STATISTICAL ANALYSIS PLAN

Protocol Code: HD01-16-30
EudraCT number: NA

"MONOCENTER, OPEN LABEL CLINICAL INVESTIGATION ON THE TREATMENT WITH XONRID®, A MEDICAL DEVICE FOR THE PREVENTION AND TREATMENT OF RADIOTHERAPY-INDUCED DERMATITIS, IN BREAST AND HEAD & NECK CANCER PATIENTS RECEIVING CURATIVE TREATMENT "

Sponsor

Helsinn Healthcare SA
Via Pian Scairolo, 9
6912 Lugano-Pazzallo, Switzerland

Contract Research Organization

Latis Srl
Viale Sauli, 39/5 - 16121 Genoa - Italy
Phone: +39 010 562234
Fax: +39 010 540699

APPROVAL

Protocol code: HD01-16-30

Title: "MONOCENTER, OPEN LABEL CLINICAL INVESTIGATION ON THE TREATMENT WITH XONRID®, A MEDICAL DEVICE FOR THE PREVENTION AND TREATMENT OF RADIOTHERAPY-INDUCED DERMATITIS, IN BREAST AND HEAD & NECK CANCER PATIENTS RECEIVING CURATIVE TREATMENT"

Document: Statistical Analysis Plan

Version No.: 1.0

Date: 18-Dec-2018

Author:

Statistician, Latis Srl

Name and Surname FABIO MONTANARO *(block letters)*

Signature _____ Date 18/12/2018

Approval:

Scientific Director, Latis Srl

Name and Surname LAURA MICHELLINI *(block letters)*

Signature _____ Date 18/12/2018

Sponsor's Representative, Helsinn Healthcare SA

Name and Surname FABIO MACCHI *(block letters)*

Signature _____ Date 18/12/2018

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	European Community
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
g/m^2h	grams per square meter per hour
Gy	Gray
ITA	Individual Typological Angle
ITT	Intention to treat
MASCC	Multinational Association for Supportive Care in Cancer
MedDRA	Medical Dictionary for Regulatory Activities
OR	Odds Ratio
PP	Per Protocol
PRO	Patient-Reported Outcome
PT	Preferred Term
RS	Reflectance Spectrometry
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAP	Statistical Analysis Plan
SOC	Standard Of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
TEWL	Trans Epidermal Water Loss

1. VERSION HISTORY

1.1 Version history of the SAP

Version Number	Summary/Reason for changes	Date issued
1.0	First version	18-Dec-2018

1.2 Version history of the Protocol

Version Number	Date	Description
1.0	06-02-2017	First version

1.3 Version history of the CRF

Version Number	Date	Description
1.0	30-Jun-2017	First version
1.1	25-Jul-2017	New fields creation, mandatory checks update

2. INTRODUCTION

Justification for the design of the clinical investigation

Acute radiation dermatitis is a common side effect of radiotherapy in many forms of cancer, first of all breast and head & neck. The intensity of the reaction depends on radiotherapy parameters (dose per fraction, total dose, use of bolus or other beam-modifying devices, type and energy of radiation, size of the treatment field and site treated) and on concomitant chemotherapy employment. Although with a lesser grade, other factors involved in determining the intensity of radiation dermatitis are comorbidities (e.g. diabetes) and individual susceptibility1-2.

Skin reactions during radiotherapy, scored according to different systems, usually span in severity from mild erythema (grade 1) to moist desquamation confined to skin folds (grade 2) or not (grade 3).

Large ulcerations that require surgical procedures (grade 4) with potential lethal consequences (grade 5) are exceptional and should be considered non-acceptable complications in routine practice.

Early onset of severe acute skin reaction during treatment could be responsible for a reduced compliance to the planned schedule of irradiation, so jeopardizing local disease control.

The most used scales for assessing toxicities (Radiation Therapy Oncology Group RTOG and CTCAE) do not capture symptoms as reported by the patients. Moreover, adverse events assessed by physicians are less accurate than patient-reported outcome (PRO) instruments and some clinicians have proposed replacing physician scales with patient-assessed reporting of adverse events[3-4].

A recent trial showed how CTCAE and the PRO Skindex-16 were supplementary and that patients reported a greater number of symptoms. The Skindex-16 allows patient rating of emotional and functional burdens that the CTCAE does not take into account[5]. These adverse events cause patient's discomfort and impact negatively on quality of life[6].

There is no gold-standard approach in the prevention and management of radiation dermatitis; however, a large variety of products and methods for the prevention of acute radiation-induced skin reactions have been tested, without identifying one product that has clearly demonstrated superiority over another[7].

Generally, preemptive treatments are aimed to reduce the drying effect of radiotherapy that causes desquamation and loss of the superficial protective layers of the skin. In this regard, the most employed agents are moisturizing creams, aimed at hydrating the skin and preventing the transcutaneous water loss.

Evidence-based recommended for practice include the employment of intensity-modulated radiation therapy and usual hygiene practices such as washing the irradiated skin and the use of mild soaps[8]. The employment of a moisturizing cream based on urea or anionic polar phospholipid is advisable[9-10].

There is a strong need to study products with a preemptive role in radiation dermatitis development, with a trial design taking into account patient subjective evaluation and compliance.

Investigational device

Xonrid® is a promising EC-marked medical device for radiation dermatitis; it is a topical gel that prevents and treats skin symptoms such as erythema, itching, burning sensation and pruritus, induced by radiotherapy or other causes.

When applied to the target skin areas, Xonrid® forms a protective film, reduces the TEWL (Trans Epidermal Water Loss) and increases moisturizing.

It promotes the healing process by restoring the physiological hydration levels of the affected skin areas.

It can be applied to the target areas including skin folds and creases, with or without minor trauma or abrasions.

Xonrid® is manufactured by Helsinn Healthcare SA.

In a recent pilot study[11] using Xonrid®, the proportion of patients treated with Xonrid® and SOC preemptive treatment that not reached G2 radiation dermatitis at week 5 was 82.9%. Xonrid® use resulted associated with a decrease in the incidence of G3 toxicity and a delay in the development of G2 toxicity when compared to the data from a previous study (historical cohort)[12]. At week 5, patients with G2 and G3 dermatitis were about 52% and 10% in the historical cohort and 15% and 2% in the pilot study, respectively.

The aim of this clinical investigation is to evaluate if the use of Xonrid® in the prevention and treatment of G2 radiation dermatitis in breast and head & neck cancer patients can be a valid support, when compared to the Standard of Care as defined by MASCC (Multinational Association for Supportive Care in Cancer) guidelines.
Forty women affected by breast cancer and forty men and/or women affected by head & neck cancer, planned to undergo postoperative or curative radiation treatment have been enrolled in this clinical investigation.

3. STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective of this clinical investigation is to evaluate the proportion of patients without G2 radiation dermatitis at week 5.

3.2 Secondary Objectives

The secondary objectives of this clinical investigation are:

1. to evaluate the median time to G2 radiation dermatitis development according to CTCAE
2. to evaluate the proportion of patients without G2 radiation dermatitis at week 6 for both cancer sites, at week 7 for head & neck cancer and two weeks after the last radiation for both cancer sites .
3. to evaluate the worst skin toxicity during treatment and until 2 weeks after the last radiation, according to CTCAE
4. to evaluate changes in skin erythema and pigmentation and trans-epidermal water loss (TEWL)
5. to evaluate the mean and worst score of Patient Reported Outcome (PRO) with Skindex-16 questionnaire performed weekly
6. to evaluate the compliance to experimental treatment use
7. to evaluate the patient global satisfaction with treatment as assessed by Likert scale.

4. STUDY METHODS

4.1 Study Design

This is a monocenter, open label, randomized, standard of care controlled, post-marketing clinical investigation.

4.2 Treatment Administration

Subjects have been randomly allocated to one of the following groups:

- Group A: Xonrid® gel + standard of care (SOC) preemptive treatment according to MASCC guidelines;
- Group B: standard of care (SOC) preemptive treatment according to MASCC guidelines.

Both Groups started treatment on the first day of radiotherapy and went on until two weeks after the last radiotherapy session.

Group B subjects received an additional standard treatment (according to Investigator's opinion) at G2 skin toxicity development.

All subjects interrupted the treatment and the study in the case of G3 skin toxicity development. This subjects have been treated according to the Investigator's opinion.

4.3 Randomization and Blinding

The study was open label. Each patient for whom written consent was obtained have been assigned a five-digit screening code, consisting of the cancer area (e.g. 01 = head & neck; 02= breast) and a progressive number within the site: for example the first subject screened for head & neck cancer was assigned the code 01-001, the second one 01-002 etc.; the first subject screened for breast cancer was assigned the code 02-001, the second one 02-002 etc.

All screened subjects received the code irrespective of whether or not they were randomized. If a subject discontinued from the study at any time, the code was not re-used.

All subjects who signed the informed consent and received the screening code was entered into a Subject's Register, containing the name and surname of the patients and the date they have signed the consent form.

Eligible patients were randomized to receive the treatment according to a randomization list.

The patient randomization list was generated by Latis S.r.l., using the PROC PLAN of SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Once eligibility of a patient was established (see Inclusion/Exclusion Criteria) the study treatment was assigned through centralized randomization system.

The Investigator also kept record of all enrolled patients in the Subject's Enrolment Log: the subject screening number, the date of consent, the treatment assigned to the patient, if applicable, or the reason for not being randomized were recorded.

5. STUDY ENDPOINTS

5.1 Primary Endpoints

- Proportion of patients without G2 radiation dermatitis at week 5

5.2 Secondary Endpoints

- Median time to G2 radiation dermatitis development according to CTCAE

- Proportion of patients without G2 radiation dermatitis at week 6 for both cancer sites, at week 7 for head & neck cancer and 2 weeks after the last radiation for both cancer sites.
- Worst skin toxicity during treatment and until 2 weeks after the last radiation, according to CTCAE
- Changes in skin erythema and pigmentation and trans-epidermal water loss (TEWL)
- Mean and worst score of Patient Reported Outcome (PRO) with Skindex-16 questionnaire performed weekly.
- Compliance to experimental treatment use
- Patient global satisfaction with treatment as assessed by Likert scale
- Study product safety and tolerability

5.3 Safety Endpoints

All randomized patients receiving at least a treatment dose have been included in the safety analysis.

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

For each SOC and preferred term, summaries will be made with respect to the proportion of patients having at least one occurrence of that event during the trial and the total number of events. The incidence of AEs in each treatment arm will be presented overall, by SOC and preferred term, and additional grouping by severity and relationship to the trial treatment. The comparisons will be analyzed using chi-square test.

6. PLANNED ANALYSIS

6.1 Interim Analysis

No interim analysis is planned.

6.2 Final Analysis

Final statistical analysis will be performed at the end of study, after database lock. Details of final statistical analysis are reported in the following paragraphs.

7. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

In a previous observational study[12], 38.2% of the patients treated with SOC preemptive treatment according to MASCC guidelines did not reach G2 radiation dermatitis at week 5. In a pilot study[11] using Xonrid®, the proportion of patients treated with Xonrid® and SOC preemptive treatment according to MASCC guidelines that did not reach G2 radiation dermatitis at week 5 was 82.9%.

According to these previous results, a two group chi-square test with a 0.05 two-sided significance level would have had 80% power to detect the difference between a proportion of patients that do not reach G2 of 38.2% in the Group B (standard of care (SOC) preemptive treatment according to MASCC guidelines) and a proportion of 82.9% in the Group A (Xonrid® and SOC preemptive treatment according to MASCC guidelines) when the sample size in each group is 18. To take into account a possible 10% dropout rate, 20 patients in each treatment group have been enrolled. As two cancer sites have been investigated, to assess the treatment effect within each site, 80 patients have been enrolled: 40 patients with breast cancer and 40 patients with head and neck cancer.

8. ANALYSIS POPULATIONS

8.1 Intent-to-Treat Population (ITT)

The study will be analyzed using an Intent-to-Treat (ITT) approach. All randomized patients receiving at least a treatment dose and having at least one post-randomization efficacy evaluation will be included in the ITT population for efficacy analysis. All randomized patients receiving at least a treatment dose will be included in the safety analysis.

8.2 Per-Protocol (PP) Population

Not applicable.

8.3 Safety Population

All randomized patients receiving at least a treatment dose will be included in the safety population.

9. GENERAL ISSUES FOR STATISTICAL ANALYSIS

9.1 Definitions, Derived Variables and Datasets

Analyses will be performed and report separately for each cancer site (i.e., breast cancer and head and neck cancer).

Erythema assessment

The assessing physicians will receive a specific training on how to assess dermatologic toxicity before study start. In case of no concordance between the two treating physicians in assessing toxicity, a third physician will be asked to evaluate the patient, and the toxicity grade receiving more agreement will be considered. Erythema assessment will be performed at each visit.

Spettrophotometry examination and TEWL examination

Objective in vivo measurements of skin erythema and pigmentation based on reflectance spectrometry (RS) will be performed. Skin reflectance measurements will be acquired in vivo by a spectrophotometric imaging system (SkinColorCatch, by Delfin Technologies Ltd. – Finland). At the clinical site, the Medical Physics Unit has a long tradition with spectrophotometric analysis, having developed a tool for automated melanoma detection[13-14] and for the description of the blood and melanin content of pigmented skin lesions[15].

Measurements will be performed before RT start and then once a week at each visit before RT session and on clean skin. Instrumental RS measurements will be performed at three different fixed regions within the area treated with RT, in any case only on flat skin regions and in absence of hair or nevus. A control measurement will be done also in a specific contralateral area.
The trans-epidermal water loss (TEWL) exam will be done at the same time-points as for the spettrophotometry exam, before RT sessions. The exam will be conducted with VapoMeter instrument (Delfin Technologies Ltd. – Finland).
Measurements will be performed before RT start and then once a week at each visit, before RT session and on clean skin. Instrumental TEWL measurements will be performed at five different fixed regions within the area treated with RT, in any case only on flat skin regions and in absence of hair or nevus. A control measurement will be done also in a specific contralateral area.

Skindex-16 questionnaire

The Skindex-16 scale is a self-administered questionnaire to comprehensively measure the complex effects of skin diseases on subject's quality of life. The Skindex-16 measure is considered appropriate for a study since it has been shown to be reliable and valid for general skin disease.
The Skindex-16 allows patient rating of emotional and functional burdens that the CTCAE does not take into account[5]. These adverse events cause patient's discomfort and impact negatively on quality of life[6].
The Skindex-16 questionnaire will be completed by the subject at each visit.

Patient Global Satisfaction

Global satisfaction evaluation by the subject will be assessed through a 5-point Likert scale (very poor, poor, medium, good, very good) at the end of the radiotherapy sessions and two weeks after the last irradiation.

Relevant variables will be derived for statistical analysis. Derived datasets will include the variables needed for any type of statistical analysis. The derived datasets will include all enrolled subjects. Flags will identify the populations to be analyzed, in order to select the subjects to be included in each statistical analysis (e.g. ITTLF = Y for ITT population).

9.1.1 Baseline Values

Baseline characteristics will be summarized using mean, median, standard deviation, minimum and maximum for continuous variables and frequencies and percentages for categorical variables.

9.1.2 Duration of Exposure

Duration of exposure will be estimated as the number of day under treatment, calculated using the following formula:

$$\text{Last day of treatment} - \text{first day of treatment} + 1$$

9.1.3 Treatment Compliance

The compliance with the treatment will be assessed through a diary where the patient will record the daily product applications and through the difference in weight of tubes when delivered to patient and when returned by the patient. The consistency between the two assessments will be checked (see paragraph 11.3).

9.1.4 Methods for Withdrawals and Missing Data

The number of patients withdrawn due to AE will be summarized by treatment arm.
Missing values will not be replaced unless specified otherwise. Missing safety data will not be replaced.

9.2 Multicenter Studies Considerations

Not applicable.

9.3 Multiple Comparisons and Multiplicity

No correction for multiplicity is needed, as the study has only a primary endpoint and the secondary endpoints have exploratory purposes. In case of clinically and statistically significant results, the exact p-value will be reported to support the strength of the findings.

9.4 Data Safety Monitoring Board (DSMB)

Not applicable

10. STUDY SUBJECTS

In this clinical investigation 80 subjects will be enrolled: 40 of them will be female affected by breast cancer and 40 will be male and female affected by head & neck cancer, undergoing to postoperative or curative radiation treatment. All the subjects will be randomized to Xonrid® + SOC or SOC alone, only if they fulfill the following eligibility criteria:

Inclusion criteria

1. Male and female which are 18 years of age or older
2. Performance status < 2
3. Epithelial carcinoma of oropharynx, nasopharynx, larynx, hypopharynx, paranasal sinus and salivary glands or breast cancer, planned to receive a total dose of at least 50 Gy
4. Postoperative or curative radiation treatment
5. Concurrent chemotherapy is accepted, in head & neck cancer patients
6. Patients willing and able to give signed informed consent and, in the opinion of the Investigator, to comply with the Clinical Investigation Plan tests and procedures.

Exclusion criteria

7. Pregnant or lactating women
8. Planned to receive concurrent cetuximab
9. Previous radiation therapy on the head and neck area or breast and thorax areas
10. Cutaneous and connective diseases (i.e. lupus erythematosus or scleroderma)
11. Systemic diseases known to delay the skin healing process such as diabetes mellitus or severe renal failure
12. Use of a tissue-equivalent bolus
13. Use of over-the-counter topical medications containing steroids
14. Presence of rashes or unhealed wounds in the radiation field
15. Recent sun exposure

Should G3 skin toxicity develop, then, in any case, the study will be interrupted and the subject will be treated according to the Investigator's opinion.

10.1 Disposition of Subjects

The disposition of subjects at each visit will be summarized.

10.2 Protocol Deviations

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

Protocol deviations will be reported. Protocol deviations will be examined and patients with critical deviations will be excluded from the analysis.

The Listing of protocol deviations will be reported in Appendix VI.2 of the Clinical Investigation Report.

11. EFFICACY ANALYSIS

11.1 Analysis datasets

The study will be analyzed using an Intent-to-Treat (ITT) approach. All randomized patients receiving at least a treatment dose and having at least one post-randomization efficacy evaluation will be included in the ITT population for efficacy analysis. All randomized patients receiving at least a treatment dose will be included in the safety analysis.

11.2 Demographics and Baseline Characteristics

Demographic (gender, age) and baseline characteristics will be summarized using mean, median, standard deviation, minimum and maximum for continuous variables and frequencies and percentages for categorical variables. To compare demographic and baseline characteristics between treatment groups, chi-square or t-tests will be used for discrete and continuous variable, respectively.

11.3 Measurements of Treatment Compliance

Compliance to the treatment will be assessed through the number of applications performed by the patients, as reported on patient's diary. As three applications a day were planned, the effective number of days of treatment will

be multiplied by three, to obtain the number of planned applications. The number of applications reported during the treatment period will be compared with the number of planned applications to obtain the compliance percentage.

$$Compliance\ \% = \frac{Number\ of\ applications\ reported}{Number\ of\ applications\ planned} \times 100$$

The bottles have been weighted before treatment and after treatment, as returned by the patients. The amount of product used will be estimated as the difference between the bottle weight before treatment and the weight of the same bottle after treatment.

The number of applications reported will be compared with the weight of product used using linear regression.

11.4 Efficacy Analysis

11.4.1 Primary Efficacy Endpoints

The primary objective of this clinical investigation is to evaluate the proportion of patients without G2 radiation dermatitis (radiation dermatitis < G2) at week 5. The proportion of subjects will be compared between treatment groups using chi-square test. The following SAS code will be used for chi-square test:

```
proc freq;
table treatment * patient_G2_yn / CHISQ;
run;
```

Logistic regression will be used to obtain Odds Ratio (OR), with 95% Confidence Interval (95% CI). No adjustment for covariates will be performed.

The following SAS code will be used for logistic regression:

```
proc logistic;
class treatment;
model depvar = trtan / expb;
run;
```

11.4.2 · Secondary Efficacy Endpoints

The median time to G2 radiation dermatitis development will be analyzed using Kaplan-Meier method. Comparisons between treatment groups will be performed using log-rank test.

```
proc lifetest;
time time_to_G2 * G2_yn(0);
strata treatment / test=( logrank);
test treatment;
run;
```

The proportion of patients without G2 radiation dermatitis at week 6 for both cancer sites, at week 7 for head & neck cancer and 2 weeks after the last radiation for both cancer sites will be assessed and compared between treatment groups using chi-square test. Logistic regression will be used to obtain ORs, with 95% CIs, and to eventually adjust for covariates. The same method used for primary objective will be applied.

The changes in skin erythema and pigmentation will be graphically described reporting the ITA (individual Typological Angle) degrees throughout the study. The ITA of the area treated with RT will be obtained averaging the ITA measured at the three different fixed regions, adjusted for the control measurement done in a specific contralateral area. Changes between visit 2, before the first RT session, and the end of RT and between the end of RT and the end of treatment will be analyzed and compared between treatment groups using ANCOVA, to adjust the estimates for baseline values.
The following SAS code will be used for ANCOVA analysis:

```
proc glm;
class treatment;
model avg_ITA = treatment avg_ITA_baseline;
run;
```

where avg_ITA at each timepoint and avg_ITA_baseline have been obtained as follows:

```
ITA_diff1 = ita_rt1 - ita_controlateral;
ITA_diff2 = ita_rt2 - ita_controlateral;
ITA_diff3 = ita_rt3 - ita_controlateral;
avg_ITA#= mean(ITA_diff1, ITA_diff2, ITA_diff3, ITA_diff4, ITA_diff5);
```

The changes in trans-epidermal water loss (TEWL) will be graphically described reporting the Evaporation rate value (ERV, measured in g/m²h) throughout the study. The ERV of the area treated with RT will be obtained averaging the ERV measured at the five different fixed regions, adjusted for the control measurement done in a specific contralateral area. Changes between visit 2, before the first RT session, and the end of RT and between the end of RT and the end of treatment will be analyzed and compared between treatment groups using ANCOVA, to adjust the estimates for baseline values.
The following SAS code will be used for ANCOVA analysis:

```
proc glm;
class treatment;
model avg_TEWL = treatment avg_TEWL_baseline;
run;
```

where avg_TEWL and avg_TEWL_baseline have been obtained as follows:

```
TEWL_diff1 = tewl_rt1 - tewl_ct;
TEWL_diff2 = tewl_rt2 - tewl_ct;
```

```
TEWL_diff3 = tewl_rt3 - tewl_ct;
TEWL_diff4 = tewl_rt4 - tewl_ct;
TEWL_diff5 = tewl_rt5 - tewl_ct;
avg_TEWL #= mean(TEWL_diff1,TEWL_diff2,TEWL_diff3,TEWL_diff4,TEWL_diff5);
```

The mean and worst score of Skindex-16 questionnaire will be compared between treatment groups using ANCOVA, to adjust the estimates for baseline values.

The following SAS code will be used for ANCOVA analysis:

```
proc glm data = DB;
class treatment;
model skindex_score = treatment skindex_score_bl ;
run;
```

Both the number of daily product applications reported on the patient's diary and the amount of used product, estimated through the difference in tubes weight between delivery to patient and return, will be used to assess the compliance to experimental treatment. The consistency between the two assessments will be checked through linear regression.

The patients' global satisfaction with treatment, assessed by Likert scale, will be compared between treatment groups using Kruskal-Wallis test.

```
proc npar1way;
class TREATMENT;
var satisfaction;
run;
```

11.5 Summary of Efficacy Analyses

Endpoint	Analysis	Populations
Proportion of patients without G2 radiation dermatitis at week 5	The proportion of patients without G2 radiation dermatitis (radiation dermatitis < G2) at week 5 will be assessed and compared between treatment groups using chi-square test. Logistic regression will be performed to obtain Odds Ratio.	ITT
Median time to G2 radiation dermatitis development according to CTCAE	Median time to G2 radiation dermatitis will be analyzed using Kaplan-Meier method and compared between treatment groups using log-rank test.	ITT
Proportion of patients without G2 radiation dermatitis at week 6 for both cancer sites, at week 7 for head & neck cancer and 2	The proportion of patients without G2 radiation dermatitis at week 6 for both cancer sites, at week 7 for head & neck cancer and 2 weeks after the last radiation for both cancer sites will be assessed and compared between treatment groups using chi-	ITT

weeks after the last radiation for both cancer sites.	square test. Logistic regression will be performed to obtain Odds Ratios	
Changes in skin erythema and pigmentation and trans-epidermal water loss (TEWL)	The changes in skin erythema and pigmentation and in in trans-epidermal water loss (TEWL) will be graphically described throughout the study. Changes between before the first RT session and the end of RT and between the end of RT and the end of treatment will be analyzed and compared between treatment groups using ANCOVA, to adjust the estimates for baseline values.	ITT
Mean and worst score of Patient Reported Outcome (PRO) with Skindex-16 questionnaire performed weekly	Weekly mean and worst score of Skindex-16 questionnaire will be compared between treatment groups using ANCOVA, to adjust the estimates for baseline values.	ITT
Compliance to experimental treatment use	The compliance with the treatment will be assessed through a diary where the patient will record the daily product applications and through the difference in weight of tubes when delivered to patient and when returned by the patient. The consistency between the two assessments will be checked.	ITT
Patient global satisfaction with treatment as assessed by Likert scale	The patients' global satisfaction with treatment, assessed by Likert scale, will be compared between treatment groups using Kruskal-Wallis test.	ITT
Study product safety and tolerability	Adverse events, coded according to MedDRA, will be summarized by treatment arm in terms of the number of patients who experienced at least one AE, study product-related AE, serious AE, severe AE and the number of patients withdrawn due to AE will be summarized. For each SOC and preferred term, summaries will be made with respect to the proportion of patients having at least one occurrence of that event during the trial and the total number of events. The comparisons will be analyzed using chi-square test.	Safety

12. SAFETY EVALUATION

12.1 Extent of Exposure

12.2 Adverse Events

Adverse events will be coded according to MedDRA, version 21.1. AEs will be summarized by treatment arm in terms of the number of patients who experienced at least one AE, study product-related AE, serious AE, severe AE and the number of patients withdrawn due to AE will be summarized. The comparisons will be analyzed using chi-square test. For each SOC and preferred term, summaries will be made with respect to the proportion of patients having at least one occurrence of that event during the trial and the total number of events.

```
proc freq;
table treatment * cat_variable / CHISQ;
run;
```

12.3 Other safety endpoints

Tolerability assessment will be based on the evaluation of site administration adverse events.

13. DEVIATIONS FROM THE PROTOCOL SPECIFIED ANALYSIS

The worst skin toxicity during treatment and until 2 weeks after the last radiation will not be analyzed, as most of the patients reached G2 skin toxicity.

14. LIST AND SAMPLES OF TABLES, FIGURES AND GRAPHS

Table 5.1.1.1. Subject disposition (Breast cancer)

Table 5.1.1.2. Dropout patients (Breast cancer)

Table 5.1.2.1. Subject disposition (Head and neck cancer)

Table 5.1.2.2. Dropout patients (Head and neck cancer)

14.1 Demographic data

Table 5.2.1.1. Demographic and baseline characteristics (Breast Cancer)

Table 5.2.1.2. Details about the disease at screening (Breast Cancer)

Table 5.2.2.1. Demographic and baseline characteristics (Head and Neck Cancer)

Table 5.2.2.2. Details about the disease at screening (Head and Neck Cancer)

Table 5.3.2.1. Compliance with device administration (Breast Cancer)

Table 5.3.2.2. Compliance with device administration (Head and neck cancer)

14.2 Efficacy data

Table 5.4.1.1.1. Number and proportion of subjects that reached and not reached G2 at week 5 (Breast cancer).

Table 5.4.1.2.1. Number and proportion of subjects that reached and not reached G2 at week 5 (Head and neck cancer).

Figure 5.4.2.1.1. Kaplan-Meier curves for time to G2 by treatment group (Breast cancer)

Table 5.4.2.1.1 Number and proportion of subjects that reached and not reached G2 at week 6 and 2 weeks after end of radiotherapy treatment (Breast cancer).

Table 5.4.2.1.2 Skindex-16 at Visits 7, 8, 9 and worst Skindex-16 observed in breast cancer patients

Table 5.4.2.1.3 Skindex-16 at Visits 7, 8, 9 and worst Skindex-16 Emotional observed in breast cancer patients

Table 5.4.2.1.4 Skindex-16 at Visits 7, 8, 9 and worst Skindex-16 Functional observed in breast cancer patients

Table 5.4.2.1.5. Changes in ITA among breast cancer patients

Figure 5.4.2.1.2 Mean ITA observed during the study (Breast cancer)

14.3 Safety data

14.4 Sample tables

14.4.1 Sample summary table

Sponsor: Helsinn Healthcare SA
Protocol HD01-16-30

Table xx.x.x
(..... Population)

Characteristic	Statistic	xxx A (N=xxx)	xxx B (N=xxx)
VAR 1	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx
VAR 2	N	xx	xx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.xx	xx.xx
	Min - Max	xx.xx / xx.xx	xx.xx / xx.xx
	p-value		x.xxx
VAR 3	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	Class C	xx (xx.x%)	xx (xx.x%)
	Class D	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx
VAR 4	N	xx	xx
	Mean (SD)	xxx.xx (x.xx)	xxx.xx (x.xx)
	Median	xxx.xx	xxx.xx
	Min - Max	xxx.xx / xxx.x	xxx.xx / xxx.x
	p-value		x.xxx
VAR 5	N	xx	xx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.xx	xx.xx
	Min - Max	xx.xx / xxx.xx	xx.xx / xxx.xx
	p-value		x.xxx
VAR 6	N	xx	xx
	Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)
	Median	xx.xx	xx.xx
	Min - Max	xx.xx / xx.xx	xx.xx / xx.xx
	p-value		x.xxx

Statistical significance: * p<0.05; ** p<0.0167; *** p<0.01
Note: xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx xxx

Program: Txxxxxx xx.sas CONFIDENTIAL Date: xxXXXxxxx

14.4.2 Sample table for efficacy analysis – continuous variables

Sponsor: Helsinn Healthcare SA
Protocol HD01-16-30

Page 1 of x

Table xx.x.x.x
Summary and Analysis of _____.
(_____ Population)

Endpoint	Statistic	ARM A (N=xxx)	ARM B (N=xxx)
Var1	n	xxx	xxx
	Mean (SD)	-x.xx (x.xx)	-x.xx (x.xx)
	Median	-x.xx	-x.xx
	Min - Max	-x.xx / x.xx	-x.xx / x.xx
	Adjusted mean (SE)	-x.xx (x.xx)	-x.xx (x.xx)
	Treatment difference		- x.xx
	95% CI		-x.xx / -x.xx
	p-value		x.xxx
Var2	n	xxx	xxx
	Mean (SD)	-x.xx (x.xx)	-x.xx (x.xx)
	Median	-x.xx	-x.xx
	Min - Max	-x.xx / x.xx	-x.xx / x.xx
	Adjusted mean (SE)	-x.xx (x.xx)	-x.xx (x.xx)
	Treatment difference		- x.xx
	95% CI		-x.xx / -x.xx
	p-value		x.xxx

Statistical significance: @ p<0.05; * p<0.01667; ** p<0.01; *** p<0.001.
Note: Results on treatment difference from an ANCOVA model with factor(s) for _____.

Program: Txxxxxxx xxx.sas CONFIDENTIAL Date: xxXXxxxx

14.4.3 Sample table for efficacy analysis – discrete variables

Sponsor: Helsinn Healthcare SA
Protocol HD01-16-30

Page 1 of x

Table xx.x.x.x
Summary and Analysis of _____.
(_____ Population)

Characteristic	Statistic	xxx A (N=xxx)	xxx B (N=xxx)
Var1	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx[a]
Var2	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx[a]

Statistical significance: $ p<0.05; * p<0.01667; ** p<0.01; *** p<0.001.
Note: p-values from a chi-square test.

Program: Xxxxxxxx xxx.sas CONFIDENTIAL Date: xxXXXxxxx

15. REFERENCES

1. Campbell IR, Illingworth MH. Can patients wash during radiotherapy to the breast or chest wall? A randomized controlled trial. Clin Oncol (R Coll Radiol). 1992; 4:78-82.
2. Ryan JL, Bole C, Hickok JT et al. Post-treatment skin reactions reported by cancer patients differ by race, not by treatment or expectations. Br J Cancer. 2007; 97: 14-21.
3. Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol. 2004; 22: 3485-90.
4. Elting LS, Keefe DM, Sonis ST et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. Cancer. 2008; 113:2704-13.
5. Atherton PJ, Burger KN, Loprinzi CL et al. Using the Skindex-16 and Common Terminology Criteria for Adverse Events to assess rash symptoms: results of a pooled-analysis (N0993). Support Care Cancer. 2012; 20: 1729-35.
6. Aistars J. The validity of skin care protocols followed by women with breast cancer receiving external radiation. Clin J Oncol Nurs. 2006; 10: 487-92.
7. Salvo N, Barnes E, van Draanen J, et al. Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. Curr Oncol. 2010; 17: 94-112.
8. Feight D, Baney T, Bruce S, McQuestion M. Putting evidence into practice. Clin J Oncol Nurs. 2011; 15: 481-92.
9. Momm F, Weissenberger C, Bartelt S, Henke M. Moist skin care can diminish acute radiation-induced skin toxicity. Strahlenther Onkol. 2003; 179: 708-12.
10. Merchant TE, Bosley C, Smith J, et al. A phase III trial comparing an anionic phospholipid-based cream and aloe vera-based gel in the prevention of radiation dermatitis in pediatric patients. Radiat Oncol. 2007; 2:45.
11. Iacovelli NA, Naimo S, Bonfantini F, Cavallo A, Bossi P, Fallai C, Pignoli E, Alfieri S, Bergamini C, Favales F, Orlandi E. Preemptive treatment with Xonrid®, a medical device to reduce radiation induced dermatitis in head and neck cancer patients receiving curative treatment: a pilot study. Support Care Cancer. 2017;25:1787-1795.
12. Palazzi M, Tomatis S, Orlandi E, Guzzo M, Sangalli C, Potepan P, Fantini S, Bergamini C, Gavazzi C, Licitra L, Scaramellini G, Cantu' G, Olmi P. Effects of treatment intensification on acute local toxicity during radiotherapy for head and neck cancer: prospective observational study validating CTCAE, version 3.0, scoring system. Int J Radiat Oncol Biol Phys 2008;70:330-337.
13. Carrara M, Tomatis S, Bono A, et al. Automated segmentation of pigmented skin lesions in multispectral imaging . Phys Med Biol. 2005; 21;N345-57.
14. Tomatis S, Carrara M, Bono A, et al. Automated melanoma detection with a novel multispectral imaging system: results of a prospective study. Phys Med Biol. 2005; 21;1675-87.
15. Marchesini R, Bono A, Tomatis S, et al. In vivo evaluation of melanoma thickness by multispectral imaging and an artificial neural network. A retrospective study on 250 cases of cutaneous melanoma Tumori. 2007;170-7.

16. APPENDICES

16.1 List and samples of Subject Data Listings

VI.1 Discontinued patients

VI.2 Protocol deviations

VI.3 Patients excluded from the efficacy analysis

VI.4 Demographic data

VI.5 Compliance and/or Drug Concentration Data

VI.6 Individual Efficacy Response data

VI.7 Adverse event listings

16.2 Sample Listing

Sponsor: Helsinn Healthcare SA
Protocol HD01-16-30

Page 1 of x

Listing xx.x.x.x

		Visit x					Visit x					Visit x				
ARM	SUBJECT	VAR 1	VAR 2	VAR 3	VAR 4	VAR 1	VAR 2	VAR 3	VAR 4	VAR 5	VAR 1	VAR 2	VAR 3	VAR 4	VAR 5
ARM A	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	x	x	x	x.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	x.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx.x	xx	xx	xx	xx.x	-x.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	x.x	xx	xx	xx	xx.x	x.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-x.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	x.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	x.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xxx	xx	xxx	xx.x	xx	xx	xx	xx.x	-x.x	xx	xx	xx	xx.x	x.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	xx.x	xx	xx	xx	xx.x	x.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	x.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	x	x	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-x.x	xx	xx	xx	xx.x	-x.x
ARM B	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	x	x	x	x.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	x.x	xx	xx	xx	xx.x	-x.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-x.x	xx	xx	xx	xx.x	-x.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-x.x					
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-x.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xxx	xxx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-x.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-xx.x	xx	xx	xx	xx.x	-xx.x
	XXxxx-xxx	xx	xx	xx	xx.x	xx	xx	xx	xx.x	-x.x	xx	x	x	x.x	-xx.x

Program: Lxxxxxxx.sas

CONFIDENTIAL

Date: xxXXxxxx