STATISTICAL ANALYSIS REPORT

Protocol Code: RELI/19/Der-Rdt/001
EudraCT number: NA

"Efficacy and tolerability evaluation of a topical medical device based on SHBF in management of radiodermatitis. An observer-masked, controlled study."

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Effect
CIP	Clinical Investigation Plan
CRF	Case report form
DD	Device Deficiency
D-OCT	Dynamic Optical Coherence Tomography
EORTC	European Organization for Research and Treatment of Cancer
ITT	Intention To Treat set
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
mm	Millimeter
OCT	Optical coherence tomography
PP	Per Protocol dataset
RDS	Radiation Dermatitis Severity
RISR	Radiation-Induced Skin Reaction
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SHBF	Sodium hyaluronate butyrate formate
SS	Safety Set
V	Visit

1. VERSION HISTORY

1.1 VERSION HISTORY OF THE STATISTICAL ANALYSIS REPORT

Version Number	Summary/Reason for changes	Date issued
1.0	First version	08/05/2023
2.0	Second version: update of the PP population and update of the classification of some deviations	14/06/2023

1.2 VERSION HISTORY OF THE SAP

Version Number	Date	Description
1.0	12/07/2022	First emission
2.0	19/09/2022	Second emission: change of statistical tests used for two secondary endpoints (RTOG/ EORTC radiodermatitis grade and RDS score)

1.3 VERSION HISTORY OF THE CIP

Version Number	Date	Description
00	05/12/2019	First emission.
01	10/03/2020	CIP modified according to Ethics Committee requests (removal of colorimetry).
02	10/02/2022	Provide details about interim analysis. Define the ITT population datasets for final statistical analysis. Update Principal Investigator details and list of Sponsor and CRO personnel involved in the Investigation. Update Study timelines. Correct the definition of hypofractionated radiation therapy and several minor mistakes. Add paragraphs "vulnerable population" and "suspension or premature termination of the clinical investigation".

2. INTRODUCTION

RELI/19/Der-Rdt/001 is 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 care of radiodermatitis in women with breast cancer. Assessments and evaluations are performed by a physician in a blind fashion.

The study groups are treated as follows:

- Test group: DermoRelizema™ cream.
- Control group: Dexeryl® cream.

If according to the Investigator's opinion at visit 3 the patient needs further treatment, this is prolonged up to visit 4, in both treatment groups. The treatments are assigned to the eligible patients in order of their inclusion in the clinical study and according to a randomized sequence, through randomization envelopes.

The study assessments scheduled according to the table below:

Visit	**V1**	**RT start (Day 7 ±3)**	**V2**	**V3**	**V4**
Activity	Screening, Randomization **Treatment start**		**RT end**	2 Weeks after RT end **End of treatment**	4 Weeks after RT end **Study End**
Day	Day 1[1]		Day 21-28[2] since RT start	Day 35-42[3](± 3) since RT start	Day 49-56[4](± 3) since RT start
Informed Consent	X				
Eligibility criteria	X				
Demography	X				
Medical history and lifestyle	X				
Past/concomitant medications	X		X	X	X
Physical examination	X				X
Randomization	X				
Dermatological assessment (RTOG/EORTC, RDS)	X		X	X	X
Dermatological assessment (area size)			X	X	X
OCT/ D-OCT	X		X	X	X
Patient's symptoms by VAS at visit	X				
Study Products supply to patient	X			X*	
Study Products application	X (every day, twice a day)				X*
Study Product return from patient				X	X*

Diary delivery to patients	X		X	X	
Diary return from patients			X	X	X
Patient's symptoms VAS on diary		X (every day)			X
Treatment adherence on diary	X (every day)				X*
Safety assessment			X	X	X
Products pleasantness				X	

1. *One week (± 3 days) prior to RT start. Study product application will start on Day 1.*
2. *The end of the RT will depend on the therapeutic plan defined by the site. RT could last of 3 or 4 weeks.*
3. *Two weeks after RT completion. End of treatment. If necessary, the patient can continue the treatment.*
4. *Four weeks after RT completion. Study end.*

* *Treatment will be continued until Visit 4, based on the Investigator's decision. If continued, new product will be given to patient.*

This Statistical Report is based on the Statistical Analysis Plan (SAP) version 2.0, dated 19/09/2022 and describes the final analysis performed on all endpoints of the study on all enrolled patients.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of the study is 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). The primary objective is measured at visit 3 (two weeks after last RT session).

3.2 SECONDARY OBJECTIVES

1. 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.
2. To evaluate the radiation dermatitis severity, assessed by the investigator using the RTOG/ EORTC scoring scale, at visit 2, 3 and 4.
3. To evaluate the radiation dermatitis severity, assessed by the investigator using the Radiation Dermatitis Severity (RDS) scoring scale at visit 2, 3 and 4.
4. To evaluate the extension of the area affected by RISR, at visit 2, 3 and 4.
5. 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.
6. Patient's adherence to treatment (assessed by patient's diary).
7. To evaluate the patient's overall opinion on products' pleasantness assessment by a 5-points Likert scale (e.g., smell, texture (respectively called odor and consistency in the CIP/SAP), spreadability, patient's satisfaction) at visit 3.

8. 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).
9. Occurrence of adverse events (including local reactions and systemic reactions).

4. GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

4.1 GENERAL STATISTICAL METHODS AND PROGRAMS

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

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

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

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

All statistical programs of the final analysis were validated. The validation of the programs is performed by a second statistician: this person, different from the one who produced the program, verifies the correctness of the program, using specific checklists. In case of error, the program will be produced again and a new validation will be implemented; otherwise, the program passes the test and the first statistician signs the checklist for approval.

4.2 MISSING DATA

Patients who discontinued before visit 2 were not evaluable for the primary endpoint. If these patients applied the treatment were included in the Safety population. Missing data were not replaced.

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

In the primary endpoint analysis, only for two patients (01-058 and 01-063) the RTOG/EORTC scoring scale was carried forward from visit 2 to visit 3, using the LOCF method.

4.3 CHANGE FROM SAP

Compared to what was described 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 will be 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 are evaluable for primary endpoint.

During the Data Review Meeting were discussed the inclusion/exclusion of patient affected by Major Protocol Deviation in Per-Protocol Population. Based on the impact on rights, safety and well-being of trial subjects and on data integrity some of them have been included in this population, even if the classification remains Major. The list of patients included/excluded and relevant details and justifications are reported in the DRM addendum minute of 18/05/2023.

5. ANALYSIS POPULATIONS

5.1 INTENT-TO-TREAT POPULATION (ITT)

The Intention to Treat set (ITT) includes all patients of the Safety population, regardless if they satisfied the CIP eligibility 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.

5.2 PER-PROTOCOL (PP) POPULATION

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

5.3 SAFETY POPULATION

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

6. METHODS FOR THE ANALYSIS OF DEMOGRAPHY, BASELINE CHARACTERISTICS AND COMPLIANCE

6.1 DEMOGRAPHIC DATA

Demographic data (gender, age, ethnic origin) were summarized in the Table 14.1.3 and in the Listing 16.2.4.1.

The descriptive statistics included number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and number of observations and their percentages for categorical parameters.

Age of the two groups of patients was compared using Student's t-test.

6.2 BASELINE CHARACTERISTICS

Data collected at visit 1, before any study treatment administration, are considered as baseline values.

Baseline characteristics (vital signs, lifestyle, medical history, surgical history and physical examination) were summarized in the Tables 14.1.4, 14.1.5, 14.1.6, 14.1.7 and in the Listings 16.2.4.2, 16.2.4.3, 16.2.4.4 and 16.2.4.5.

The descriptive statistics included number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and number of observations and their percentages for categorical parameters.

Baseline characteristics of the two groups of patients were compared using Student's t-test or Chi-square test, as appropriate.

6.3 COMPLIANCE

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 by the Investigator in the CRF for each period (visit 1 – visit 2, visit 2 – visit 3 and visit 3 – visit 4, if applicable).

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

The following formula was used by Investigator:

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

Patient's adherence to treatment was summarized in the Table 14.2.2.13 and in the Listing 16.2.5.

7. METHODS FOR THE ANALYSIS OF PRIMARY ENDPOINT

7.1 PROPORTION OF PATIENTS WITH RTOG / EORTC RADIODERMATITIS GRADE ≤ 1 AND >1 AT V3

The primary endpoint was assessed at visit 3 by comparing, between groups, the proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1. One-sided Fisher's exact test was applied.

The primary endpoint outcome is described in Tables 14.2.1.1 (ITT population) and 14.2.1.2 (PP population). Details about RTOG / EORTC radiodermatitis grade by patient are reported in Listing 16.2.6.1.

8. METHODS FOR THE ANALYSIS OF SECONDARY ENDPOINTS

8.1 TIME TO ONSET AND TIME TO PEAK OF RISR SYMPTOMS

The first secondary endpoint is time to onset and time to peak of RISR symptoms as reported daily by the patient through VAS. Four symptoms were evaluated: pain at site, itch at site, burning at site 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.

This endpoint is described from Table 14.2.2.1 to Table 14.2.2.4. Details about VAS by patient are reported in Listing 16.2.6.2.

8.2 RADIATION DERMATITIS SEVERITY ASSESSED BY THE INVESTIGATOR USING THE RTOG/ EORTC SCORING SCALE

The second secondary endpoint is the evaluation of the radiation dermatitis severity, assessed by the investigator according to the RTOG/ EORTC scoring scale, at visit 1, 2, 3 and 4. 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.

This endpoint is described in the Table 14.2.2.5. Details about RTOG / EORTC radiodermatitis grade by patient are reported in Listing 16.2.6.1.

8.3 RADIATION DERMATITIS SEVERITY ASSESSED BY THE INVESTIGATOR USING THE RADIATION DERMATITIS SEVERITY (RDS) SCORING SCALE

The third secondary endpoint is the evaluation of the radiation dermatitis severity, assessed by the investigator according to the Radiation Dermatitis Severity (RDS) scoring scale, at visit 1, 2, 3 and 4. 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.

This endpoint is described in the Table 14.2.2.6. Details about RDS scoring scale are reported by patient in Listing 16.2.6.1.

8.4 AREA AFFECTED BY RISR

The fourth secondary endpoint was the evaluation of the extension of the area affected by RISR. The Investigator recorded major and minor diameters of the skin area affected by dermatitis at visit 2, 3 and 4. Mann-Whitney U test was used for the comparison between groups instead of Student's t-test, because the variable was not normally distributed.

This endpoint is described in the Table 14.2.2.7. Details about the area affected by RISR by patient (major and minor diameters) are reported in Listing 16.2.6.1.

8.5 SKIN DAMAGE MEASURED BY INSTRUMENTAL ASSESSMENTS

The fifth secondary endpoint is the evaluation of the skin damage by instrumental assessment (OCT and D-OCT) at visit 1, 2, 3 and 4. The skin damage was evaluated through the following parameters:

- Epidermal thickness (in mm)
- Collagen density (automatic calculation with dedicated software)
- Collagen attenuation (automatic calculation with dedicated software)
- Vascular extent at 300-micron depth (automatic calculation with dedicated software)
- Vascular extent at 500-micron depth (automatic calculation with dedicated software)

The value of epidermal thickness reported in the CRF is the mean value of 3 measurements in 3 different points of the region of interest (ROI). The ROI is positioned just below the junction in areas without artifacts or obstructive structures that can alter the signal and it is selected by an experienced evaluator.

The value of collagen density is automatically calculated by a dedicated software and it is the average of the pixels of the ROI.

The attenuation coefficient, which represents the property of the tissue to attenuate the laser light penetration, is automatically calculated by a dedicated software.

The vascular extent at 300-micron depth and at 500-micron depth represent the vessel density to superficial and intermediate dermis; these values are the count of pixels in a predefined area at the two depths and are automatically calculated by a dedicated software.

The analysis of the skin damage was performed using absolute values and change from baseline. Comparison of the values before-after treatment was evaluated with Student's t-test for paired data/Wilcoxon signed-rank test. 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.

This endpoint is described from Table 14.2.2.8 to Table 14.2.2.12. Details about the OCT and D-OCT parameters are reported by patient in Listing 16.2.6.4.

8.6 PATIENT'S ADHERENCE TO TREATMENT

The sixth secondary endpoint was the evaluation of the patient's adherence to treatment. Mann-Whitney U test was used for the comparison between groups instead of Student's t-test, because the variable was not normally distributed. Also, the treatment days was described; Student's t-test was used for the comparison between groups.

This endpoint is described in the Table 14.2.2.13. Details about compliance to the treatment by patient are reported in Listing 16.2.5.

8.7 PLEASANTNESS OF THE PRODUCT

The seventh secondary endpoint is the patient's overall opinion on products' pleasantness assessed by a 5-points Likert scale (e.g., smell, texture (respectively called odor and consistency in the CIP/SAP), spreadability, satisfaction) at visit 3. 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.

This endpoint is described in the Table 14.2.2.14. Details about patient's product pleasantness are reported by patient in Listing 16.2.6.3.

8.8 PROPORTION OF PATIENTS WITH RTOG / EORTC RADIODERMATITIS GRADE ≤ 1 AND >1 AT V2 AND V4

The eight secondary endpoint is the proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1 at visit 2 and 4. One-sided Fisher's exact test was used for the comparison between groups.

This endpoint is described in the Table 14.2.2.15. Details about RTOG / EORTC radiodermatitis grade by patient are reported in Listing 16.2.6.1.

8.9 OCCURRENCE OF ADVERSE EVENTS

The nineth secondary endpoint is the proportion of patients who experienced at least one adverse event. 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.

This endpoint is described in the Table 14.2.2.16.

9. METHODS FOR THE ANALYSIS OF SAFETY ENDPOINTS

9.1 ADVERSE EVENTS

The safety analysis included only related events (ADE/SADE).

The number of patients who experienced at least one AE or ADE, serious AE or ADE was summarized through number (N) and proportion of patients (%).

The analysis of adverse events is summarized in the Table 14.3.1.

Related adverse events were coded using the version 26.0 of the Medical Dictionary for Regulatory Activities (MedDRA) to give a preferred term (PT) and a system organ class (SOC) for each event and summarized by treatment group. The display of adverse events by SOC and PT was described in the Table 14.3.2.

All adverse events by patient are described in the Listing 16.2.7.

10. STUDY SUBJECTS

10.1 DISPOSITION OF SUBJECTS

The disposition of subject at each visit was assessed through information reported in the CRF. The number and percentage of dropouts were reported, together with the reason for dropout.

For the final analysis, all patients (from 01-001 to 01-070) were considered.

All 70 patients were randomized. Among the 70 randomized patients, three patients (01-005, 01-025 and 01-038) were not included in the Safety population, because we have no data after the visit 1. The remaining 67 patients were randomized as follows: 35 patients were treated with DermoRelizema™ cream and 32 patients were treated with Dexeryl® cream.

61 patients completed the study (31 DERMORELIZEMA CREAM group and 30 DEXERYL group) and 6 patients withdrew prematurely (01-024, 01-029, 01-050, 01-058 DERMORELIZEMA CREAM group and 01-030, 01-063 DEXERYL group) due to the use of a medication/treatment not allowed (Table 14.1.1). Details about discontinued patients are reported in Listing 16.2.1.

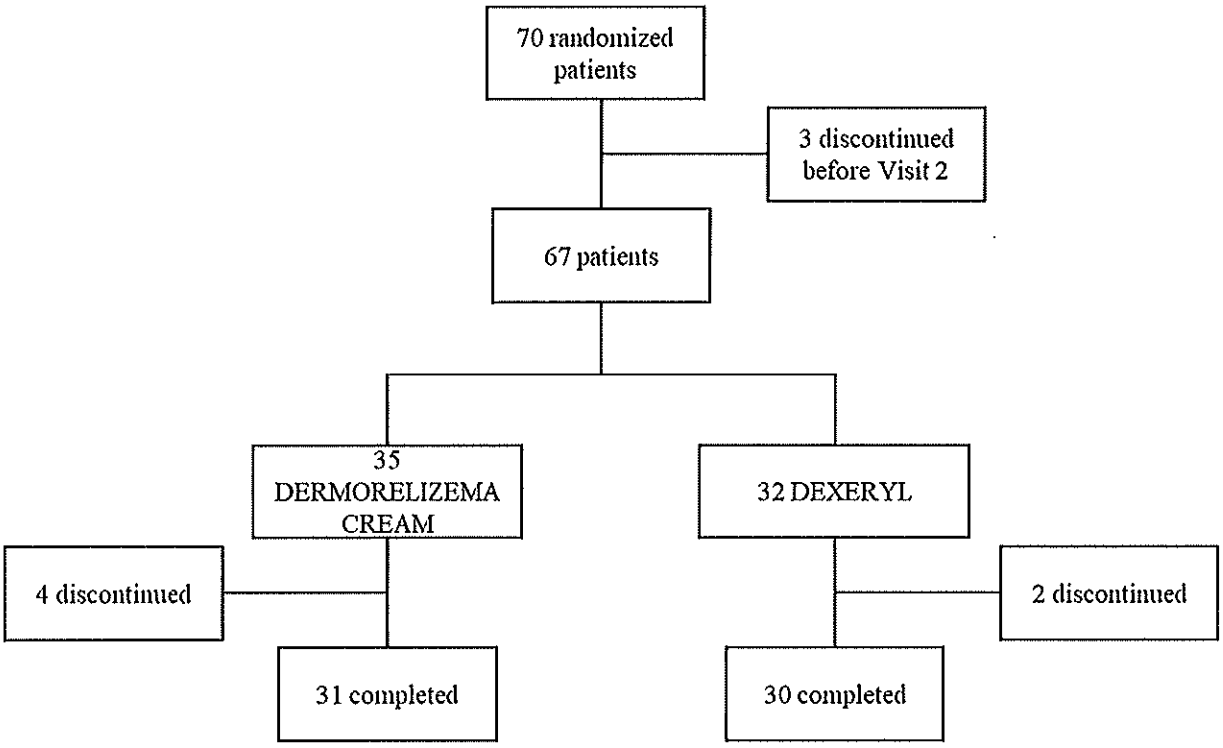


Figure 1 Patients' disposition

10.2 PROTOCOL DEVIATIONS

Protocol deviations were summarized, separately for each treatment group.

52 patients (77.6%) present at least one protocol deviation: 27 patients (77.1%) in DERMORELIZEMA CREAM group and 25 patients (78.1%) in DEXERYL group. A total of 114 protocol deviations occurred during the study (64 in DERMORELIZEMA CREAM group and 50 in DEXERYL group), of which only 29 deviations were Major (15 in DERMORELIZEMA CREAM group and 14 in DEXERYL group) (Table 14.1.2). Details about protocol deviations by patient are reported in Listing 16.2.2.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

70 patients were screened and randomized; 67 patients received at least one dose of the study product.

Primary endpoint and secondary endpoints were analyzed on ITT population; additionally, a Per-Protocol (PP) analysis was also performed on primary endpoints. Safety endpoints were analyzed on the Safety population.

The distribution of populations used for the statistical analysis is reported in the Listing 16.2.3.

11.2 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic data are reported in Table 14.1.3.

All patients of the Safety population are female and Caucasian (35 patients in DERMORELIZEMA CREAM group and 32 patients in DEXERYL group). No statically significant difference was detected for age (mean (SD): 59.11 (10.86) years, median: 60.00 years in DERMORELIZEMA CREAM group and mean (SD): 59.56 (9.43) years, median: 60.00 years in DEXERYL group).

Vital signs and patient's habits (drinking, smoking, and sport) are reported in Table 14.1.4. A statically significant difference between treatment groups were detected at baseline for the systolic blood pressure (p=0.0383) and for the number of smoked cigarettes (p= 0.0358). No statically significant differences between treatment groups were detected for the other parameters.

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. No noteworthy differences between treatment groups were detected.

Details about demographics and baseline characteristics are reported from Listing 16.2.4.1 to Listing 16.2.4.5.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance was calculated by arithmetic mean of compliances recorded by the Investigator in the CRF for each period (visit 1 – visit 2, visit 2 – visit 3 and visit 3 – visit 4, if applicable). Compliance was calculated as a percentage and compared between treatment groups using Mann-Whitney U Test: the difference between treatment groups was not statistically significant (mean (SD): 92.56% (7.98), median: 96.50% in DERMORELIZEMA CREAM group and mean (SD): 94.43% (8.82), median: 97.50% in DEXERYL group) (Table 14.2.2.13).

Treatment compliance details are reported in the Listing 16.2.5.

11.4 EFFICACY RESULTS

11.5 *ANALYSIS OF EFFICACY*

11.4.1.1 Primary efficacy endpoint

11.4.1.1.1 Proportion of patients with RTOG / EORTC radiodermitis grade ≤ 1 and >1 at V3

The treatment success (RTOG / EORTC radiodermatitis grade ≤ 1 at visit 3) or failure (RTOG / EORTC radiodermatitis grade > 1 at visit 3) was described using the number (N) and the proportion of patients (%). Treatment success was observed in 96.8% of patients treated with DermoRelizema™ cream and in 96.6% of patients treated with Dexeryl® cream. Treatment failure was observed in only 1 patient (3.2%) of DERMORELIZEMA CREAM group and in 1 patient (3.4%) of DEXERYL group. The difference between treatment groups was not statistically significant (Table 14.2.2.1).

The same analysis was performed on the PP population: treatment success was observed in all patients treated with DermoRelizema™ cream and in 95.7% of patients treated with Dexeryl® cream;

consequently, treatment failure was observed in only 1 patient (4.3%) of DEXERYL group. The difference between treatment groups was not statistically significant (Table 14.2.2.2).

11.4.1.2 Secondary efficacy endpoints

11.4.1.2.1 Time to onset and time to peak of RIRS symptoms

Time to onset and time to peak of RISR symptoms was evaluated through patient's VAS (pain at site, itch at site, burning at site and tenderness at site).

Time to onset was calculated as difference (in days) between the date of the first radiotherapy session and the date of onset of symptom and time to peak as difference (in days) between the date of the first radiotherapy session and the date of peak of symptom.

Pain at application site

Time to onset of pain was compared between treatment groups using Mann-Whitney U Test: the difference between treatment groups was not statistically significant (mean (SD): 15.56 (15.58) days, median: 12.50 days in DERMORELIZEMA CREAM group and mean (SD): 17.90 (14.05) days, median: 17.00 days in DEXERYL group) (Table 14.2.2.1).

Time to peak of pain was compared between treatment groups using Student's t-test: the difference between treatment groups was not statistically significant (mean (SD): 25.22 (14.11) days, median: 27.00 days in DERMORELIZEMA CREAM group and mean (SD): 30.80 (12.37) days, median: 28.00 days in DEXERYL group) (Table 14.2.2.1).

Itch at application site

Time to onset of itch was compared between treatment groups using Student's t-test: the difference between treatment groups was not statistically significant (mean (SD): 14.42 (10.29) days, median: 16.00 days in DERMORELIZEMA CREAM group and mean (SD): 15.79 (10.81) days, median: 18.00 days in DEXERYL group) (Table 14.2.2.2).

Time to peak of itch was compared between treatment groups using Student's t-test: the difference between treatment groups was not statistically significant (mean (SD): 26.88 (11.12) days, median: 27.00 days in DERMORELIZEMA CREAM group and mean (SD): 27.25 (9.02) days, median: 28.00 days in DEXERYL group) (Table 14.2.2.2).

Burning at application site

Time to onset of burning was compared between treatment groups using Mann-Whitney U Test: the difference between treatment groups was not statistically significant (mean (SD): 15.53 (11.97) days, median: 21.00 days in DERMORELIZEMA CREAM group and mean (SD): 12.65 (10.21) days, median: 11.00 days in DEXERYL group) (Table 14.2.2.3).

In the same way, the time to peak of burning was analyzed and the same conclusions can be drawn: (mean (SD): 24.37 (11.88) days, median: 28.00 days in DERMORELIZEMA CREAM group and mean (SD): 27.39 (10.33) days, median: 29.00 days in DEXERYL group) (Table 14.2.2.3).

Tenderness at application site

Time to onset of tenderness was compared between treatment groups using Mann-Whitney U Test: the difference between treatment groups was statistically significant (p=0.0290) (mean (SD): 8.00 (9.28) days, median: 3.00 days in DERMORELIZEMA CREAM group and mean (SD): 12.96 (9.58) days, median: 13.00 days in DEXERYL group) (Table 14.2.2.4).

Time to peak of tenderness was compared between treatment groups using Student's t-test: the difference between treatment groups was not statistically significant (mean (SD): 22.70 (10.40) days, median: 25.00 days in DERMORELIZEMA CREAM group and mean (SD): 27.57 (11.48) days, median: 25.00 days in DEXERYL group) (Table 14.2.2.4).

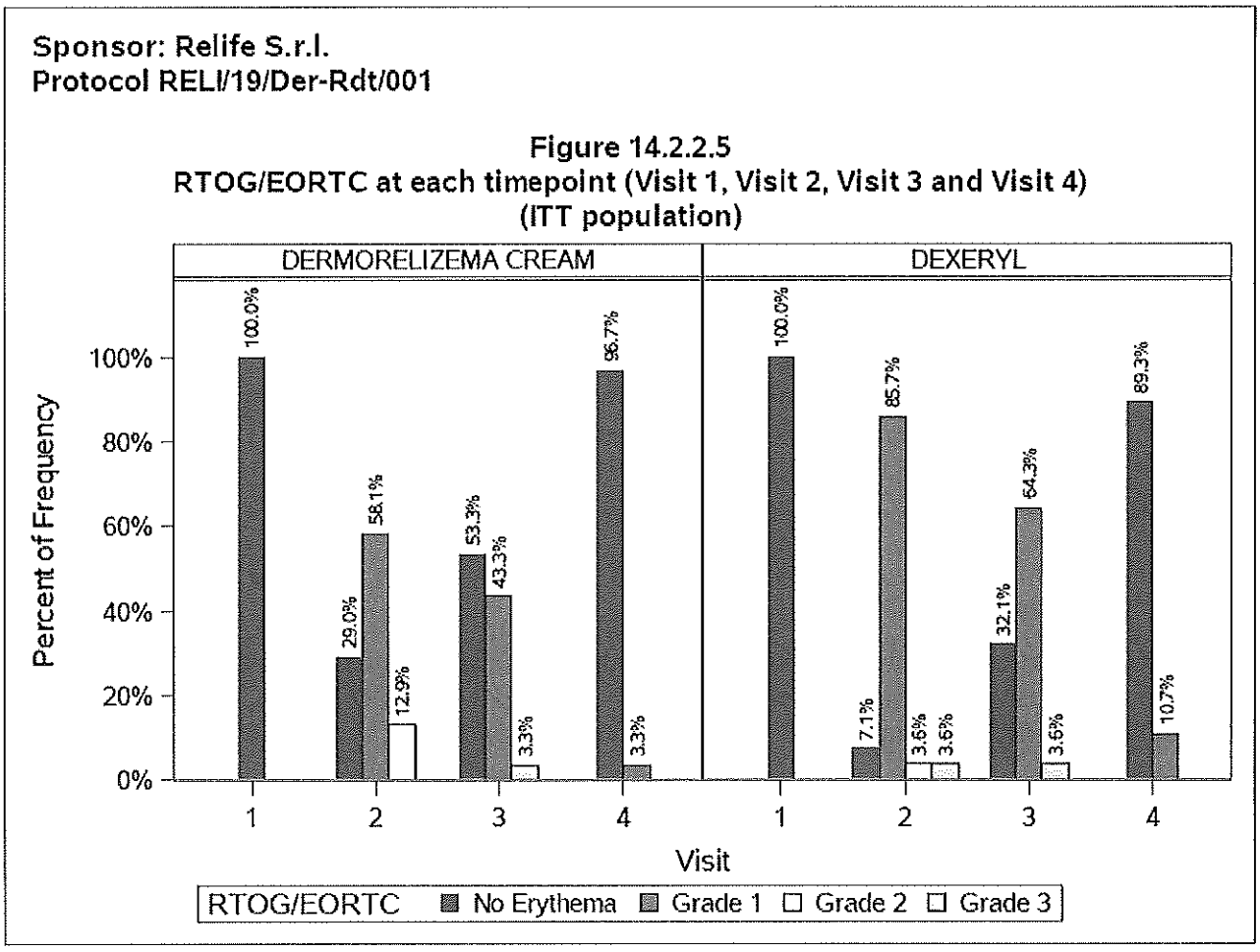
11.4.1.2.2 Radiation dermatitis severity assessed by the investigator using the RTOG/ EORTC scoring scale

At visit 1, 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.

During the study, patients experienced erythema of RTOG/ EORTC grade 1 to 3 or no erythema; at visit 4 almost all patients returned to the condition of "No Erythema": 29 patients (96.7%) in DERMORELIZEMA CREAM group and 25 patients (89.3%) in DEXERYL group, only 1 patient in DERMORELIZEMA CREAM group and 3 patients in DEXERYL group had RTOG/ EORTC radiodermatitis grade equal to 1.

To compare the distribution of RTOG/ EORTC radiodermatitis grade between treatment groups, Fisher's Exact Test was used; a statically significant difference was detected at visit 2 (p= 0.0321), while no statically significant differences were detected at the other time points (visit 3 and 4) (Table 14.2.2.5).

Figure 14.2.2.5 shows the RTOG/EORTC radiodermatitis grade distribution at visits.



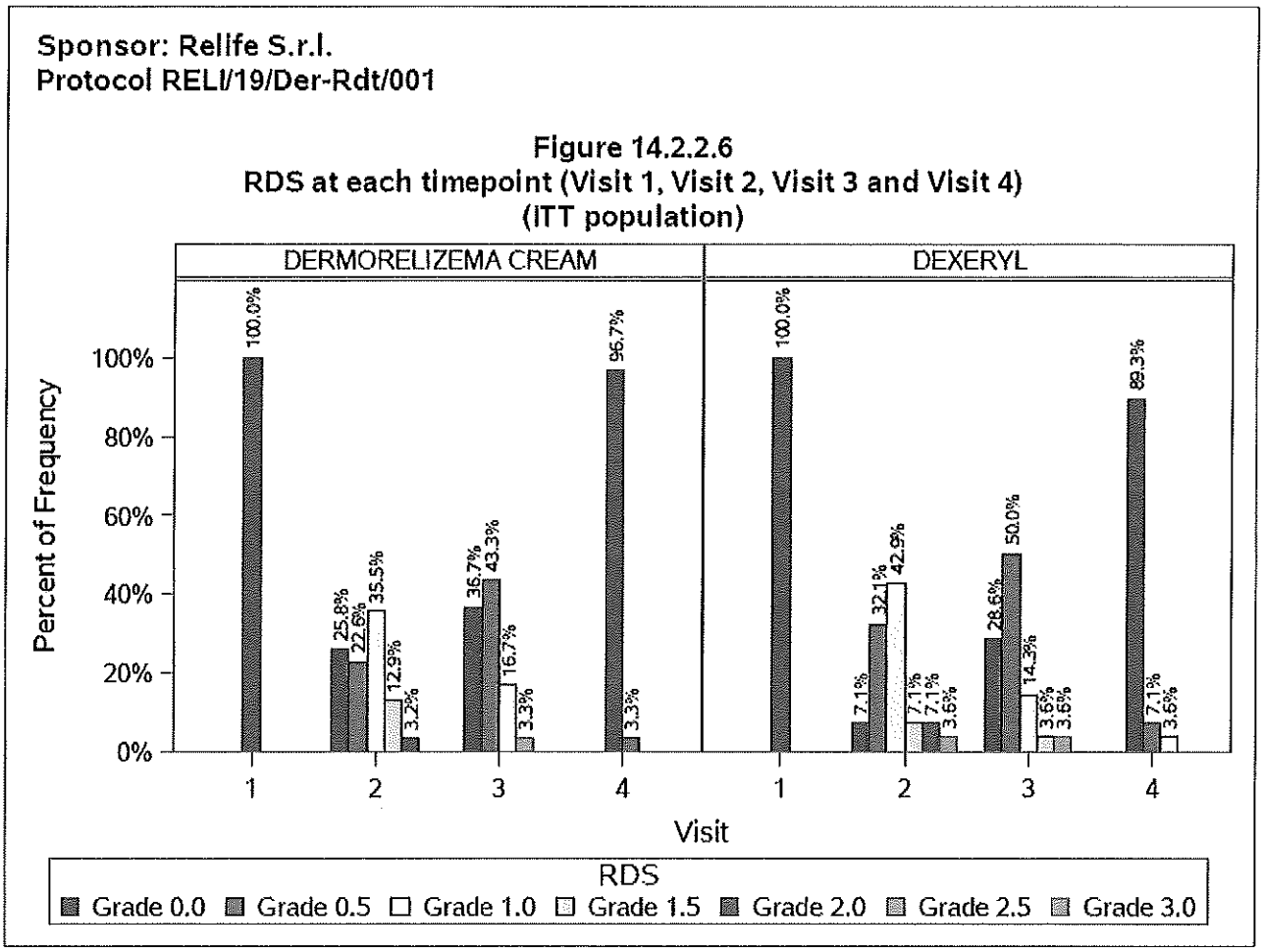
11.4.1.2.3 Radiation dermatitis severity assessed by the investigator using the radiation dermatitis severity (RDS) scoring scale

At visit 1, 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 RTOG/ EORTC radiodermatitis grade equal to 0.5; 2 patients in DEXERYL group had RTOG/ EORTC radiodermatitis grade equal to 0.5 and 1 patient had RTOG/ EORTC radiodermatitis grade equal to 1.0.

To compare the distribution of RDS scoring scale between treatment groups, Fisher's Exact Test was used; no statically significant differences were detected at each time point (visit 2, 3 and 4) (Table 14.2.2.6).

Figure 14.2.2.6 shows the RDS score distribution at visits.



11.4.1.2.4 Area affected by RIRS

The size of the area affected by dermatitis was evaluated using maximum and minimum diameters (cm) at each time point (visit 2, 3 and 4). The maximum and the minimum diameters were compared between treatment groups using Mann-Whitney U Test.

Maximum diameter

At visit 2 the difference between treatment groups was statistically significant (p=0.0384) (mean (SD): 5.35 (4.14) cm, median: 6.00 cm in DERMORELIZEMA CREAM group and mean (SD): 8.07 (4.71) cm, median: 8.00 cm in DEXERYL group).

At visit 3 and visit 4 the differences between treatment groups were not statistically significant (visit 3 – mean (SD): 4.13 (4.61) cm, median: 3.50 cm in DERMORELIZEMA CREAM group and mean (SD): 5.71 (5.02) cm, median: 5.00 cm in DEXERYL group; visit 4 – mean (SD): 0.17 (0.91) cm, median: 0.00 cm in DERMORELIZEMA CREAM group and mean (SD): 0.61 (1.97) cm, median: 0.00 cm in DEXERYL group) (Table 14.2.2.7).

Minimum diameter

At visit 2 the difference between treatment groups was not statistically significant (mean (SD): 3.65 (3.27) cm, median: 4.00 cm in DERMORELIZEMA CREAM group and mean (SD): 5.93 (4.25) cm, median: 4.50 cm in DEXERYL group). The same conclusions can be drawn at visit 3 and visit 4 (visit 3 – mean (SD): 2.77 (3.22) cm, median: 2.00 cm in DERMORELIZEMA CREAM group and mean (SD): 3.86 (3.91) cm, median: 2.50 cm in DEXERYL group; visit 4 – mean (SD): 0.10 (0.55) cm, median: 0.00 cm in DERMORELIZEMA CREAM group and mean (SD): 0.32 (1.19) cm, median: 0.00 cm in DEXERYL group) (Table 14.2.2.7).

11.4.1.2.5 Skin damage measured by instrumental assessments

Epidermal thickness

Epidermal thickness decreased in both treatment groups between visit 1 and visit 2 (mean (SD): -0.01 (0.02) mm, median 0.00 mm in DERMORELIZEMA CREAM group and mean (SD): -0.01 (0.01) mm, median: 0.00 in DEXERYL group) and the difference between treatment groups was not statistically significant; the differences within groups were statistically significant (p=0.0486 and p=0.0235, respectively in DERMORELIZEMA CREAM group and in DEXERYL group).

The analysis of epidermal thickness between visit 1 and visit 3 provided similar results (mean (SD): -0.01 (0.02) mm, median -0.00 mm in DERMORELIZEMA CREAM group and mean (SD): -0.01 (0.01), median: -0.00 mm in DEXERYL group) and again the difference between groups; the difference within DERMORELIZEMA CREAM group was not statistically significant while the difference within DEXERYL group was statistically significant (p=0.0100).

Similar conclusions can be drawn for the change of epidermal thickness between visit 1 and visit 4 (mean (SD): -0.01 (0.02) mm, median 0.00 mm in DERMORELIZEMA CREAM group and mean (SD): -0.00 (0.02) mm, median: -0.01 mm in DEXERYL group) (Table 14.2.2.8).

Collagen density

Collagen density decreased in both treatment groups between visit 1 and visit 2 (mean (SD): -3.44 (8.83) molecule/µm2, median -4.33 molecule/µm2 in DERMORELIZEMA CREAM group and mean (SD): -6.10 (9.97) molecule/µm2, median: -4.42 molecule/µm2 in DEXERYL group) and the difference between treatment groups was not statistically significant; the differences within DERMORELIZEMA CREAM group and within DEXERYL group were statistically significant (p=0.0382 and p=0.0032, respectively).

The analysis of collagen density between visit 1 and visit 3 provided similar results (mean (SD): -3.56 (7.86) molecule/µm2, median -3.78 molecule/µm2 in DERMORELIZEMA CREAM group and mean (SD): -3.51 (9.56) molecule/µm2, median: -3.54 molecule/µm2 in DEXERYL group) and again the difference between groups was not statistically significant; the difference within DERMORELIZEMA CREAM group was statistically significant (p=0.0191) while the difference within DEXERYL group was not statistically significant.

Similar conclusions can be drawn for the change of collagen density between visit 1 and visit 4 (mean (SD): -3.91 (10.79) molecule/µm2, median -2.44 molecule/µm2 in DERMORELIZEMA CREAM group and mean (SD): -5.67 (8.20) molecule/µm2, median: -7.00 molecule/µm2 in DEXERYL group) and again the difference between groups was not statistically significant; the difference within DERMORELIZEMA CREAM group was not statistically significant while the difference within DEXERYL group was statistically significant (p=0.0011) (Table 14.2.2.9).

Collagen attenuation

Collagen attenuation increased in both treatment groups between visit 1 and visit 2 (mean (SD): -0.000041 (0.001091) mm-1, median -0.000187 mm-1 in DERMORELIZEMA CREAM group and mean (SD): 0.000219 (0.000746) mm-1, median: 0.000299 mm-1 in DEXERYL group) and the difference between treatment groups was not statistically significant; the difference within DERMORELIZEMA CREAM and within DEXERYL group was not statistically significant.

Collagen attenuation increased in both treatment groups between visit 1 and visit 3 (mean (SD): -0.000296 (0.000938) mm-1, median 0.000186 mm-1 in DERMORELIZEMA CREAM group and mean (SD): 0.000269 (0.000741) mm-1, median: 0.000320 mm-1 in DEXERYL group) and again the difference between groups and within groups was not statistically significant.

The same conclusions can be drawn for the change of collagen attenuation between visit 1 and visit 4 (mean (SD): 0.000229 (0.001027) mm-1, median 0.000357 mm-1 in DERMORELIZEMA CREAM group and mean (SD): 0.000324 (0.000872) mm-1, median: 0.000322 mm-1 in DEXERYL group) and again the difference between groups 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 visit 1 and visit 2 (mean (SD): 7657.65 (7423.32) red pixels, median 4764.00 red pixels in DERMORELIZEMA CREAM group and mean (SD): 10177.50 (12023.13) red pixels, median: 6497.00 red pixels in DEXERYL group) and the difference between treatment groups was not statistically significant; the difference within groups was statistically significant (p=<0.0001 in DERMORELIZEMA CREAM group and p=<0.0001 in DEXERYL group).

Between visit 1 and visit 3 the analysis provided similar results and again the difference between groups was not statistically significant (mean (SD): 3113.97 (4077.80) red pixels, median 2082.50 red pixels in DERMORELIZEMA CREAM group and mean (SD): 3802.11 (6857.72) red pixels, median: 2418.50 red pixels in DEXERYL group). The difference between treatment groups was not statistically significant; the difference within each group was statistically significant (p=<0.0001 in DERMORELIZEMA CREAM group and p=<0.0001 in DEXERYL group).

Vascular extent at 300-micron depth increased in both groups between visit 1 and visit 4 (mean (SD): 2349.40 (3646.62) red pixels, median 1340.50 red pixels in DERMORELIZEMA CREAM group and mean (SD): 460.36 (4175.40) red pixels, median: 794.50 red pixels in DEXERYL group). The difference between groups was not statistically significant; the difference within

DERMORELIZEMA CREAM group was statistically significant (p=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 visit 1 and visit 2 (mean (SD): 14180.65 (21738.75) red pixels, median 7035.00 red pixels in DERMORELIZEMA CREAM group and mean (SD): 11844.64 (24755.39) red pixels, median: 8972.50 red pixels in DEXERYL group) and the difference between treatment groups was not statistically significant; the difference within DERMORELIZEMA CREAM group and within DEXERYL group was statistically significant (p=0.0010 and p=0.0175, respectively).

Between visit 1 and visit 3 vascular extent at 500-micron depth increased in DERMORELIZEMA CREAM group and in DEXERYL group (mean (SD): 2365.23 (14762.87) red pixels, median 4226.50 red pixels in DERMORELIZEMA CREAM group and mean (SD): 4995.04 (22270.35) red pixels, median: 2328.50 red pixels in DEXERYL group); the difference between treatment groups and within groups was not statistically significant.

Vascular extent at 500-micron depth increased in DERMORELIZEMA CREAM group and decreased in DEXERYL group between visit 1 and visit 4 (mean (SD): 4881.43 (18051.29) red pixels, median 3598.00 red pixels in DERMORELIZEMA CREAM group and mean (SD): -5863.25 (15602.13) red pixels, median: -2812.50 red pixels in DEXERYL group); the difference between groups was statistically significant (p=0.0222) while the difference within each group was not statistically significant (Table 14.2.2.12).

11.4.1.2.6 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 (SD): 92.56 (7.98) days, median 96.50 days in DERMORELIZEMA CREAM group and mean (SD): 94.43 (8.82) days, median: 97.50 days in DEXERYL group). The difference between groups was not statistically significant.

Also, treatment days were summarized: in DERMORELIZEMA CREAM group the average days is 55.32 (7.43), with a minimum of 42.00 days and a maximum of 71.00 days, while in DEXERYL group the average days is 55.03 (10.26), with a minimum of 33.00 days and a maximum of 78.00 days. The difference between groups was not statistically significant.

11.4.1.2.7 Pleasantness of the product

The patient's pleasantness of the product was assessed at visit 3 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 subjects (%) 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 (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 (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 (Table 14.2.2.14).

Satisfaction

1 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 (Table 14.2.2.14).

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

At visit 2 the treatment success (RTOG / EORTC radiodermatitis grade ≤ 1) or failure (RTOG / EORTC radiodermatitis grade > 1) was described using the number (N) and the proportion of patients (%). Treatment success was observed in the 87.1% of patients treated with DermoRelizema™ cream and in the 92.9% of patients treated with Dexeryl® cream. Treatment failure was observed in only 4 patients (12.9%) in DERMORELIZEMA CREAM group and in only 2 patients (7.1%) in DEXERYL group. The difference between treatment groups was not statistically significant (Table 14.2.2.15).

At visit 4 treatment success (RTOG / EORTC radiodermatitis grade ≤ 1) was observed in all patients treated with DermoRelizema™ cream and in all patients treated with Dexeryl® cream.

11.4.1.2.9 Occurrence of adverse events

During the study, 6 patients (17.1%) in DERMORELIZEMA CREAM group and 6 patients (18.8%) in DEXERYL group experienced at least an adverse event. The occurrence of adverse events was

compared between treatment groups using Fisher's Exact Test: the difference between treatment groups was not statistically significant (table 14.2.2.16).

12. SAFETY EVALUATION

12.1 ADVERSE EVENTS

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 (01-007, 01-016, 01-029, 01-032, 01-049 and 01-050) and 8 adverse events involving 6 patients treated with Dexeryl® cream (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 01-049, was possibly related to the study product (Table 14.3.1 and Listing 16.2.7).

According to clinical investigation plan, only related events were coded using the MedDRA dictionary; Table 14.3.2 shows the single related adverse event summarized by body system and preferred terms.

13. DISCUSSION

The discussion will be reported in the clinical investigation report.

14. ADDITIONAL TABLES, FIGURES AND GRAPHS

14.1 DEMOGRAPHIC DATA

Table 14.1.1 Patients' disposition (Safety population)

Table 14.1.2 Protocol deviations (Safety population)

Table 14.1.3 Demographic characteristics (Safety population)

Table 14.1.4 Baseline characteristics (Safety population)

Table 14.1.5 Medical history (Safety population)

Table 14.1.6 Surgical history (Safety population)

Table 14.1.7 Physical examination (Safety population)

14.2 EFFICACY DATA

14.3 *PRIMARY ENDPOINT*

Table 14.2.1.1 Proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1 at Visit 3 (ITT population)

Table 14.2.1.2 Proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1 at Visit 3 (PP population)

14.4 *SECONDARY ENDPOINTS*

Table 14.2.2.1 Time to onset and time to peak – Patient's reported pain at application site (VAS) severity (ITT population)

Table 14.2.2.2 Time to onset and time to peak – Patient's reported itch at application site (VAS) severity (ITT population)

Table 14.2.2.3 Time to onset and time to peak – Patient's reported burning at application site (VAS) severity (ITT population)

Table 14.2.2.4 Time to onset and time to peak – Patient's reported tenderness at application site (VAS) severity (ITT population)

Table 14.2.2.5 RTOG/EORTC radiodermatitis grade (investigator) at each time point (Visit 1, 2, 3 and 4) (ITT population)

Table 14.2.2.6 RDS score (investigator) at each time point (Visit 1, 2, 3 and 4) (ITT population)

Table 14.2.2.7 Size of the area (cm) affected by dermatitis (major and minor diameters) at each time point (Visit 2, 3 and 4) (ITT population)

Table 14.2.2.8 Change from baseline (Visit 1) to each time point (Visit 2, 3 and 4) in the Epidermal thickness (mm) (ITT population)

Table 14.2.2.9 Change from baseline (Visit 1) to each time point (Visit 2, 3 and 4) in the Collagen density (molecule/µm2 (mean)) (ITT population)

Table 14.2.2.10 Change from baseline (Visit 1) to each time point (Visit 2, 3 and 4) in the Collagen attenuation (mm-1 (mean)) (ITT population)

Table 14.2.2.11 Change from baseline (Visit 1) to each time point (Visit 2, 3 and 4) in the Vascular extent at 300-micron depth (red pixels (mean)) (ITT population)

Table 14.2.2.12 Change from baseline (Visit 1) to each time point (Visit 2, 3 and 4) in the Vascular extent at 500-micron depth (red pixels (mean)) (ITT population)

Table 14.2.2.13 Patient's adherence to treatment (ITT population)

Table 14.2.2.14 Pleasantness of the product (Likert scale for smell, texture, spreadability, satisfaction) at Visit 3 (ITT population)

Table 14.2.2.15 Proportion of patients with RTOG / EORTC radiodermatitis grade ≤ 1 and >1 at Visit 2 and Visit 4 (ITT population)

Table 14.2.2.16 Occurrence of Adverse Event at the end of study (ITT population)

14.5 SAFETY DATA

Table 14.3.1 Analysis of adverse events observed (Safety population)

Table 14.3.2 Display of related adverse events observed (Safety population)

15. REFERENCES

None.

16. APPENDICES

16.1 STUDY INFORMATION

These appendices will be attached to the clinical investigation report.

16.2 SUBJECT DATA LISTINGS

Listing 16.2.1 Discontinued Patients

Listing 16.2.2 Protocol Deviations

Listing 16.2.3 Patients Excluded from the Efficacy Analysis

Listing 16.2.4.1 Demographic Data and Other Baseline Characteristics – Demography

Listing 16.2.4.2 Demographic Data and Other Baseline Characteristics – Medical History

Listing 16.2.4.3 Demographic Data and Other Baseline Characteristics – Surgical History

Listing 16.2.4.4 Demographic Data and Other Baseline Characteristics – Breast Cancer Surgery

Listing 16.2.4.5 Demographic Data and Other Baseline Characteristics – Lifestyle

Listing 16.2.5 Compliance

Listing 16.2.6.1 Individual Efficacy Response Data – Dermatitis Characteristics