p value= 0. 6539). Mean time to peak was of 26.88 days (SD=11.12, with median 27.0 days) and 27.25 days (SD=9.02, with median 28.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups (Table 14.2.2.2). No difference between groups resulted (p value= 0. 8985).

Burning mean time to onset was 15.53 days (SD=11.97, with median 21.0 days) in DermoRelizema™ cream group and 12.65 days (SD=10.21, with median 11.0 days) in Dexeryl® group (Table 14.2.2.3). No difference between groups resulted (p value= 0. 5776). Mean to time to peak was of 24.37 days (SD=11.88, with median 28.0 days) and 27.39 days (SD=10.33, with median 29.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups. No difference between groups resulted (p value= 0. 4033).

Tenderness mean time to onset was 8.00 days (SD=9.28, with median 3.0 days) in DermoRelizema™ cream group and of 12.96 days (SD=9.58, with median 13.0 days) in Dexeryl® group (Table 14.2.2.4). A statistically significant difference between groups resulted (p value= 0.0290) in favor of Dexeryl®. Mean to time to peak, it was of 22.70 days (SD=10.40, with median 25.0 days) and 27.57 days (SD=11.48, with median 25.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups. No difference between groups resulted (p value= 0. 1388).

Radiation dermatitis severity assessed by the Investigator using the RTOG/ EORTC scoring scale

At first visit the skin was healthy in all patients. At V2, in DermoRelizema™ cream group 9 patients (29.0%) had no erythema, 18 (58.1%) had erythema grade 1, 4 (12.9%) had erythema grade 2 and none had erythema grade 3 (Table 14.2.2.5). In Dexeryl® group 2 patients (7.1%) had no erythema, 24 (85.7%) had erythema grade 1, one (3.6%) had erythema grade 2 and one (3.6%) had erythema grade 3. The difference between groups resulted statistically significant (p value= 0.0321) in favor of DermoRelizema™ cream group.

At V3, in DermoRelizema™ cream group 16 patients (53.3%) had no erythema, 13 (43.3%) had erythema grade 1, one (3.3%) had erythema grade 3. In Dexeryl® group 9 patients (32.1%) had no erythema, 18 (64.3%) had erythema grade 1, one (3.6%) had erythema grade 3. The difference between groups was not statistically significant (p value= 0.1976). However, the major effect of DermoRelizema™ cream was observed.

At V4, in DermoRelizema™ cream group 29 patients (96.7%) had no erythema and only one (3.3%) had erythema grade 1. In Dexeryl® group 25 patients (89.3%) had no erythema and 3 (10.7%) had erythema grade 1. The difference between groups was not statistically significant (p value= 0.3445) but the improving effect of DermoRelizema™ cream was observable.

Radiation dermatitis severity assessed by the Investigator using the RDS scoring scale

At first visit the skin was healthy in all patients.

During the study, patients split between the RDS grades; at the end of the study almost all patients returned to grade 0.0 (29 patients (96.7%) in DermoRelizema™ cream group and 25 patients (89.3%) in Dexeryl® group), only 1 patient in DermoRelizema™ cream group had RDS grade equal to 0.5; 2 patients in Dexeryl® group had RDS grade equal to 0.5 and 1 patient had RDS grade equal to 1.0. No statically significant differences were detected at each time point (p values at V2, V3 and V4 were respectively 0.3169, 0.8029 and 0.4115, Table 14.2.2.6).

Area affected by RIRS

Maximum diameter

At V2 the difference between treatment groups was statistically significant (p value=0.0384): mean diameter 5.35 cm (SD=4.14), median 6.00 cm in DermoRelizema™ cream group and mean diameter 8.07 cm (SD=4.71), median 8.00 cm in Dexeryl® group (Table 14.2.2.7).
At V3 and V4 the differences between treatment groups were not statistically significant (p values respectively 0.1837 and 0.2800).

Minimum diameter

At each timepoint no statistically significant difference was detected between groups (p values=0.1421, 0.3158 and 0.2880 at V2, V3 and V4).

Skin damage measured by instrumental assessments

Epidermal thickness

Epidermal thickness decreased in both treatment groups between V1 and V2 (Table 14.2.2.8).
Thedifference between treatment groups was not statistically significant (p value=0.6906) but the differences within groups were statistically significant, in both groups (p value=0.0486 and p value=0.0235, respectively in DermoRelizema™ cream group and in Dexeryl® group).
From V1 to V3 the difference between groups was not statistically significant (p value=0.6043), while it was only within Dexeryl® group (p value=0.0100).
From V1 to V4 no difference was observed between groups (p value=0.6580) and within each group.

Collagen density

Collagen density decreased in both treatment groups between V1 and V2 (Table 14.2.2.9). The difference between treatment groups was not statistically significant (p value=0.2817), while it was within each group (p value=0.0382 in DermoRelizema™ cream group and p value=0.0032 in Dexeryl® group).

From V1 to V3 the difference between groups was not statistically significant (p value= 0.9826); the difference within DermoRelizema™ cream group was statistically significant (p value=0.0191) while the difference within Dexeryl® group was not statistically significant.
From V1 to V4 the difference between groups was not statistically significant (p value=0.4900); the difference within DermoRelizema™ cream group was not statistically significant while the difference within Dexeryl® group was statistically significant (p value=0.0011).

Collagen attenuation
Collagen attenuation increased in both treatment groups between V1 and V2 (Table 14.2.2.10). The difference between treatment groups (p value=0.4725) and within each group was not statistically significant.
From V1 to V3 the difference between groups (p value=0.9013) and within groups was not statistically significant.
From V1 to V4: the difference between groups (p value=0.7081) and within groups was not statistically significant.

Vascular extent at 300-micron depth
Vascular extent at 300-micron depth increased in both groups between V1 and V2 (Table 14.2.2.11). The difference between treatment groups was not statistically significant (p value=0.6434); the difference within groups was statistically significant in both groups: p value=<0.0001 in DermoRelizema™ cream group and p value=<0.0001 in Dexeryl® group.
From V1 to V3 the difference between groups was not statistically significant (p value= 0.8825) while the difference within each group was statistically significant: p value=<0.0001 in DermoRelizema™ cream group and p value=<0.0016 in Dexeryl® group.
From V1 to V4 the difference between groups was not statistically significant (p value=0.1501); the difference within DermoRelizema™ cream group was statistically significant (p value=0.0003) while the difference within Dexeryl® group was not.

Vascular extent at 500-micron depth
Vascular extent at 500-micron depth increased in both groups between V1 and V2 (Table 14.2.2.12). The difference between treatment groups was not statistically significant (p value=0.7010) while the difference within DermoRelizema™ cream group and within Dexeryl® group was statistically significant (p value=0.0010 and p value=0.0175, respectively).
From V1 to V3 the difference between treatment groups (p value=0.5958) and within groups was not statistically significant.
From V1 to V4 the difference between groups was statistically significant (p value=0.0222), in favor of Dexeryl® while the difference within each group was not statistically significant.

Patient's adherence to treatment

Mean treatment compliance was 92.56 (SD=7.98), median 96.50 days in DermoRelizema™ cream group and 94.43 (D=8.82) days, median 97.50 days in Dexeryl® group (Table 14.2.2.13). The difference between groups was not statistically significant (p value=0.4846).
Also, the average days of treatment resulted 55.32 (SD=7.43), in DermoRelizema™ cream group and 55.03 (SD=10.26) in Dexeryl® group. The difference between groups was not statistically significant (p value=0.9008).

Pleasantness of the product

The patient's opinion on pleasantness of the product was assessed at V3 by evaluating smell, texture, spreadability and satisfaction of the product (Table 14.2.2.14).
Smell: the 66.7% of patients and the 57.1%, respectively, evaluated the smell of DermoRelizema™ cream and Dexeryl® cream as "Pleasant" or "Very pleasant". No statistical difference between groups (p value= 0.3439).
Texture: the 100% of patients and the 92.9%, respectively, evaluated the texture of DermoRelizema™ cream and Dexeryl® cream as "Pleasant" or "Very pleasant". No statistical difference between groups (p value= 0.4297).
Spreadability: the 100% of patients in both groups evaluated the spreadability of the products as "Pleasant" or "Very pleasant". No statistical difference between groups (p value= 0.7866).
Satisfaction: the 96.7% of patients and the 92.9%, respectively, evaluated the satisfaction with DermoRelizema™ cream and Dexeryl® cream as "Pleasant" or "Very pleasant". No statistical difference between groups (p value= 0.7582).

Safety endpoints

Overall, 14 adverse events were registered during the study: 6 patients in DermoRelizema™ cream group had 6 adverse events and 6 patients in Dexeryl® cream group had 8 adverse events (Table 14.2.2.16).
None of them was serious and only 1 adverse event (hypersensitivity at the application site), involving patient ID 01-049, was evaluated as possibly related to the study product. The event was of mild intensity and spontaneously resolved within the same day.
Two AEs (not related to study treatment) lead to two patients premature study interruption in DermoRelizema™ cream group.

Conclusion

DermoRelizemaTM cream is a non-pharmacologic, safe product for the control and

improvement of the RISR. The use of emollient and hydrating products is confirmed as a valid treatment to prevent damages caused by RT and to reduce the risk of premature interruption of RT.

Clinical investigation initiation date: 02-Nov-2020 (first subject in).

Clinical investigation completion date: 16-Feb-2023 (last subject out).

2. Introduction

DermoRelizema™ cream is a CE marked Class IIa Medical Device commercialized by RELIFE Italia Srl (Menarini Group). The product is indicated for the symptomatic treatment of dermatitis and erythema (Product information leaflet DermoRelizema™ cream) and has been already tested in vitro, in vivo and clinically in adults, both in experimental models and in patients with cancer exposed to radiotherapy. It has a light texture that allows ease application on wide areas.

2.1 Rationale

More than 14 million new cases of cancer are reported worldwide per year and with more than 3.7 million new cases each year, cancer represents the second most important cause of morbidity in Europe (IARC 2010; Barton MB et al., 2014).

Approximately 50 percent of all cancer patients can benefit from radiation therapy (RT) in the management of their disease. RT has the potential to improve the rates of cure of 3.5 million people and provide palliative relief for an additional 3.5 million people (Tyldesley S et al., 2011).

Even if RT damages both normal cells as well as cancer cells, its use is rationally justified on the fact that cancer cells in general are not as efficient as normal cells in repairing the damage caused by radiation treatment resulting in differential cancer cell killing. The biological target of radiation in the cell is DNA with cell damage and death occurring as direct interaction of the radiation with cellular DNA and also indirect DNA damage caused by the free radicals derived from the ionization or excitation of the water component of the cells (Begg AC et al., 2011).

Acute and chronic radiation-induced skin reactions (RISR) represent an inevitable consequence for up to 95% of people receiving RT (Porock D et al., 2002). RISRs are the result of interference and disruption of the physiological process of cell division and renewal leading to resulting in deep cell damage, local acute inflammation and overproduction of cytokines leading into chronic inflammation and consequent cell death (Hymes SR et al., 2006).

Patient-related, environmental and treatment-related factors influence the course and the characteristics of radiodermatitis. Patient-related, usually not or poorly modifiable, factors include: genetic factors, age, nutritional status, ethnicity, radio-sensitiveness, obesity and diabetes, skin trophism and integrity and concurrent chemotherapy. Environmental factors, modifiable or controllable, include mainly smoking and acute and chronic sun exposure. Finally, treatment-related factors include: level of energy used, duration, total dose of radiation, size of the treated area and somehow anatomical location (breast, head and neck and genital areas are more likely to cause RISRs (Porock D et al., 2002)).

The development of RISR usually occurs within few weeks after the initiation of the RT and persists up one month. RISR are usually characterised by objective early signs such as swelling, redness, pigmentation, followed dry and then mostly desquamation, epilation, fibrosis, and ulceration of the skin and subjective symptoms including pain, warmth, burning, itching, psychological distress, leading even to discontinuation of the RT. In some cases, complex surgical reconstruction of damaged skin may be required (Kole AJ, et al., 2017; Porock D et al., 2002, Naylor W at al, 2001, Cohn AB et al., 2001).

Today there are no national guidelines for the management of RISRs but only very few widely recognised guidelines (Bernier J et al., 2008; Bensadoun RJ et al., 2013). Several topical or systemic treatments have been proposed to prevent or cure RISRs, including dressing (hydrogel with vegetal extracts), skincare practices (mainly based on washing practices and deodorant use), application of steroidal topical creams or gels, use of non-steroidal topical treatment and also systemic therapies including proteolytic enzymes (papain, trypsin and chymotrypsin), pentoxifylline, antioxidants, oral surfactant suspension or oral zinc (Chan RJ et al., 2014). In general, any of these treatments is far to be ideal, suffering, in various extent, from poor or doubtful efficacy or poor acceptability or safety problems. Also, a recent meta-analysis on the use of topical corticosteroids in breast cancer has led to similar conclusions with no benefits on dermatitis and pain and with partial effects on desquamation (Haruna F et al., 2017).

Preclinical and clinical studies with DermoRelizema™ cream suggest that it is a safe and effective treatment for dermatitis and erythema. In particular, several evidences suggest that topical administration of HA, the most important ingredient of DermoRelizema™ cream is helpful and safe in the treatment of RISR (Guida C., 2009; Leonardi MC et al., 2008; Primavera G et al., 2006; Liguori V et al., 1997) and in the treatment of patients with inflammatory conditions at the level of the vaginal and anal mucosa, following radio and chemo-therapies (Cosentino D et al., 2018).

This clinical study was conducted to investigate the benefit of DermoRelizema™ cream in the treatment of RISR in breast cancer patients. The restriction of the evaluation to breast cancer only was justified by the need to minimize the heterogeneity of anatomical sites and by the fact that breast cancer is the most common female malignancy. In addition, since the effects of the product were studied by using instrumentals assessments such as Dynamic Optical Coherence Tomography (D-OCT) in parallel with traditional clinical assessments, there was also the need to have skin areas sufficiently flat, like breast, to easily investigated with D-OCT.

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

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

3. Investigational device and methods

3.1 Investigational device description

3.1.1 Description of the investigational device

The product under investigation was DermoRelizema™ cream. It is a class IIa, CE marked medical device for indicated for the symptomatic treatment of dermatitis and erythema. The primary package was a 75 ml labelled tubes.

Manufacturer:	RELIFE Italia Srl, Via dei Sette Santi 3 - 50131 Firenze (FI) – Italy
Trade Name:	DermoRelizema™ cream
Formulation:	Cream
Route of administration:	topical application on breached/compromised skin
Composition:	aqua, candelilla/jojoba/rice bran polyglyceryl-3 esters, glyceryl stearate, cetearyl alcohol, sodium stearolyl lactylate, octyldodecyl myristrate, caprylic/capric triglyceride, dimethicone, glycerin, C10-18 triglycerides, cetyl alcohol, magnesium aluminum silicate, betaine, xylitol, xanthan gum, chondrus crispus extract, glucose, caprylyl glycol, phenoxyethanol, ethylhexylglycerin, tocopheryl acetate, biotin, panthenol, sodium butyroyl/formoyl hyaluronate, disodium EDTA.

The mode of action of DermoRelizema™ cream mainly lays on physic and chemical properties of four of its ingredients that allow:

a) to create and maintain a physical barrier effect with consequent hydrating and emollient effect and

b) to promote physiologic antioxidant and anti-inflammatory actions.

It was therefore expected that in case of erythema and skin damages due to RT, hydrating, emollient, antioxidant and soothing properties of DermoRelizema™ cream might help to maintain a good integrity of the skin layers.

Glyceryl stearate ensure humidifying action based on a chemical-physical interaction with water molecules of the extracellular environment leading to increase in moisture retention and maintenance of hydration (Product information leaflet DermoRelizema™ cream).

Dimethicone is a silicone and oxygen polymer that works as an effective filming emollient due to its oil-free occlusion properties that helps to separate the skin from the surrounding environment, useful for generating favourable conditions for the maintenance or the restoration of the physiological cutaneous layer (Pacha O et al., 2012).

Tocopherol acetate (vitamin E) is an antioxidant agent that delay or prevent oxidative damage caused by the presence of Reactive Oxygen Species (ROS), such as superoxides, hydrogen peroxides and hydroxyl radicals, highly unstable and reactive molecules, which contribute to the microbicidal action of phagocytes but, on the other hand, also damage DNA, cells, membranes and proteins leading to inflammation. UV radiations and X-rays are potent factors promoting the formation of ROS in the skin (Pilkington SJ et al., 2015).

Sodium hyaluronate butyrate formate (SHBF) (0.1%) as key functional ingredient. HA is produced from fibroblasts and keratinocytes, is one of the main components of the extracellular matrix and is present in all layers of the epidermis and dermis. HA is crucial for the integrity and reparative processes of the skin and for wound healing. HA butyrate formate, a patented polymer, derived from HA. It has been demonstrated that, in addition to elasticising and moisturizing properties, SHBF has an anti-inflammatoryactivity caused by a decreased adhesion of polymorphonuclear cells and contrast to ROS (Relife, 2019) and that might be helpful in the minimization of signs and RISR symptoms (Guida C., 2009; Leonardi MC et al., 2008; Primavera G et al., 2006; Liguori V et al., 1997).

DermoRelizema™ can be directly applied by the subject or a caregiver, there is no specific need of training or professional experience to use it.

3.1.2 Intended use of the investigational device

DermoRelizema™ cream is indicated for the symptomatic treatment of dermatitis and erythema.

3.1.3 Previous intended use or indication for use, if relevant

The study is a PMCF study, therefore this paragraph is not applicable.

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

Being the present study a post-market clinical follow-up study, no IB was issued and no change to the investigational device occurred.

3.2 Clinical investigation plan (CIP)

3.2.1 Clinical investigation objectives

The primary objective of this clinical investigation was to evaluate the effects of DermoRelizema™ cream, in the management of the progression of RT-induced skin reactions and toxicity using the grading system of the Radiation Therapy Oncology Group / European Organization for Research and Treatment of Cancer (RTOG/ EORTC) (Cox JD et at., 1995). The primary objective was measured at visit 3 (two weeks since last RT session).

The secondary objectives of this clinical investigation were:

- to evaluate the effects of DermoRelizema™ cream in the management of the progression of RT-induced skin reactions and toxicity, using the grading system RTOG/ EORTC at RT conclusion (visit 2) and at study end (visit 4);
- to evaluate the RISR symptoms management as reported by the patient through VAS (pain at site, itch at site, burning at site and tenderness at site), with their time to onset and time to peak (Schnur JB at al., 2011).
- to evaluate the radiation dermatitis severity, assessed by the investigator using the RTOG/ EORTC scoring scale, at visit 2, 3 and 4;
- to evaluate the radiation dermatitis severity, assessed by the investigator using the Radiation Dermatitis Severity (RDS) scoring scale (Ryan JL, 2013) at visit 2, 3 and 4;
- to evaluate, the extension of the area affected by RISR, at visit 2, 3 and 4;
- to evaluate the skin damage by instrumental assessments (erythema intensity measured with colorimetry, vascular parameters evaluated with D-OCT, tissue integrity and structural parameters evaluated with OCT), at visit 2, 3 and 4;
- to evaluate the patient's overall opinion on products' pleasantness assessment by a 5-points Likert scale (e.g. odour, consistency, spreadability, patient's satisfaction) at visit 3;
- to evaluate the patient's adherence to treatment (assessed by patient's diary);
- to evaluate the occurrence of Adverse Events (including local reactions and systemic reactions).

3.2.1.1 Clinical investigation tools description

RTOG / EORTC Radiodermatitis Grading

RTOG / EORTC and CTC/AE are universally the most used acute radiation dermatitis scoring systems (Cox JD et at., 1995; NCI, 2019) and they are about equivalent. The first is typically

used in Europe, the latter in the United States. As this study was conducted in Europe, the RTOG / EORTC radiation dermatitis scoring system was adopted.

RD grading consists of 5 levels of severity, each with descriptive clarification, in a range 0 (no change) to 5 (death), as reported below. The assessment is referred to the skin area receiving radiotherapy and was performed for a given patient, preferably always by the same blind investigator at all study visits (from V1, before RT start, to V4).

RTOG/EORTC Acute radiation dermatitis scoring systems
and comparison with CTC/AE scoring system

	RTOG/EORTC
Grade 0	**No change**
Grade 1	**Faint erythema, dry desquamation, epilation, decreased sweating**
Grade 2	**Tender or bright erythema, moderate edema, patchy moist desquamation**
Grade 3	**Moist desquamation in areas other than in skin folds, pitting edema**
Grade 4	**Ulceration, hemorrhage, necrosis**
Grade 5	**Death**
Reference	*Cox et al., 1995*

Radiation Dermatitis Severity (RDS)

Radiation Dermatitis Severity (RDS) scoring scale was already used in published SR (Ryan JL, 2013; Ryan WJ at al., 2018) and non-published (ClinicalTrial.gov NCT02289365; NCT02556632) studies for the treatment of RISRs.

RDS scoring scale consists of 9 levels of severity, each with descriptive clarification, in a range 0.0 to 4.0 and increments of 0.5, as shown below. The RDS score incorporates changes in redness, pigment, texture and integrity of the skin. RDS scoring was performed for a given patient, preferably always by the same blind investigator at all study visits, from V1 (before RT start) to V4, in conjunction with the RTOG / EORTC radiodermatitis grading.

RDS - Radiation Dermatitis Severity

Ryan JL at al., 2013

Radiation Dermatitis Severity Score (RDS)	
Grade	**Criteria/Characteristics**
0.0	None.
0.5	Patchy faint follicular erythema; faint hyperpigmentation.
1.0	Faint diffuse erythema; diffuse hyperpigmentation
1.5	Definite erythema; extreme darkening/hyperpigmentation.
2.0	Definite erythema (or hyperpigmentation) with fine desquamation and pruritis (itchiness).
2.5	Definite erythema (or hyperpigmentation) with branny desquamation.
3.0	Deep red erythema, diffuse desquamation; some desquamation in sheets.
3.5	Violaceous erythema, diffuse desquamation in sheets, and patchy crusting.
4.0	Violaceous erythema, diffuse desquamation in sheets, patchy crusting, and superficial ulceration

Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a non-invasive imaging technology, which allows the evaluation, few millimeters deep, of the structure of the skin at high resolution and with no discernible effect on the tissue.

Dynamic OCT (D-OCT) allows to investigate, in vivo and in 3D, the vascular architecture and the blood flow of the skin. In particular this technique offers the ability to visualize and to measure vessel morphology of inflammatory and neoplastic skin lesions (Schuh S et al., 2017).

OCT and D-OCT were performed according to the standard practices in place at the site at all visits but screening visit, and were performed for a given patient, preferably always by the same blind investigator at all study visits (from V1, before RT start, to V4).

The extension of the RISR affected area was measured through the major and minor diameters (cm).

Patient's Overall Opinion on Products' Pleasantness

Odour, consistency, spreadability, satisfaction for products use was assessed by the patient at the end of the treatment (V3) with a five points Likert scale (1=very pleasant, 2=pleasant, 3=not pleasant nor unpleasant, 4=unpleasant, 5=absolutely unpleasant).

Treatment Adherence

The treatment adherence of the patient was assessed by reviewing the patient's diary.

The investigator was requested to review the diary and in case of missing information to ask the patient about treatment application not recorded in the diary.

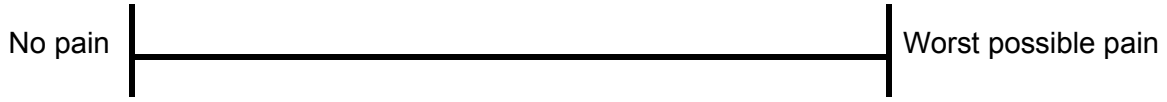
Patient's Subjective Assessments (by VAS)

There is no “gold standard” measure of patient-rated radiodermatitis symptoms (pain, itch, burning and tenderness). However, the only scales that appear to be frequently used in the published papers are VAS (Schnur JB et al., 2011).

Patient’s subjective symptoms (Pain, Itch, Burning and Tenderness at site) were assessed by mean of a standard 100 mm VAS printed in paper and administered directly to the patient by the investigator at V1 and included in the patient’s diary, to collect the information every day from the RT start to V4. Patient’s subjective assessments were performed at initial study visits and on the diary.

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

Example:



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

A VAS scale for each of the 4 symptoms was completed by the subject.

3.2.2 Clinical investigation design

This was a post marketing, interventional, randomized, single-center, prospective, observer-masked, controlled study, for the evaluation of the clinical performance and tolerability of a cream-based medical device (DermoRelizema™ cream) in the management of RISR in women with breast cancer.

The study aimed to recruit women with breast cancer at any stage who had undergone quadrantectomy, for whom hypofractionated adjuvant RT of the thoracic region was indicated.

To better evaluate the efficacy of treatment with DermoRelizema™ cream and for ethical reasons, a comparator was chosen. The comparator suggested by the principal investigator was Dexeryl® cream (Pierre Fabre Dermatologie), a product with a moisturizing and emollient action, based on glycerol, vaseline and liquid paraffin, the only reimbursed by social security in France (Pierre Fabre, 2019-leaflet).

The test group only received DermoRelizema™ cream from V1 to V3 and the control group received in the same fashion, Dexeryl® cream. Based on the investigator’s opinion if at visit 3 the patient needed further treatment, this could be prolonged up to visit 4, in both treatment groups.

The study treatment allocation was through randomization. Randomization was guaranteed by a pre-defined site-specific, computer-generated, randomization sequence. The treatments

were assigned to the eligible subjects in order of their presentation at the site and according to a randomized sequence. The investigator was not aware of the treatment to assign to a specific subject until the randomization, performed through randomization envelopes. Date, time and the responsible for the randomization for each subject was recorded.

The design of the study did not allow a double-blind design and therefore observer-masked clinical assessments were performed on tests performed at V2, V3 and V4, compared to baseline results. The observer-masked clinical assessment involved one or more experienced clinicians who were trained on the protocol and related procedures and assessments but who were not involved in randomization and product management for individual patients (assignment, withdrawal, accountability) during the study and therefore were not informed about the treatment assigned to them.

3.2.3 Ethical considerations

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

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

DermoRelizema™ cream is intended for topical use only. The use of DermoRelizema™ cream is free from systemic adverse reactions and substantially free from topical adverse reactions, with exception of possible hypersensitivity to one of the components. There are no known interactions with potential concomitant medical treatments given in combination to DermoRelizema™ cream.

All study procedures planned by the protocol were harmless and the participation in this study did not imply additional risks compared to the treatment that would be anyway necessary to manage the complications of the RT.

In order to control or mitigate the risks described, the study protocol:

a) addressed specific restrictions (mainly as inclusion and exclusion criteria)
b) required safety and efficacy verifications at study time-points
c) prescribed instructions to the patients for the use of the study products and in general to minimize the risks of RISR
d) provided study product interruption rules and the use of rescue strategies in case of lack of efficacy of the treatments.

According to current Evidence Based Medicine (EBM), the risk-benefit ratio for the participation in this study was not substantially different from the risk-benefit ratio of alternative treatments. Finally, this study did not imply the use of placebo.

3.2.4 Data quality assurance

During each subject's study visit, the study Investigator or designee collected and reported study data in the relevant subject's chart, documenting all significant observations.
Paper CRFs (CRFs) were used to record subject's study data. The Investigator ensured that the CRFs were properly and completely filled in. The Investigator reviewed all CRFs and signed and dated them for each subject, verifying that the information was complete, accurate and correct. All the information included into the CRF were recorded from source documents. Queries were generated by the CRO Data Management staff. The Investigator was responsible for the review and approval of all queries.

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

3.2.5 Subject population for the clinical investigation

No. 82 subjects were planned to be enrolled in this clinical investigation, selected on the basis of the following inclusion/exclusion criteria.

Inclusion criteria

1. Women who give their written consent for participation in the study and willing to comply with all its procedures.
2. Age ≥18 years.
3. Women with breast cancer at any stage who have undergone quadrantectomy, for whom hypofractionated adjuvant RT of the thoracic region is indicated.
4. RTOG/ EORTC radiodermatitis grade equal to 0 (zero) and good cutaneous trophism, in the region to be treated, according to investigator's judgement.
5. Patients who are supposed will be cooperative with regard to compliance with study-related constraints.

Exclusion criteria

Vulnerable subjects

1. Pregnant or lactating women (as not eligible to RT), and fertile women not following, at the investigators' judgement, an adequate contraceptive method.
2. Subjects incapable of giving consent.

Abnormalities, previous conditions and comorbidities

3. Concomitant inflammatory skin diseases in acute phase such as: atopic dermatitis, contact dermatitis, psoriasis, lichen planus, pityriasis rosea.
4. Collagen vascular disease, vasculitis, scleroderma, dermatomyositis, or systemic lupus erythematosus.
5. Unhealed surgical sites, breast infections.
6. Bilateral breast cancer or multiple neoplasia needing other independent RT treatments.
7. Prior breast reconstructions, implants, and/or expanders.
8. Known radio-sensitivity syndromes (e.g. ataxia-telangiectasia).
9. Medical history of intolerance or hypersensitivity to cosmetic products and to any ingredient or excipients of the study products.

Past and Concomitant medications or treatments

10. Previous RT in the same or for different location.
11. Topical pharmacological and medical device treatments on the skin region affected by the RT, in the last 2 weeks prior V1.
12. Systemic or topical (including inhaled or intranasal) treatments containing corticosteroids of any class in the 2 days preceding the enrolment.
13. Photo-therapy (PUVA, UVB) in the 2 weeks preceding the enrolment and/or planned to be administered during the course of the study.

Miscellaneous

14. Participation in another clinical trial at the time of the randomization or within 28 days before randomization.
15. Patient's difficulties or problems, in the judgment of the investigator, in being compliant with study procedures and requirements, including social or mental constrains.

3.2.1 Treatment and treatment allocation schedule

Patients were randomly allocated to DermoRelizema™ cream or Dexeryl® cream.

Randomization was assured by a pre-defined site-specific, computer-generated, randomization sequence. The supplies were labelled with identification numbers and assigned, according to a randomization sequence, to the eligible subjects in order of their presentation at the sites. Randomization envelopes were used to assign the treatment.

After the randomization the duration of the overall exposure to the investigational device and its comparator was the same. Both products were applied twice daily and therefore the total exposure was in the range 35-42 (± 6) days until visit 3 or 49-56 (± 6) days if the treatment continued until visit 4.

In both groups the exact total amount of cream applied could not be estimated in advance, as the quantity of the cream was determined by the extension of the area of the affected skin. Such area differed subject to subject and could change over time during the study.

For both study groups, instructions were given so that the quantity of product to be applied was sufficient to cover the surface of irritated skin and a small contiguous portion (to this purpose, a FingerTip Units (FTU) was the amount of cream squeezed from the tube and which covered completely the distal phalanx of an adult's index and that allowed to treat a skin area of about 200 cm^2).

The following instructions were given to patients:

- Study group DermoRelizema™ cream. FTUs depending on the extent of the affected skin to treat, two times per day for 7 (±3) days prior RT until about 14 (±3) days post RT end. The product could be used for further 2 weeks (from V3 to V4) in case of need, according to the Investigator's judgment. During RT, the product was not applied within 4 hours before the treatment, as indicated in IFU (to avoid a bolus effect that means an increased radiation dose delivered to the epidermis).

- Control group Dexeryl® cream. FTUs depending on the extent of the affected skin to treat, two times per day for 7 (±3) days prior RT and until about 14 (±3) days post RT end. The product could be used for further 2 weeks (from V3 to V4) in case of need, according to the Investigator's judgment. During RT, the product was not applied within 4 hours before the treatment.

The investigational device was used according to its Instructions for Use.

The study device and comparator were provided for the study by the Sponsor of this clinical investigation and shipped to the clinical site 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).

Daily management of the area interested by RT:

The following recommendations were also provided to patients in order to further prevent skin irritation and damage (Seité S, et al 2017)

• *Skin cleansing*
  - use liquid soap or dermatological soap bar with a pH close to 5, without perfume, plant or fruit extracts
  - dry skin delicately but meticulously.

• *Photoprotection*
  - protect the irradiated skin zone from sun exposure
  - apply a sunscreen SPF 50+ with UVA/UVB protection.

• *Clothing*
  - wear ample, soft cotton clothing
  - avoid wearing synthetic clothes.

• *Additional advice*
  - use an electric razor and do not shave too close to the skin.
  - avoid applying products that contain alcohol (perfume, eau de toilette, ether, talcum powder)
  - avoid applying sticky plaster
  - avoid rubbing or scratching.

3.2.2 Concomitant medications/treatments

Radiotherapy

As for clinical practice at the investigational site, patients with breast carcinomas were treated according to a hypofractionated regimen of 2.66 Gy per day, up to a total dose of 42.56 Gy, through tangential portals. Patients could undergo an additional boost up to a total dose of 10 Gy on the surgical site. Photon beams of 6 MV were used to treat this patient population.

Other concomitant medications

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

The following medications and procedures were not allowed at screening (see also exclusion criteria) and during the study (their use caused the exclusion the patient from the study).

- Topical pharmacological products or medical device treatments on the skin region affected by the RT, in the last 2 weeks prior V1 and during the study.
- Systemic or topical (including inhaled or intranasal) treatments containing corticosteroids of any class in the 2 days preceding the enrolment and during the study.

- Photo-therapy (PUVA, UVB) in the 2 weeks preceding the enrolment and/or planned to be administered during the course of the study.

Rescue strategies

In the event that the subject did not benefit from the use of the assigned product, she was allowed to use another topical or systemic treatment as suggested by the Investigator. In this case, the patient was considered as drop-out (not a violator).

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

3.2.3 Duration of follow-up, study visits description

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

Visit 1: screening, baseline and treatment start (Day 1)

The following activities were performed at Visit 1, after informed consent release. Visit 1, (Screening, randomization and treatment start) was planned about 7 (±3) days prior to RT start.
The assessments and procedures approximately followed the described sequence:

- Evaluation of the eligibility and assessments of the inclusion / exclusion criteria.
- Collection of data on: demography, lifestyle, medical history, past and concomitant medications.
- Physical examination, including vital signs (blood pressure and heart rate) in sitting position.
- Dermatological assessment (RTOG/ EORTC, RDS).
- OCT/ D-OCT assessments.
- Patient's VAS for local pain, local itch, local burning and tenderness, to be completed at site.
- Randomization.
- Dispensing of study products, instructions for use (including definition of the area to be treated and instructions on standard of care to be followed).
- Dispensing of patient's diary and instructions on how to fill it in.

Study product application (twice a day, every day) was started on Day 1 (one or two applications depending on the visit conclusion time).

Visit 2 (Days 21-28 since RT start) – follow-up visit:

The following activities were performed at Visit 2 (corresponding to RT completion):

- New or change of any concomitant medication from previous visit.
- Dermatological assessments (RTOG/ EORTC and RDS, size of affected area).
- OCT/D-OCT assessments.
- Diary collection and check for: VAS for local pain, local itch, local burning and tenderness completion.
- Diary collection and check for: treatment adherence evaluation.
- New diary delivery.
- Safety assessments (AE/SAE/ADE/SADE/DD).

Visit 3 – End of treatment (Days 35-42 ±3 since RT start):

The following activities were done at Visit 3:

- New or change of any concomitant medication from previous visit.
- Dermatological assessments (RTOG/ EORTC and RDS, size of affected area).
- OCT/ D-OCT assessments.
- Diary collection and check for: VAS for local pain, local itch, local burning and tenderness completion.
- Diary collection and check for: treatment adherence evaluation.
- New diary delivery.
- Patient's assessment on product pleasantness.
- Collecting returned and/or used product.
- Safety assessments (AE/SAE/ADE/SADE/DD).

On the investigator's decision, the study treatment could be concluded at this visit or further two-weeks treatment could be necessary. In such case, new products was delivered to patients. Patients maintained their treatment as assigned by the randomization process.

Visit 4 – End of study (Days 49-56 ±3 since RT start):

The following activities were done at Visit 4:

- New or change of any concomitant medication from previous visit.
- Changes from the previous visit in the physical examination.
- Dermatological assessments (RTOG/ EORTC and RDS, size of affected area).
- OCT/ D-OCT assessments.
- Safety assessments (AE/SAE/ADE/SADE/DD).
- Diary collection and check for: VAS for local pain, local itch, local burning and tenderness completion.
- Diary collection and check for: treatment adherence evaluation (if study treatment continued).

3.2.4 Statistical design, analysis and justifications

The sample size of 68 evaluable patients (34 per group) was based on the expectation that data generated from such sample of patients was adequate to determine a sufficiently accurate effect size.

Assuming that about 9% of patients included in the test group (3 out of 34) and about one third (11 out of 34) in the control group experienced a grade of toxicity >1, this sample was assumed as sufficient to demonstrate a statistically significant difference between treatment arms using a Fisher's exact test with a one-sided significance level of 0.05. According to the results of a

previous open-label non-controlled study the effects of DermoRelizema™ cream in breast cancer, this objective appeared to be realistic.
In order to reach 68 evaluable patients, considering a possible rate of 20% between violators and drop-out patients, it was estimated that it was necessary to enroll about 82 patients. For more details, please refer to the Statistical Analysis Plans (version 1.0 date 12-Jul-2022 and version 2.0 date 19-Sept-2022).

General Issues

The following populations were defined for this investigation:

INTENT-TO-TREAT POPULATION (ITT)

The Intention to Treat set (ITT) included all patients of the Safety population, regardless if they satisfied the entry criteria, who received the study treatment and performed a post-baseline assessment. Patients using prohibited medications and procedures were included in the ITT dataset for the endpoints that were not affected by the protocol violation, i.e. timepoints before the start date of the forbidden treatment/procedure.

PER-PROTOCOL (PP) POPULATION

The Per Protocol set (PP) included patients of the ITT population fulfilling the protocol requirements and schedule. Patients with major deviation(s) were excluded from the Per Protocol dataset.

SAFETY POPULATION

The Safety Set (SS) population included all patients who received at least one dose of the study product.

The analysis of safety endpoints was performed on the Safety Set population (SS). Analysis of performance endpoints will be performed on the ITT population. The analysis of primary endpoint will be repeated on the Per-Protocol population.

Data collected at Visit 1, before any study treatment administration, were considered as baseline values.
Baseline characteristics of the two groups of patients were compared by Student's t-test or Chi-square 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.

The significance level of statistical tests was set at 0.05.

An interim analysis was performed on reaching 34 evaluable patients. The purpose of the interim analysis was to obtain preliminary data on the efficacy and tolerability profile; all endpoints were evaluated. For the results, please refer to the Statistical Analysis Report (version 1.0 date 24-Oct-2022, included in Annex G) and Interim Statistical Analysis Summary Report (date 27-Oct-2022, included in Annex G).

The statistical analysis was carried out using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA), as planned.

Methods for Withdrawals and Missing Data

As per protocol, evaluable patients for primary endpoint were 68. Patients who discontinued before Visit 2 were not evaluable for primary endpoint, therefore in order to reach 68 evaluable patients, considering a possible rate of 20% between violators and drop-out patients, it was estimated that it will be necessary to enroll about 82 patients. If these patients applied the treatment will be included in the Safety population. Missing data was not replaced.

Patients who discontinued between Visit 2 and Visit 3 were considered evaluable for available efficacy endpoints. Missing data of primary endpoint was treated statistically according to Last Observation Carried Forward (LOCF) method for ITT, regardless the reason of discontinuation. Missing data of secondary endpoints was not replaced.

Multicenter Studies Considerations

Not applicable; this was a single-center study.

Multiple Comparisons and Multiplicity

Not applicable.

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 (held on the 6th of April 2023, with a follow-up meeting on 18th May 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.

The analysis of demographic and baseline characteristics was performed on the Safety Set population.

Performance Analysis

Primary Performance Endpoints

The primary endpoint was assessed at V3 by comparing, between groups, the proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1. One-sided Fisher's exact test was applied.

Secondary Performance Endpoints

Secondary endpoints were:

- Proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1 at V2 and V4 by comparison between groups and versus baseline; one-sided Fisher's exact test was used for the comparison between groups.
- Patient's reported pain, itch, burning and tenderness at application site (VAS) severity, time to onset and time to peak; Student's t-test (or Mann-Whitney U test in case of non-normal distribution) was used for the comparison between groups.
- RTOG / EORTC radiodermatitis grade (investigator) at V2, V3 and V4; Fisher's Exact test was used for the comparison between groups.
- RDS score (investigator) at V2, V3 and V4; Fisher's Exact test was used for the comparison between groups.
- Size of the affected area measured at V2, V3 and V4 (major and minor diameters were measured); Mann-Whitney U test was used for the comparison between groups.
- OCT and D-OCT parameters (instrumental descriptive assessment of tissue vascularization and integrity and structural parameters) at V2, V3 and V4; the following parameters were evaluated as absolute values and as change from baseline (V1):
    - Epidermal thickness (in mm); Student's t-test was used for the comparison between groups;
    - Collagen density (automatic calculation with dedicated software); Student's t-test (or Mann-Whitney U test in case of non-normal distribution) was used for the comparison between groups;
    - Collagen attenuation (automatic calculation with dedicated software); Student's t-test (or Mann-Whitney U test in case of non-normal distribution) was used for the comparison between groups;

  - Vascular extent at 300 micron depth (automatic calculation with dedicated software); Student's t-test (or Mann-Whitney U test in case of non-normal distribution) was used for the comparison between groups;
  - Vascular extent at 500 micron depth (automatic calculation with dedicated software); Student's t-test (or Mann-Whitney U test in case of non-normal distribution) was used for the comparison between groups.
- Patient's adherence to treatment (assessed by patient's diary); Mann-Whitney U test was used for the comparison between groups.
- Pleasantness of the product (Likert scale for odor, consistency, spreadability, satisfaction), at V3; Fisher's Exact test was used for the comparison between groups.

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The exact total amount of cream could not be estimated in advance, as the quantity of the cream was determined by the extension of the area of the affected skin.
In order to quantify the adherence to treatment, the Investigator recorded in the CRF the number of expected applications and the number of applications recorded by the patient in the diary for each period (Visit 1 – Visit 2, Visit 2 – Visit 3 and Visit 3 – Visit 4).
Treatment compliance was estimated for the period Visit 1–Visit 3 if the patient ended the treatment at Visit 3; treatment compliance was estimated for the period Visit 1–Visit 4 if the patient needed to prolong the treatment up to Visit 4. Treatment compliance was estimated by arithmetic mean of compliances recorded in the CRF for each period.
The patient was considered compliant to the treatment if the arithmetic mean of compliances was greater than or equal to 80%.

Safety Evaluation

Extent of Exposure

After the randomization, the duration of the overall exposure to the investigational device and its comparator was the same. Both products are applied twice daily and therefore the total exposure was in the range 35-42 (± 6) days until visit 3 or 49-56 (± 6) days if the treatment continued until visit 4.

Adverse Events

All enrolled subjects receiving at least one treatment application were included in the safety analysis. The safety analysis included only related events (ADE/SADE/DD).

Related Adverse Events (AEs) and Adverse Device Events (ADEs) were coded using the version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA) to give a preferred term (PT) and a system/organ class term (SOC) for each event.

The number of patients who experienced at least one study product-related AE or ADE, serious AE or ADE, severe related AE or ADE and the number of patients withdrawn due to related AE were summarized through number (N) and proportion of patients (%).

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

Chi-square test was used for the comparison between groups.

CHANGES TO THE ANALYSIS PLANNED

Compared to what was described in the protocol and in the Statistical Analysis Plan, which provided the use of LOCF method also for patients who used prohibited therapies before visit 3, the LOCF method was re-discussed: the RTOG/ EORTC evaluations of visit 2 was carried forward only for the RTOG/EORTC evaluations missing at visit 3 in the ITT population.

Furthermore, in the Statistical Analysis Plan it was estimated that it was necessary to enroll about 82 patients, considering a possible rate of 20% between violators and drop-out patients, to reach 68 evaluable patients; the enrollment was completed reaching 70 patients, of which only 60 patients were evaluable for primary endpoint.

4. Results

4.1 Clinical investigation initiation date

The clinical investigation involved one clinical site in Italy:

- Struttura Complessa di Dermatologia, Azienda Ospedaliero-Universitaria di Modena, Modena University Hospital, Largo del Pozzo, 71 - 41134 Modena, Italy; PI Dr. Mariangela Francomano

The local Ethics Committee (EC) favourable opinion was obtained on the 04-May-2020. Following the completion of authorization process, with contract signature (16-Jun-2020), the site was initiated on the 15-Jul-2020.

The first subject was enrolled on 02-Nov-2020 and in the same day the study start was notified to the National Competent Authority, the Italian Ministero della Salute, on the 4-Nov-2020.

4.2 Clinical investigation completion/suspension date

The last subject in (LSI) was enrolled on the 15-Dec-2022 and the last subject out (LSO) visit was on 16-Feb-2023.

The end of study (LSO) was communicated the National Competent Authority on 17-Feb-2023 to and the clinical site was officially closed on 11-May-2023.

4.3 Disposal of subjects and investigational devices

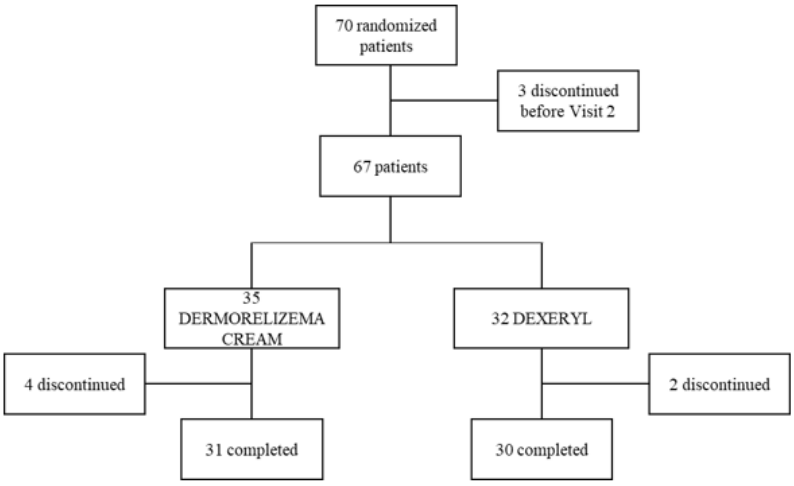
A total of 70 patients were enrolled in the study and all of them started the treatment.

The enrolment phase of the study lasted about 25 months: the first subject signed the informed consent and performed the Visit 1 on 02-Nov-2020 and the last subject on 15-Dec-2022.

At the Visit 1, after eligibility confirmation, subjects received the treatment to start on the same day (the time of the first application depending on the time of the visit). After that, three visits were performed: one follow-up visit (V2) between day 21 and 28, at RT conclusion, one follow-up visit (V3) 2 weeks after RT conclusion (± 3 days) and one follow-up visit (V4) 4 weeks after RT conclusion (± 3 days). The study treatment could stop at V3 or be continued, if needed, until V4, based on Investigator's judgement.

The last patient completed the study on 16-Feb-2023. Overall, the study lasted about 27 months.

Figure 1. *Patients' disposition*



Source: Table 14.1.1 and Listing 16.2.1.

No. 70 patients signed the informed consent forms, attended the first visit and were randomized to start the treatment.

Among the 70 randomized patients, 35 were randomized to DermoRelizema™ cream and 35 to Dexeryl®.

In the DermoRelizema™ cream group four patients interrupted prematurely the study:

Pt. ID 01-024 needed to use a not allowed treatment;

Pt. ID 01-029 needed to use a not allowed treatment;

Pt. ID 01-050 interrupted RT due to suspect breast cancer relapse;

Pt. ID 01-058 was lost to follow-up.

In the Dexeryl® group three patients (pts. ID 01-005, 01-025 and 01-038) withdrew before V2:

- Pt. ID 01-005 withdrew the consent;
- Pt. ID 01-025 was lost to follow-up;
- Pt. ID 01-038 withdrew the consent.

These 3 patients were not included in the Safety population, because no data after the Visit 1 was available.

Two further patients interrupted prematurely the study:

Pt. ID 01-030 needed to use a not allowed treatment;

P. ID 01-063 needed to use a not allowed treatment.

Table 14.1.1 and Listing 16.2.1 show the patients' disposition and the discontinued patients. Based on this, 31 and 30 patients regularly completed the study respectively in the DermoRelizema™ cream and Dexeryl® groups.

4.4 Subject demographics

All patients of the Safety population (n=67, 35 patients in DermoRelizema™ cream group and 32 patients in Dexeryl® group) were female and of Caucasian origin. As shown in Table 14.1.3, no statically significant difference (p value = 0.8580) was detected between groups for age (mean age 59.11 (SD=10.86) years in DermoRelizema™ cream group; mean age 59.56 (SD=9.43) years in Dexeryl® group). Details are in Listing 16.2.4.1.

Vital signs and patient's habits (drinking, smoking, and sport) are reported in Table 14.1.4 and detailed in Listing 16.2.4.5. No statistically significant difference was evidenced between the

two groups except than for the baseline systolic blood pressure (p value=0.0383, mean value 125.77 (SD=14.58) in DermoRelizema™ cream group and 133.59 (SD=15.70) in Dexeryl® group) and for the number of smoked cigarettes (p value= 0.0358, mean value 4.80 (SD=2.49) in DermoRelizema™ cream group and 13.71 (SD=7.85) in Dexeryl® group).

The medical history, the surgical history and the physical examination of the patients are reported in Table 14.1.5, Table 14.1.6 and Table 14.1.7, respectively. Details are in Listings 16.2.4.2-16.2.4.4 All the patients had at least one medical history and the most frequent (apart from breast cancer) involved the cardiovascular, endocrine/metabolic, gastrointestinal and musculoskeletal systems. No noteworthy differences between treatment groups were detected.

4.5 CIP compliance

Overall, 114 protocol deviations (Table 14.1.2 and Listing 16.2.2) were registered during the study, no. 64 in the DermoRelizema™ cream group and 50 in the Dexeryl® group.
The majority of deviations regarded the treatment compliance, the incorrect or missing diary filling, the delay in the visits and mistakes in informed consent and privacy consent completion and signature.
In both treatment groups occurred some major deviations: no. 15 and no.14 respectively in DermoRelizema™ cream and in Dexeryl® groups.

Protocol deviations were duly examined during the two Data Review Meetings and, once evaluated the impact of the deviation on the data collected, it was decided to include 8 patients major protocol deviations in the PP analysis (Pts. ID 01-007, 01-020, 01-032, 01-047, 01-058, 01-068 in the DermoRelizema™ cream group and 01-004, 01-041 in Dexeryl® group). On patient (ID 01-067 from Dexeryl® group) was instead excluded form PP analysis even if her protocol deviation was classified as minor, because the deviation met the discontinuation criteria drafted in the study protocol.

4.6 Analysis

4.6.1 Primary endpoint performance analysis

Primary endpoint data was analyzed in the ITT population (overall 60 patients, 31 in DermoRelizema™ cream and 29 in Dexeryl® group) and the analysis was then repeated in the PP population (overall 50 patients, 27 in DermoRelizema™ cream and 23 in Dexeryl® group).

The primary endpoint was assessed at V3 by comparing, between groups, the proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1. One-sided Fisher's exact test was applied.

In ITT population, 30 patients (96.8%) had radiodermatitis grade ≤ 1 in DermoRelizema™ cream group and 28 (96.6%) in Dexeryl® group. Only 1 patient in each group had grade >1. No difference between groups was detected (p value= 0.737). See table 14.2.1.1.

In PP population, 27 patients (100.0%) had radiodermatitis grade ≤ 1 in DermoRelizema™ cream group and 22 (95.7%) in Dexeryl® group. Only 1 patient in Dexeryl® group had grade >1. No difference between groups was detected (p value= 0.460). See table 14.2.1.2.

Details about RTOG / EORTC radiodermatitis grade by patient are reported in Listing 16.2.6.1.

4.6.2 Secondary endpoints performance analysis

Secondary endpoints analysis was conducted on the ITT population only.

Proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1 at V2 and V4

One-sided Fisher's exact test was used for the comparison between groups (Table 14.2.2.15).
At V2, 27 patients (87.1%) had radiodermatitis grade ≤ 1 in DermoRelizema™ cream group and 26 (92.9%) in Dexeryl® group. Four patients (12.9%) in DermoRelizema™ cream group had grade >1 and two (7.1%) in Dexeryl® group. No difference between groups was detected (p value= 0.8781).
At V4, 30 patients (100.0%) had radiodermatitis grade ≤ 1 in DermoRelizema™ cream group and 28 (100.0%) in Dexeryl® group.

Details about RTOG / EORTC radiodermatitis grade by patient are reported in Listing 16.2.6.1.

Time to onset and time to peak of RISR symptoms

Time to onset and time to peak of RISR symptoms was reported daily on the diary by the patient through VAS. Four symptoms were evaluated: pain, itch, burning and tenderness at site. Student's t-test/ Mann-Whitney U test were used for the comparison between groups. Student's t-test was used when the variable was normally distributed; Mann-Whitney U test was used when the variable was not normally distributed.

The symptom ***pain*** (Table 14.2.2.1) had a mean time to onset of 15.56 days (SD=15.58, with median 12.5 days) in DermoRelizema™ cream group and of 17.90 days (SD=14.05, median 17.0 days) in Dexeryl® group. No difference between groups resulted (p value= 0.5482).
With regard to mean time to peak, it was of 25.22 days (SD=14.11, with median 27.0 days) and of 30.80 days (SD=12.37, with median 28.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups. No difference between groups resulted (p value= 0.2059).

The symptom ***itch*** (Table 14.2.2.2) had a mean time to onset of 14.42 days (SD=10.29, with median 16.0 days) in DermoRelizema™ cream group and of 15.79 days (SD=10.81, with median 18.0 days) in Dexeryl® group. No difference between groups resulted (p value= 0. 6539).
With regard to mean time to peak, it was of 26.88 days (SD=11.12, with median 27.0 days) and of 27.25 days (SD=9.02, with median 28.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups. No difference between groups resulted (p value= 0. 8985).

The symptom ***burning*** (Table 14.2.2.3) had a mean time to onset of 15.53 days (SD=11.97, with median 21.0 days) in DermoRelizema™ cream group and of 12.65 days (SD=10.21, with median 11.0 days) in Dexeryl® group. No difference between groups resulted (p value= 0. 5776).
With regard to mean time to peak, it was of 24.37 days (SD=11.88, with median 28.0 days) and of 27.39 days (SD=10.33, with median 29.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups. No difference between groups resulted (p value= 0. 4033).

The symptom ***tenderness*** (Table 14.2.2.4) had a mean time to onset of 8.00 days (SD=9.28, with median 3.0 days) in DermoRelizema™ cream group and of 12.96 days (SD=9.58, with median 13.0 days) in Dexeryl® group. A statistically significant difference between groups resulted (p value= 0.0290) in favor of Dexeryl®.
With regard to mean time to peak, it was of 22.70 days (SD=10.40, with median 25.0 days) and of 27.57 days (SD=11.48, with median 25.0 days) respectively in DermoRelizema™ cream and Dexeryl® groups. No difference between groups resulted (p value= 0. 1388).

Details about VAS by patient are reported in Listing 16.2.6.2

Radiation dermatitis severity assessed by the Investigator using the RTOG/ EORTC scoring scale

The evaluation of the radiation dermatitis severity, assessed by the Investigator according to the RTOG/ EORTC scoring scale, at V2, V3 and V4 was analysed by Fisher's Exact Test, for

the comparison between groups instead of Chi-square test, because Fisher's Exact Test is particularly suitable for small samples (Table 14.2.2.5).

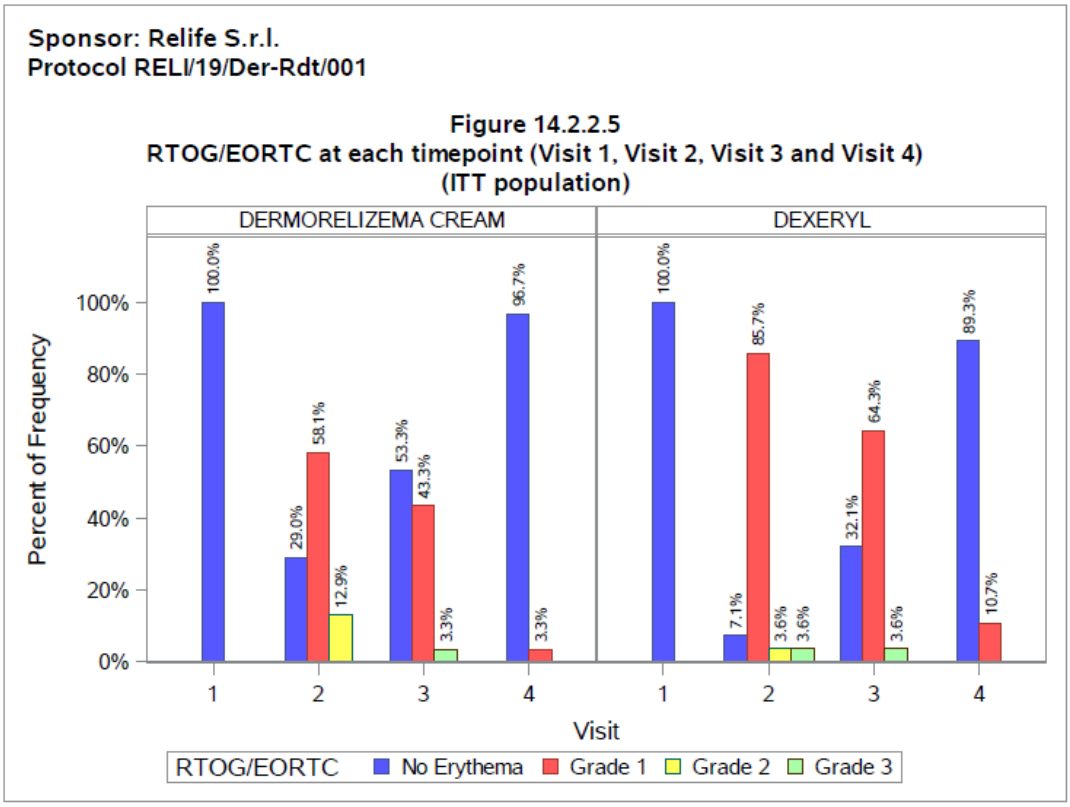
At V1, all patients had RTOG/ EORTC radiodermatitis grade equal to 0, as this was required by the clinical investigation plan: 31 patients (100%) in DermoRelizema™ cream group and 29 (100%) in Dexeryl® group.

At V2, in DermoRelizema™ cream group 9 patients (29.0%) had no erythema, 18 (58.1%) had erythema grade 1, 4 (12.9%) had erythema grade 2 and none had erythema grade 3.
In Dexeryl® group 2 patients (7.1%) had no erythema, 24 (85.7%) had erythema grade 1, one (3.6%) had erythema grade 2 and one (3.6%) had erythema grade 3.
The difference between groups resulted statistically significant (p value= 0.0321) in favor of DermoRelizema™ cream group.

At V3, in DermoRelizema™ cream group 16 patients (53.3%) had no erythema, 13 (43.3%) had erythema grade 1, one (3.3%) had erythema grade 3.
In Dexeryl® group 9 patients (32.1%) had no erythema, 18 (64.3%) had erythema grade 1, one (3.6%) had erythema grade 3.
The difference between groups was not statistically significant (p value= 0.1976). However, the major effect of DermoRelizema™ cream was observed.

At V4, in DermoRelizema™ cream group 29 patients (96.7%) had no erythema and only one (3.3%) had erythema grade 1.
In Dexeryl® group 25 patients (89.3%) had no erythema and 3 (10.7%) had erythema grade 1.
Also in this case, the difference between groups was not statistically significant (p value= 0.3445) but the improving effect of DermoRelizema™ cream was observable.

Figure 14.2.2.5 displays the RTOG/ EORTC at each time point (including baseline, before RT start) in the two treatment groups.



Details about RTOG / EORTC radiodermatitis grade by patient are reported in Listing 16.2.6.1.

Radiation dermatitis severity assessed by the Investigator using the Radiation Dermatitis Severity (RDS) scoring scale

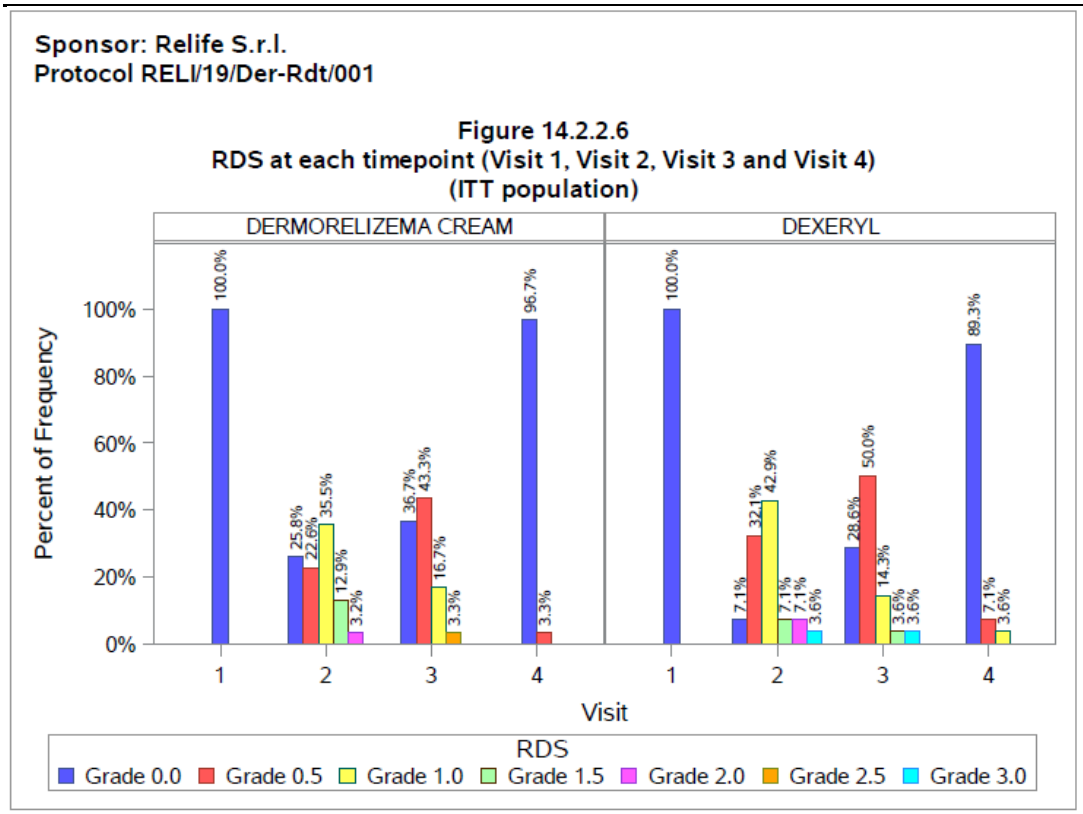
Fisher's Exact Test was used for the comparison between groups instead of Chi-square test, because Fisher's Exact Test is particularly suitable for small samples.

At V1, all patients had RDS score equal to 0.0: 31 (100%) in DermoRelizema™ cream group and 29 (100%) in Dexeryl® group.

During the study, patients split between the RDS grades; at the end of the study almost all patients returned to grade 0.0 (29 patients (96.7%) in DermoRelizema™ cream group and 25 patients (89.3%) in Dexeryl® group), only 1 patient in DermoRelizema™ cream group had RDS grade equal to 0.5; 2 patients in Dexeryl® group had RDS grade equal to 0.5 and 1 patient had RDS grade equal to 1.0.

No statically significant differences were detected at each time point (p values at V2, V3 and V4 were respectively 0.3169, 0.8029 and 0.4115) (Table 14.2.2.6).

Figure 14.2.2.6 shows the RDS score distribution at visits.



Details about RDS scoring scale are reported by patient in Listing 16.2.6.1.

Area affected by RIRS

The size of the area affected by dermatitis was evaluated using maximum and minimum diameters (cm) at each time point. The maximum and the minimum diameters were compared between treatment groups using Mann-Whitney U Test.

Maximum diameter

At V2 the difference between treatment groups was statistically significant (p value=0.0384) in favor of DermoRelizema™ cream: mean diameter 5.35 cm (SD=4.14), median 6.00 cm in DermoRelizema™ cream group and mean diameter 8.07 cm (SD=4.71), median 8.00 cm in Dexeryl® group.

At V3 and V4 the differences between treatment groups were not statistically significant (p values respectively 0.1837 and 0.2800).

At V3: mean diameter 4.13 cm (SD=4.61), median 3.50 cm in DermoRelizema™ cream group and mean diameter 5.71 cm (SD=5.02), median 5.00 cm in Dexeryl® group.

At V4: mean diameter 0.17 cm (SD=0.91), median 0.00 cm in DermoRelizema™ cream group and mean diameter 0.61 cm (SD=1.97), median 0.00 cm in Dexeryl® group) (Table 14.2.2.7).

Minimum diameter

At V2 the difference between treatment groups was not statistically significant (p value=0.1421). In DermoRelizema™ cream group mean diameter was 3.65 cm (SD=3.27), median 4.00 cm and in Dexeryl® group mean diameter was 5.93 cm (SD=4.25), median 4.50 cm).

The same conclusions can be drawn at V3 and V4 (p values respectively 0.3158 and 0.2880). At V3 mean diameter was 2.77 cm (SD=3.22), median 2.00 cm in DermoRelizema™ cream group and mean diameter was 3.86 cm (SD=3.91), median 2.50 cm in Dexeryl® group.

At V4 mean diameter was 0.10 cm (SD=0.55), median 0.00 cm in DermoRelizema™ cream group and mean diameter 0.32 cm (SD=1.19), median 0.00 cm in Dexeryl® group (Table 14.2.2.7).

Skin damage measured by instrumental assessments

Epidermal thickness

Epidermal thickness decreased in both treatment groups between V1 and V2.

The mean change from V1 to V2 was -0.01 mm (SD=0.02), median 0.00 mm in DermoRelizema™ cream group and -0.01 mm (0.01), median: 0.00 in Dexeryl® group.

The difference between treatment groups was not statistically significant (p value=0.6906) but the differences within groups were statistically significant, in both groups (p value=0.0486 and p value=0.0235, respectively in DermoRelizema™ cream group and in Dexeryl® group).

The analysis of epidermal thickness between V1 and V3 provided similar results: mean change -0.01 mm (SD0.02), median -0.00 mm in DermoRelizema™ cream group and mean change -0.01 mm (SD=0.01), median: -0.00 mm in Dexeryl® group).

Also in this case, the difference between groups was not statistically significant (p value=0.6043), while it was only within Dexeryl® group (p value=0.0100).

The change from V1 to V4 was not different between groups (p value=0.6580) and within each group (p value=0.1586 and p value= 0.0679 respectively in DermoRelizema™ cream and in Dexeryl® groups).

From V1 to V4 mean change was -0.01 mm (SD=0.02), median 0.00 mm in DermoRelizema™ cream group and -0.00 mm (SD=0.02), median -0.01 mm in Dexeryl® group (Table 14.2.2.8).

Collagen density

Collagen density decreased in both treatment groups between V1 and V2.

Mean change was -3.44 molecule/µm2 (SD=8.83), median -4.33 molecule/µm2 in DermoRelizema™ cream group and -6.10 molecule/µm2 (SD=9.97), median -4.42 molecule/µm2 in Dexeryl® group. The difference between treatment groups was not statistically significant (p value=0.2817), while it was within each group (p value=0.0382 in DermoRelizema™ cream group and p value=0.0032 in Dexeryl® group).

The analysis of collagen density between V1 and V3 was as follows: mean change -3.56 molecule/µm2 (SD=7.86), median -3.78 molecule/µm2 in DermoRelizema™ cream group and mean -3.51 molecule/µm2 (SD=9.56), median -3.54 molecule/µm2 in Dexeryl® group. Again, the difference between groups was not statistically significant (p value= 0.9826); the difference within DermoRelizema™ cream group was statistically significant (p value=0.0191) while the difference within Dexeryl® group was not statistically significant.

The change of collagen density between V1 and V4 was as follows: mean change -3.91 molecule/µm2 (SD=10.79), median -2.44 molecule/µm2 in DermoRelizema™ cream group and -5.67 molecule/µm2 (SD=8.20), median -7.00 molecule/µm2 in Dexeryl® group. The difference between groups was not statistically significant (p value=0.4900); the difference within DermoRelizema™ cream group was not statistically significant while the difference within Dexeryl® group was statistically significant (p value=0.0011) (Table 14.2.2.9).

Collagen attenuation

Collagen attenuation increased in both treatment groups between V1 and V2: mean change 0.000041 mm-1 (SD=0.001091), median -0.000187 mm-1 in DermoRelizema™ cream group and 0.000219 mm-1 (SD=0.000746), median 0.000299 mm-1 in Dexeryl® group. The difference between treatment groups was not statistically significant (p value=0.4725); the difference within DermoRelizema™ cream and within Dexeryl® group was not statistically significant, as well.

Collagen attenuation increased in both treatment groups between V1 and V3: mean change 0.000296 mm-1 (SD=0.000938), median 0.000186 mm-1 in DermoRelizema™ cream group and 0.000269 mm-1 (SD=0.000741), median 0.000320 mm-1 in Dexeryl® group and again the difference between groups (p value=0.9013) and within groups was not statistically significant.

The same conclusions can be drawn for the change of collagen attenuation between V1 and V4: mean change 0.000229 mm-1 (SD=0.001027), median 0.000357 mm-1 in DermoRelizema™ cream group and 0.000324 mm-1 (SD=0.000872), median 0.000322 mm-1 in Dexeryl® group. Also in this case the difference between groups (p value=0.7081) and within groups was not statistically significant (Table 14.2.2.10).

Vascular extent at 300-micron depth

Vascular extent at 300-micron depth increased in both groups between V1 and V2: mean change was 7657.65 red pixels (SD=7423.32), median 4764.00 red pixels in DermoRelizema™ cream group and 10177.50 red pixels (SD=12023.13), median 6497.00 red pixels in Dexeryl® group. The difference between treatment groups was not statistically significant (p value=0.6434); the difference within groups was statistically significant in both

groups: p value=<0.0001 in DermoRelizema™ cream group and p value=<0.0016 in Dexeryl® group.

Between V1 and V3 the analysis provided similar results and again the difference between groups was not statistically significant (p value= 0.8825): mean change 3113.97 red pixels (SD=4077.80), median 2082.50 red pixels in DermoRelizema™ cream group and 3802.11 red pixels (SD=6857.72), median 2418.50 red pixels in Dexeryl® group. The difference within each group was statistically significant: p value=<0.0001 in DermoRelizema™ cream group and p value=<0.0001 in Dexeryl® group.

Between V1 and V4 the change was as follows: 2349.40 red pixels (SD=3646.62), median 1340.50 red pixels in DermoRelizema™ cream group and 460.36 red pixels (SD=4175.40), median 794.50 red pixels in Dexeryl® group. The difference between groups was not statistically significant (p value=0.1501); the difference within DermoRelizema™ cream group was statistically significant (p value=0.0003) while the difference within Dexeryl® group was not statistically significant (Table 14.2.2.11).

Vascular extent at 500-micron depth

Vascular extent at 500-micron depth increased in both groups between V1 and V2: mean change was 14180.65 red pixels (SD=21738.75), median 7035.00 red pixels in DermoRelizema™ cream group and 11844.64 red pixels (SD=24755.39), median 8972.50 red pixels in Dexeryl® group. The difference between treatment groups was not statistically significant (p value=0.7010) while the difference within DermoRelizema™ cream group and within Dexeryl® group was statistically significant (p value=0.0010 and p value=0.0175, respectively).

Between V1 and V3 vascular extent at 500-micron depth increased in DermoRelizema™ cream group and in Dexeryl® group: mean change 2365.23 red pixels (SD=14762.87), median 4226.50 red pixels in DermoRelizema™ cream group and 4995.04 red pixels (SD=22270.35), median 2328.50 red pixels in Dexeryl® group; the difference between treatment groups and within groups was not statistically significant (p value=0.5958).

Vascular extent at 500-micron depth increased in DermoRelizema™ cream group and decreased in Dexeryl® group between V1 and V4 mean 4881.43 red pixels (SD=18051.29), median 3598.00 red pixels in DermoRelizema™ cream group and -5863.25 red pixels (SD=15602.13), median -2812.50 red pixels in Dexeryl® group. The difference between groups was statistically significant (p value=0.0222), in favor of Dexeryl® while the difference within each group was not statistically significant (Table 14.2.2.12).

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 14.2.2.13 treatment compliance was generally very high in both treatment groups: mean compliance was 92.56 (SD=7.98), median 96.50 days in DermoRelizema™ cream group and 94.43 (D=8.82) days, median 97.50 days in Dexeryl® group. The difference between groups was not statistically significant (p value=0.4846).

Also, treatment days were summarized: in DermoRelizema™ cream group the average days resulted 55.32 (SD=7.43), with a minimum of 42.00 days and a maximum of 71.00 days, while in Dexeryl® group was 55.03 (SD=10.26), with a minimum of 33.00 days and a maximum of 78.00 days. The difference between groups was not statistically significant (p value=0.9008).

Pleasantness of the product

The patient's opinion o pleasantness of the product was assessed at V3 by evaluating smell, texture, spreadability and satisfaction of the product. Each characteristic was obtained by means of a 5-item Likert scale; for each item the number (N) and the proportion of patients (%) were reported (Table 14.2.2.14).

Smell

10 patients (33.3%) treated with DermoRelizema™ cream and 12 patients (42.9%) treated with Dexeryl® cream evaluated "Not pleasant nor unpleasant" the smell of the product. The remaining 20 patients (66.7%) treated with DermoRelizema™ cream and 16 patients (57.1%) treated with Dexeryl® cream evaluated "Pleasant" or "Very pleasant" the smell of the product. The difference between groups was not statistically significant (p value=0.3439) (Table 14.2.2.14).

Texture

No patients treated with DermoRelizema™ cream evaluated "Not pleasant nor unpleasant" the texture of the product while 2 patients (7.1%) treated with Dexeryl® cream evaluated "Not pleasant nor unpleasant" the texture of the product. All 30 patients treated with DermoRelizema™ cream and the remaining 26 patients (92.9%) treated with Dexeryl® cream evaluated "Pleasant" or "Very pleasant" the texture of the product. The difference between groups was not statistically significant (p value=0.4297) (Table 14.2.2.14).

Spreadability

All patients (30 in DermoRelizema™ cream group and 28 in Dexeryl® group) evaluated "Pleasant" or "Very pleasant" the spreadability of the product. The difference between groups was not statistically significant (p value=0.7866) (Table 14.2.2.14).

Satisfaction

One patient (3.3%) in DermoRelizema™ cream group and 2 patients (7.1%) in Dexeryl® group evaluated “Not pleasant nor unpleasant” the satisfaction of the product. The remaining 29 patients (96.7%) treated with DermoRelizema™ cream and 26 patients (92.9%) treated with Dexeryl® cream evaluated “Pleasant” or “Very pleasant” the satisfaction of the product. The difference between groups was not statistically significant (p value=0.7582) (Table 14.2.2.14).

4.6.3 Safety analysis

Safety analysis was conducted on the Safety population (i.e., 67 patients). The safety analysis included only related events (ADE/SADE/DD).

Overall, 14 adverse events were registered during the study: 6 adverse events involving 6 patients treated with DermoRelizema™ cream (pts. ID 01-007, 01-016, 01-029, 01-032, 01-049 and 01-050) and 8 adverse events involving 6 patients treated with Dexeryl® cream (pts. ID 01-010, 01-015, 01-017, 01-018, 01-041 and 01-055).

None of them was serious and only 1 adverse event (Hypersensitivity), involving patient ID 01-049, was possibly related to the study product, of mild intensity and spontaneously resolved within the same day (Table 14.3.1 and Listing 16.2.7).

Two AEs (not related to study treatment) lead to premature study interruption:

- Pt. ID 01-029 (DermoRelizema™ cream group) needed to start a not allowed treatment for dermatitis reacutization;
- Pt. ID 01-050 (DermoRelizema™ cream group) had a suspected cancer relapse, subsequently evaluated as false positive.

5. Discussion and overall conclusions

Approximately 50 percent of all cancer patients can benefit from radiation therapy (RT) in the management of their disease. However, RT is not free from toxicity. Acute and chronic radiation-induced skin reactions (RISR) represent an inevitable consequence for up to 95% of people receiving RT.

The development of RISR usually occurs within few weeks after the initiation of the RT and persists up one month. RISR are usually characterized by objective early signs such as swelling, redness, pigmentation, followed dry and then mostly desquamation, epilation, fibrosis, and ulceration of the skin and subjective symptoms including pain, warmth, burning, itching, psychological distress, leading even to discontinuation of the RT.

Currently there are no unanimously recognised guidelines for the management of RISRs and consequently many centres develop their own prophylactic or therapeutic protocols. So far there is no treatment considered gold standard.

Based on DermoRelizema™ cream ingredients properties and based on pre-clinical and clinical evidence, it can constitute a safe and effective treatment for dermatitis and erythema.
In this study, DermoRelizema™ cream was investigated in the management of RISRs in patients with breast cancer who started the treatment with the study product about one week before the start of RT, to prevent, delay and reduce the radiodermatitis onset and severity. To better evaluate the efficacy of DermoRelizema™ cream and for ethical reasons, Dexeryl® cream was used as comparator, being a product widely used in Europe and indicated for the management of various types of dermatoses including atopic dermatitis, ichthyosis, xerosis and in case of erythema induced by radiotherapy. Furthermore, in order to collect objective and reliable data, the study was conducted with an observer-masked method: clinical assessments were performed by an experienced physician unaware of the treatment used by the patient.
Finally, patients started the study treatment 1 week before RT start, to prepare the skin to receive RT. For this reason, baseline values/assessments were those of a healthy skin (no signs nor symptoms of dermatitis).

The primary performance endpoint was the treatment success measured as the proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 at V3 (i.e. 2 weeks after RT conclusion). In the ITT population, the 96.8% of patients treated with DermoRelizema™ cream and the 96.6% of patients treated with Dexeryl® cream had radiodermatitis grade ≤ 1. When the analysis was repeated in PP population, success was observed in 100% of patients treated with DermoRelizema™ cream and in 95.7% of patients treated with Dexeryl® cream. The difference between treatment groups was not statistically significant (Table 14.2.2.1 and Table 14.2.2.2), however DermoRelizema™ cream showed to be as performant as Dexeryl® or even slightly more. Also, at V2 (i.e. at RT conclusion) and V4 (i.e. 4 weeks after RT conclusion) both products showed a high success rate. In particular, at V2 the rate of success was 87.1% and 92.9% respectively in DermoRelizema™ cream and Dexeryl® groups, while at V4 the 100% of patients had radiodermatitis grade ≤ 1 in both treatment groups.

During the study, patients experienced erythema measured through the RTOG/ EORTC grade (scoring from no erythema to grades 1 to 3); at V2 DermoRelizema™ cream showed a very good performance in the erythema management, with a difference statistically significant respect to Dexeryl® (p value= 0.0321). At V2 in fact the 29.0% of patients under DermoRelizema™ cream had no erythema and the 58.1% had grade 1, while only the 7.1% of patients under Dexeryl® had no erythema and the 85.7% had grade 1. No erythema grade 3 was observed in DermoRelizema™ cream group while 1 patient reached grade 3 in Dexeryl®

group. No statically significant differences were detected at other time points. At V4 almost all patients returned to the initial condition of “No Erythema” (Table 14.2.2.5).

Radiation dermatitis severity was assessed by the Investigator using the Radiation RDS scoring scale. During the study, patients split between the RDS grades; at the end of the study almost all patients returned to grade 0.0. Even if no statically significant differences were detected at each time point between the two treatment groups, a trend in favor of DermoRelizema™ cream was observable: at V2 the 25.8% of patients had grade 0.0 vs 7.1% in Dexeryl®, the 22.6% vs 32.1% had grade 0.5, the 35.5% vs. 43.3% had grade 1.0 (diffuse erythema). Grade 2 was observed in 3.2% vs 7.1% of the patients and grade 3 was only detected in Dexeryl® group (3.6%). Same trend was observed at V3, with 36.7% of patients with grade 0.0 in DermoRelizema™ cream group and the 28.6% in Dexeryl® group, the 43.3% with grade 0.5 vs the 50%. Finally, no grade 3 was observed in DermoRelizema™ cream group, while it was in Dexeryl® group (3.6%) (Table 14.2.2.6).

RISR symptoms were reported by patients every day by compiling VAS scales on the diary. Time to onset and time to peak were evaluated for 4 symptoms: pain, itch, burning and tenderness at RT site. Both DermoRelizema™ cream and Dexeryl® showed similar time to onset and time to peak for pain (Table 14.2.2.1), itch (Table 14.2.2.2) and burning (Table 14.2.2.3), with a trend in favor of Dexeryl® cream. Only in the tenderness time to onset resulted a statistically significant difference between groups, in favor of Dexeryl® (p value= 0.0290). No difference in the time to peak for this symptom (Table 14.2.2.4).

With regards to OCT and D-OCT parameters measured during the study, a statistically significant result (p value=0.0384) was observed on the dimension of the area affected by RIRS: at V2 the mean maximum diameter of the area was 5.35 cm in DermoRelizema™ cream group and 8.07 cm in Dexeryl® group. At V3 and V4 the differences between treatment groups were not statistically significant.
Skin damage was instrumentally measured through the change from baseline in epidermal thickness, collagen density, collagen attenuation, vascular extent at 300 and 500 micron depth. In general, no differences were identified between the two groups, except than in Vascular extent at 500-micron depth between V1 and V4, where Dexeryl® resulted reduce the vascular extent more than to decrease more than DermoRelizema™ cream (p value=0.0222).
Both treatments groups had a very good compliance and patients’ evaluation on the peasantness of the two creams was generally very good with a slight preference for DermoRelizema™ cream.

From the safety point of view, 14 adverse events were registered during the study but only one was related to DermoRelizema™ cream: one case of mild and transient hypersensitivity at application site (Table 14.3.1 and Listing 16.2.7). No serious adverse events occurred.

Based on this evidence, it can be concluded that DermoRelizema™ cream is a non-pharmacologic, safe product for the control and improvement of the RISR, as the comparator. The use of emollient and hydrating products is confirmed as a valid treatment to prevent damages caused by RT and to reduce the risk of premature interruption of RT.

6. Abbreviated terms and definitions

ADE	Adverse Device Effect
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification System
AOU	Azienda Ospedaliero Universitaria
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
DM	Data manager
D-OTC	Dynamic Optical Coherence Tomography
DRM	Data Review Meeting
EC	Ethics Committee
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full Analysis Set
FTU	Fingertip Unit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation 679/2016
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IFU	Instructions For Use
LLT	Low Level Term
LOCF	Last Observation Carried Forward
LSI	Last Subject In
LSO	Last Subject Out
MDD	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Medical Device Regulation
ml	Milliliters
mm	Millimeters
OTC	Over the Counter

PI	Principal Investigator
PMCFS	Post Market Clinical Follow-up Study
PP	Per-Protocol
PT	Preferred Term
QoL	Quality of Life
RDS	Radiation Dermatitis Severity
RISR	Radiation-Induced Skin Reaction
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SHBF	Sodium Hyaluronate Butyrate Formate
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TEWL	Trans-Epidermal Water Loss
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

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 everyone.

One clinical site was involved and the competent EC approval was requested and obtained. The EC of the coordinating site (Comitato Etico Azienda Ospedaliero-Universitaria di Modena), evaluated this clinical investigation in the meeting of the 04-May-2020 and expressed a favourable opinion.

The Italian CA (Ministry of Health) was notified about the study start on the 02-Nov-2020, after the first subject was enrolled on the same day.

During the study two substantial amendments were issued:

1. Amendment 1 date 02-Jan-2021 for the PI change at clinical site
2. Amendment 2 date 10-Feb-2022 to specify the interim analysis process, to update timelines of the project and make some changes in the Sponsor's and CRO personnel and some corrections in the protocol.

The end of study (LSO) was communicated the National Competent Authority on 17-Feb-2023 to and the clinical site was officially closed on 11-May-2023.

The study essential documents were archived according to the CRO SOPs (in line with ISO 14155 guideline) and will be kept by the investigational sites and the Sponsor according to MDR 2017/45 requirements. It will be responsibility of the Principal Investigator to assure that the study essential documents are duly filed in the Trial Centre File and that the Trial Centre File is correctly stored and preserved after the study closure.

8. Investigators and administrative structure of clinical investigation

Study Site 01 – Coordinating Site Struttura Complessa di Dermatologia Azienda Ospedaliero-Universitaria di Modena Largo del Pozzo, 71 - 41134 Modena, Italy	**Principal Investigator** Mariangela Francomano
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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.

27 / 07 /2023
Date

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

28 / 07 / 23
Date

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

28/07/2023
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.

31/08/2023
Date

Mariangela Francomano
Struttura Complessa di Dermatologia
Azienda Ospedaliero-Universitaria di Modena

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

Statistical Analysis Report version 1.0 date 24 Oct 2022

Interim Statistical Analysis Summary Report date 27 Oct 2022

Statistical Analysis Report version 2.0 date 14 Jun 2023

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J. SUPPLEMENTARY TABLES