Clinical Investigation Plan (CIP) HD01-16-30

# 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

Version 1.0, 06/02/2017

*Sponsor*

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

*Coordinating Principal Investigator*

Dr. Ester Orlandi
Radiation Oncology Unit 2
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Venezian, 1
Milan, Italy

# Clinical Investigation Plan approval

_____ ____/_____/_____

**Sponsor** **Date**

Fabio Macchi
Head of Scientific & Clinical Portfolio Development
Helsinn Integrative Care
Helsinn Healthcare SA

# Investigator Agreement

I have read and understood all pages of this Clinical Investigation Plan (CIP) and appendices and I agree that they contain all information required to conduct this study. I agree to conduct the study as outlined in the CIP and to comply with all terms and conditions set out therein. I will conduct the study in accordance with local regulations, ICH GCP guidelines and the provisions of the Declaration of Helsinki. I will direct, assist and oversee sub-Investigator(s) and other relevant staff members under my responsibility and will ensure that all study staff members have access to copies of this Clinical Investigation Plan and to all information relating to preclinical and prior clinical experience, ICH GCP guidelines, local regulations and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.

I will use only the informed consent form approved by the Independent Ethics Committee (IEC).

I agree that the Sponsor or its representatives shall have access to any source documents from which data collected for the study may have been generated.

I agree that all documentation supplied to me by the Sponsor and the CRO concerning this study will be kept in the strictest confidence.

_____ _____/_____/_____

**Principal Investigator** **Date**

**Clinical Site Name and Address**

_____

_____

_____

**General information**

| | |
|---|---|
| **Sponsor Representative Contact** | Fabio Macchi, M.Sc. Manager<br>Head of Scientific & Clinical Portfolio Development<br>Helsinn Integrative Care<br>Helsinn Healthcare SA<br>Via Pian Scairolo, 9<br>6912 Lugano-Pazzallo, Switzerland<br>Phone: +41 (0)91 - 985 21 06<br>Fax : +41 (0)91 - 985 21 94<br>e-mail: fabio.macchi@helsinn.com |
| **Clinical CRO** | Latis S.r.l.<br>Viale Sauli, 39/5<br>16121 Genova – Italy<br>Phone: +39 010 562234<br>Fax: +39 010 540699<br>e-mail: info@latiscro.it |
| ***Contacts for safety reporting*** | |
| **CRO Contact for Serious Adverse Events (SAEs)** | Laura Michellini<br>Phone:+39 010 562234<br>Fax: +39 010 540699<br>Mobile: +39 347 4785898<br>e-mail: michellini@latiscro.it<br>e-mail: info@latiscro.it |
| **Sponsor Drug Safety Officer** | Koprivec Diana, MD, Ph.D.<br>Helsinn Healthcare SA<br>P.O. Box 357<br>6915 Pambio-Noranco, Switzerland<br>Phone: +41 (0) 91 9851957<br>Fax: +41 (0) 91 9852171<br>e-mail: diana.koprivec@helsinn.com<br>Copies to: drug-safety@helsinn.com |

# Table of contents

# 1. Synopsis of the Clinical Investigation Plan

| | |
|---|---|
| Study 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"** |
| Study Number | HD01-16-30 |
| Sponsor | Helsinn Healthcare SA<br>Via Pian Scairolo, 9<br>6912 Lugano-Pazzallo, Switzerland. |
| Countries and Sites | 1 recruiting clinical site will be involved in Italy:<br>- INT, Milano. |
| Indication | Radiation induced dermatitis prevention and treatment |
| Study Design | Randomized, parallel groups, open-label study |
| Objectives | To evaluate the performance of Xonrid® in the prevention and treatment of G2 radiation dermatitis in breast and head & neck cancer patients. |
| Treatment groups | **Group A**: Xonrid® gel + standard of care (SOC) preemptive treatment according to MASCC guidelines.<br>**Group B**: standard of care (SOC) preemptive treatment according to MASCC guidelines.<br><br><u>Xonrid®</u>:<br>To apply the gel on the irradiated area three times daily, the first application 1–2 h after the morning radiotherapy session, the second in the early afternoon, and the third in the evening, starting on the first day of irradiation and continuing for 2 weeks after the completion of the radiation treatments or the development of Grade ≥ 3 skin toxicity.<br><br><u>SOC preemptive treatment according to MASCC guidelines</u>:<br>1) Washing with lukewarm water and a mild pH-neutral or non-alkaline soap. Shaving with a sharp, disinfected wet razor or with non-traumatizing electric razor<br>2) during or after radiation treatment, avoiding the use of metallic-based topical products (zinc oxide, creams or deodorants with an aluminum base, for instance), because they may increase the surface dose to skin<br>3) wearing loose-fitting clothes in order to prevent friction injuries over the irradiated area<br>4) Avoiding extreme temperatures<br>5) Avoiding the use of tapes and adhesives. |

| | |
|---|---|
| | When a patient develops G2 skin toxicity:<br>1. If he/she was in the treatment group "Xonrid® + SOC", the same treatment (Xonrid® + SOC) can continue until G3 toxicity occurrence.<br>2. If he/she was in the treatment group "SOC", an adjunctive standard treatment should be introduced and continued until G3 toxicity occurrence.<br>When a patient develops G3 skin toxicity, he/she should be withdrawn from the study and treated according to the Investigator's opinion. |
| Study Duration | 6 months expected (3-4 months recruitment, plus about 8/9 weeks intervention per patient). |
| Number of Patients | 80 planned (40 patients affected by head & neck cancer and 40 patients affected by breast cancer). |
| Target Study Population | Adult male and female patients diagnosed with head and neck cancer or female patients diagnosed with breast cancer undergoing to postoperative or curative radiation treatment. |
| Selection Criteria | *Inclusion Criteria:*<br>1. Male and female which are 18 years of age or older<br>2. Performance status < 2<br>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<br>4. Postoperative or curative radiation treatment<br>5. Concurrent chemotherapy is accepted, in head & neck cancer patients<br>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.<br><br>*Exclusion Criteria:*<br>1. Pregnant or lactating women<br>2. Planned to receive concurrent cetuximab<br>3. Previous radiation therapy on the head and neck area or breast and thorax areas<br>4. Cutaneous and connective diseases (i.e. lupus erythematosus or scleroderma)<br>5. Systemic diseases known to delay the skin healing process such as diabetes mellitus or severe renal failure<br>6. Use of a tissue-equivalent bolus<br>7. Use of over-the-counter topical medications containing steroids |

| | |
|---|---|
| | 8. Presence of rashes or unhealed wounds in the radiation field<br>9. Recent sun exposure<br>10. Mental conditions that could adversely affect patients' adherence to the study. |
| Primary study endpoints | ▪ Proportion of patients without G2 radiation dermatitis at week 5 |
| Secondary study endpoints | ▪ Median time to G2 radiation dermatitis development according to CTCAE<br>▪ 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.<br>▪ Worst skin toxicity during treatment and until 2 weeks after the last radiation, according to CTCAE<br>▪ Changes in skin erythema and pigmentation and trans-epidermal water loss (TEWL)<br>▪ Mean and worst score of Patient Reported Outcome (PRO) with Skindex-16 questionnaire performed weekly<br>▪ Compliance to experimental treatment use<br>▪ Patient global satisfaction with treatment as assessed by Likert scale<br>▪ Study product safety and tolerability |
| Sample size determination | In previous studies, the proportion of patients without G2 radiation dermatitis at week 5 was 38.2% among patients treated with SOC and 82.9% among patients treated with Xonrid® + SOC. Assuming that the same proportions can be observed in the present study, 36 patients (18 per treatment group) are needed to achieve a power of 80%, with an alpha of 0.05. Four more patients will be enrolled to take into account a possible 10% dropout rate. To better evaluate the effects of Xonrid® + SOC within each cancer site, 80 patients will be enrolled (40 patients with head and neck cancer + 40 patients with breast cancer). |
| Statistical Analysis – Primary efficacy | 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. |
| Statistical Analysis – Secondary efficacy | Median time to G2 radiation dermatitis will be analyzed using Kaplan-Meier method and compared between treatment groups using log-rank test. |

| | |
|---|---|
| | 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 performed to obtain Odds Ratios.<br><br>The worst skin toxicity during treatment and until 2 weeks after the last radiation will be compared between treatment groups using ANOVA.<br><br>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.<br><br>Weekly mean and worst score of Skindex-16 questionnaire will be compared between treatment groups using ANCOVA, to adjust the estimates for baseline values.<br><br>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.<br><br>The patients' global satisfaction with treatment, assessed by Likert scale, will be compared between treatment groups using Kruskal-Wallis test. |
| Statistical Analysis – Safety | 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. |
| Population | An intention to treat approach will be applied to assess efficacy. All the patients randomized and receiving at least one treatment dose and having a 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 population. |

***Table 1:*** *Study Flow-Chart for head & neck cancer subjects*

| **Phase of the study** | Screening | RT & treatment start | RT (expected 33-35 sessions) | | | | | | RT end | 2 weeks treatment without RT |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| **Week** | - | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 |
| **Time (Days) ± 2 days** | -3 to 0 | 1 | 7 | 14 | 21 | 28 | 35 | 42 | 49 | 63 |
| Informed consent signature | X | | | | | | | | | |
| Inclusion/Exclusion criteria | X | X | | | | | | | | |
| Patient randomization | | X | | | | | | | | |
| Socio-demographic data | X | | | | | | | | | |
| Medical and surgical history collection | X | | | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications and therapies | X | X | X | X | X | X | X | X | X | X |
| ECOG performance status | X | | | | | | | | | |
| Erythema assessment | X | X | X | X | X | X | X | X | X | X |
| Skindex-16 questionnaire | X | X | X | X | X | X | X | X | X | X |
| Spettrophotometry & TEWL | | X | X | X | X | X | X | X | X | X |
| Study treatment dispensation to patient | | X | | | | | | | X | |
| Study treatment return and accountability | | | | | | | | | X | X |
| Patient diary dispensation | | X | | | | | | | X | |
| Patient diary collection | | | | | | | | | X | X |
| Patient Global Satisfaction score | | | | | | | | | X | X |
| Adverse events | | X | X | X | X | X | X | X | X | X |

***Table 2:*** *Study Flow-Chart for breast cancer subjects*

| **Phase of the study** | Screening | RT & treatment start | RT (expected 30 sessions) | | | | | RT end | 2 weeks treatment without RT |
|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Week** | - | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 8 |
| **Time (Days) ± 2 days** | -3 to 0 | 1 | 7 | 14 | 21 | 28 | 35 | 42 | 56 |
| Informed consent signature | X | | | | | | | | |
| Inclusion/Exclusion criteria | X | X | | | | | | | |
| Patient randomization | | X | | | | | | | |
| Socio-demographic data | X | | | | | | | | |
| Medical and surgical history collection | X | | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X | X |
| Concomitant medications and therapies | X | X | X | X | X | X | X | X | X |
| ECOG performance status | X | | | | | | | | |
| Erythema assessment | X | X | X | X | X | X | X | X | X |
| Skindex-16 questionnaire | X | X | X | X | X | X | X | X | X |
| Spettrophotometry & TEWL | | X | X | X | X | X | X | X | X |
| Study treatment dispensation to patient | | X | | | | | | X | |
| Study treatment return and accountability | | | | | | | | X | X |
| Patient diary dispensation | | X | | | | | | X | |
| Patient diary collection | | | | | | | | X | X |
| Patient Global Satisfaction score | | | | | | | | X | X |
| Adverse events | | X | X | X | X | X | X | X | X |

***Table 3:*** *CTCAE v4.0 Term Dermatitis Radiation*

| **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
|---|---|---|---|---|
| Faint erythema or dry desquamation | Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema | Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion | Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated | Death |

# 2. Identification and description of the investigational device

Xonrid® is an EC-marked medical device class IIa 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.

# 3. 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 susceptibility[1-2].

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.

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.

In a recent pilot study using Xonrid® *(Iacovelli et al. 2016, accepted for publication on "Supportive care Cancer", 02 jan-2016)*, 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)[11]. 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 will be enrolled in this clinical investigation.

# 4. Risk and benefits of the investigational device and clinical investigation

To date a large variety of products and methods for the prevention of acute radiation-induced skin reactions have been tested but there is not yet a gold-standard approach in the prevention and management of radiation dermatitis.

Xonrid® is an EC-marked medical device that prevents and treats skin symptoms such as erythema, itching, burning sensation and pruritus, induced by radiotherapy or other causes, by restoring the physiological hydration levels of the affected skin areas.

A previous experience on head & neck cancer patients has shown that Xonrid® is safe and well tolerated and is effective in reducing and delaying high-grade radiation dermatitis.

In this study subjects will be randomly allocated to Xonrid® + Standard of Care or Standard of Care alone. The Standard of Care that subjects will be requested to follow is according to MASCC guidelines, that means evidence-based clinical practice guidelines known and recognized worldwide.

Subjects will receive their planned radiotherapy treatment and will be constantly followed by clinicians. The study visits will be done every week. Participants will undergo a careful, frequent and accurate evaluation of their irradiated area equal if not better than what is the normal practice for subjects undergoing radiotherapy.

In the case a subject allocated to the group “SOC alone” develops a G2 skin toxicity, an additional treatment will be introduced, according to the Investigator’s opinion.

Should a G3 skin toxicity develops the subject will immediately interrupt the study treatment and the study participation. The Investigators will thereafter choose the best treatment for that subject.

In the light of the above, no additional risk arising from the participation to this clinical investigation can be envisioned.

# 5. Objectives and hypotheses of the clinical investigation

## 5.1 Primary Objective

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

## 5.2 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.

## 5.3 Tolerability and safety objectives

The study product safety and tolerability will be evaluated.

# 6. Design of the clinical investigation

## 6.1 General

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

Subjects will be 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 will start treatments on the first day of radiotherapy and will go on until two weeks after the last radiotherapy session.

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

All subjects will interrupt the treatment and the study in the case of G3 skin toxicity development. Should this occur, the subject will be treated according to the Investigator's opinion.

Each patient for whom written consent is obtained will be 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 will be assigned the code 01-001, the second one 01-002 etc.; the first subject screened for breast cancer will be assigned the code 02-001, the second one 02-002 etc.

All screened subjects will receive the code irrespective of whether or not they will be randomized. If a subject discontinues from the study at any time, the code will not be re-used.

All subjects who will sign the informed consent and receive the screening code will be 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 will be randomized to receive the treatment according to a randomization list.

The patient randomization list will be 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 is established (see Inclusion/Exclusion Criteria) the study treatment will be assigned through centralized randomization system.

The Investigator will also keep 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 will be recorded.

## 6.2 Investigational device and comparator

### 6.2.1 Xonrid®

The product under investigation is Xonrid®.

Name: Xonrid®

Formulation: Gel

Route of administration: Topical

Composition: the composition of Xonrid®, including ingredient function, as reported in the commercial available product, is reported in Table 4.

Xonrid® is a short term use, Class IIa Medical Device, a topical gel designed for RT-induced dermatitis. When applied to the target skin areas, Xonrid® forms a protective film, reduces the trans-epidermal water loss (TEWL) effect induced by external factors and increases moisturizing. The component responsible for the formation of this film is mainly Hyaluronic Acid, that also helps to achieve an optimal moisturizing effect. The other components responsible for the formation of this film are: polyacrylamide gluconolactone, and Xanthan gum. In particular, gluconolactone is a polyhydroxy acid, with a strong hygroscopic moisturizing power, as well as a glycerin effect. Moreover, the device includes sweet almond oil, known for its emollient, softening, nourishing and soothing properties, and is particularly effective in the treatment of dry, reddened and sensitive skin areas. 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, either presenting or not minor traumas or abrasions. On these bases, Xonrid® may represent a promising device for the prevention of radiation dermatitis.

***Table 4:*** *Xonrid® ingredients with relative function*

| **Ingredient** | **Function** |
|---|---|
| Glycerin (Glycerol) | Humectant |
| Gluconolactone, sodium benzoate, calcium gluconate | Preservative |
| Chamomilla recutita water | Masking agent |
| Xanthan gum | Rheology additive |
| C12-15 alkyl benzoate | Emollient |
| Ethylhexyl palmitate | Emollient |
| Disodium EDTA | Chelanting agent |
| Glyceryl stearate | Emollient |
| Prunus amygdalus dulcis oil | Emollient |
| Polyacrylamide, C13-14 isoparaffin, laureth-7 | Viscosity increasing agent |
| Vitis vinifera extract, aqua, propylene glycol | Skin conditioning agent |
| Aqua | Solvent |
| Sodium hyaluronate | Skin conditioning agent |
| Propylene glycol, aqua, camelia sinensis extract | Skin conditioning agents |
| Propylene glycol, hydrolyzed RNA, hydrolyzed DNA | Skin conditioning agents |

| | |
|---|---|
| Raspberry ketone | Skin conditioning agent |
| Propylene glycol | Solvent |
| Tocopheryl acetate | Preservative/ Antioxidant agent |

#### *6.2.1.1 Packaging and labelling*

Xonrid® will be manufactured and provided for the study by Helsinn Healthcare SA, the Sponsor of this clinical investigation.

The study product shipment to the study site will be done only after the completion of all Ethics and Administrative procedures.

The product will be labeled as experimental treatment in accordance with Good Manufacturing Practice (GMP, Annex 13).

The primary package is a bottle containing 75 ml of gel. Subjects randomized to Xonrid® + SOC will receive a total of:

1. no. 12 bottles if head & neck cancer subjects
2. no. 4 bottles if breast cancer subjects.

The number of bottles assigned should be enough for the whole study duration (56 ± 2 days / 63 ± 2 days).

#### *6.2.1.2 Study device instructions for use*

Patients will be instructed to apply Xonrid® on the irradiated area three times daily, the first application 1–2 h after the morning radiotherapy (RT) session, the second in the early afternoon, and the third in the evening, starting on the first day of irradiation.

Head & neck cancer subjects will use 12-18 puffs for each application.

Breast cancer subjects will use 6 puffs for each application.

The skin will be perfectly clear before the irradiation.

The treatment with Xonrid® will continue until 2 weeks after the completion of the radiation treatments or until the development of Grade ≥ 3 skin toxicity.

When G3 toxicity occurs, the subject has to discontinue the study and the skin toxicity will be managed according to site internal guidelines. The use of other topical medications for the treatment of dermatitis, in particular topical steroidal creams, is not allowed.

When the subject does not receive RT, e.g. during the weekends, Xonrid® has to be applied every day in the morning, afternoon and evening.

The treatment duration for each subject will be of maximum 58-65 days respectively for breast and head & neck cancer, or until G3 skin toxicity.

#### *6.2.1.3 Handling and storage*

It is the Investigator/Institution's responsibility to set up a system for handling the clinical investigation treatment, so as to ensure that:

- deliveries of product supply from the Sponsor are correctly received
- products are handled and stored safely and properly in a secured area
- treatments are only dispensed to study subjects in accordance with the clinical investigation plan
- any unused, used, partially used product is returned to the Investigator (including empty bottles).

The study product shall be carefully stored at the study site, in a safe area and separately from other drugs/products. It shall be stored in a dry and cool place, away from direct sunlight or heat.

The pharmacist and or the Investigator shall maintain records of the study products receipt by the study site and an updated inventory of the study product.

Treatments will be dispensed to the subjects enrolled in this clinical investigation only by authorized personnel.

After study conclusion, all unused study product shall be returned to the Sponsor or destroyed after written Sponsor approval.

#### *6.2.1.4 Study product accountability and compliance*

The Investigator is responsible for ensuring the accountability of the study product.

Accountability records will include:

- confirmation of product delivery and receipt to/at the clinical site
- records concerning the product delivery to each subject and the return from each subject
- the return to the Sponsor or alternative disposition of unused products.

The Investigator should maintain records that adequately document:

- that the subjects were provided with the doses specified by the clinical investigation plan/amendment(s)
- that all products provided by the Sponsor were fully reconciled.

Unused products must not be discarded or used for any purpose other than the present clinical investigation.

Products that has been allocated to one subject must not be re-dispensed to a different subject.

Subjects will be reminded of the importance of strictly complying with the instructions received from the Investigator and to return all unused treatment or empty bottles to the Investigator.
The Monitor, at monitoring visits, will verify the products accountability and will check all products returned by the subjects (unused, used and partially used) before arranging for their return to the Sponsor.
Compliance to the treatment will be checked by the Investigators when the subjects are bringing back to the Site the used/unused products. A cross check will be done with patient's diary information.
The treatment compliance will be then evaluated by weighing the bottles before return to the Sponsor.

### 6.2.2 Standard of Care (SOC)

The SOC preemptive treatment will be according to MASCC guidelines and it includes:

1. washing with lukewarm water and a mild pH-neutral or non-alkaline soap. Shaving with a sharp, disinfected wet razor or with non-traumatizing electric razor
2. during or after radiation treatment, avoiding the use of metallic-based topical products (zinc oxide, creams or deodorants with an aluminum base, for instance), because they may increase the surface dose to skin
3. wearing loose-fitting clothes in order to prevent friction injuries over the irradiated area
4. avoiding extreme temperatures
5. avoiding the use of tapes and adhesives.

All the subjects enrolled in this clinical investigation will be recommended to comply with SOC guidelines above listed. SOC will be followed every day, continuatively, since the beginning of the radiotherapy until 2 weeks after the last RT session.
In the treatment group with SOC alone, when G2 skin toxicity develops, an adjunctive standard treatment will be introduced, at discretion of the Investigator.
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.

### 6.2.3 Concomitant medications

Any medications (other than those excluded by the clinical investigation plan) that were considered necessary for the patients' well-being and do not interfere with the study product can be given at the Investigator's discretion.
According to exclusion criteria, the following prior and concomitant medications are prohibited:

- concurrent cetuximab;
- previous radiation therapy on the head and neck area or breast and thorax areas;
- use of a tissue-equivalent bolus;
- over-the-counter topical medications containing steroids.

In the treatment group with SOC alone, when G2 skin toxicity develops, an adjunctive standard treatment will be introduced, at discretion of the Investigator. The treatment will be recorded in the appropriate section of the CRF.

## 6.3 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:

### 6.3.1 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.

### 6.3.2 Exclusion criteria

1. Pregnant or lactating women
2. Planned to receive concurrent cetuximab
3. Previous radiation therapy on the head and neck area or breast and thorax areas
4. Cutaneous and connective diseases (i.e. lupus erythematosus or scleroderma)
5. Systemic diseases known to delay the skin healing process such as diabetes mellitus or severe renal failure

6. Use of a tissue-equivalent bolus
7. Use of over-the-counter topical medications containing steroids
8. Presence of rashes or unhealed wounds in the radiation field
9. Recent sun exposure
10. Mental conditions that could adversely affect patients' adherence to the study.

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.

## 6.4 Procedures

### 6.4.1 Study visits and assessments

*Visit 1 screening (days from -3 to 0)*:

Subjects will be pre-selected on the basis of their medical history and the need of radiotherapy as curative or postoperative treatment for head & neck or breast cancer. Subjects will be evaluated with regard to the inclusion and exclusion criteria that will allow their participation into the study.

Before any study specific evaluation is carried out, subjects will receive all the information about the study by the Investigators and will sign an informed consent form.

The following assessments will be performed:

- Collection of information about demography
- Medical and surgical history
- Physical examination
- Concomitant medications and therapies
- ECOG performance status
- Erythema assessment
- Skindex-16 questionnaire
- Inclusion/exclusion criteria assessment

*Visit 2 – randomization (Day1):*

At visit 2 the subject eligibility will be re-assessed. Eligible patients will be randomized 1:1 in the two groups, treated respectively with Xonrid® + SOC or SOC alone.

The radiotherapy will start at this visit.

The following activities will be done at visit 2, before the first RT session:

- Inclusion/exclusion criteria assessment
- Randomization
- Physical examination
- Concomitant medications and therapies
- Erythema assessment
- Skindex-16 questionnaire
- Spettrophotometry examination and TEWL examination
- Treatment dispensation and instructions (the first application will be after RT session)
- Patient's diary dispensation and instructions on how to fill it in every day
- Adverse events recording

*Visit 3 to 8/9 – RT and treatment:*

Subjects will receive radiotherapy treatment every day for 6 or 7 consecutive weeks, with suspension only in the weekends. Breast cancer subjects are expected to attend 30 radiotherapy sessions (that means 6 weeks) while head & neck cancer subjects are expected to attend 33-35 radiotherapy sessions (that means about 7 weeks). One weekly visit for the study will be performed according to the subject availability (a ± 2 days window will be allowed and any delay will be recovered in the following visits).
The following activities will be done at visits:

- Physical examination
- Concomitant medications and therapies
- Erythema assessment
- Skindex-16 questionnaire
- Spettrophotometry examination and TEWL examination. Both exams will be done with clean skin, before the RT session
- Treatment collection from subject and accountability (only at visit 8/9)
- Diary collection from subject (only at visit 8/9; the diary will be checked for completeness at every visit)
- Treatment dispensation and instructions (only at visit 8/9)
- Diary dispensation to subject (only at visit 8/9)
- Patient Global Satisfaction score (only at visit 8/9)

- Adverse events recording

*Visit 9/10 – end of study & end of treatment (Day 56/63):*

After RT completion (expected at visit 8/9), all the subjects will go on with their assigned treatment for further 2 weeks.

At day 56 ± 2 or 63 ± 2 days (visit 9/10), depending on cancer typology, a conclusive visit will be performed.

The following activities will be done at conclusive visit:

- Physical examination
- Concomitant medications and therapies
- Erythema assessment
- Skindex-16 questionnaire
- Spettrophotometry examination and TEWL examination. Both exams will be done with clean skin
- Treatment collection and accountability
- Diary collection
- Patient Global Satisfaction score
- Adverse events recording.

### 6.4.2 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.

### 6.4.3 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[12-13] and for the description of the blood and melanin content of pigmented skin lesions[14].

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 (by 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.

### 6.4.4 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.

### 6.4.5 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.

## 6.5 Monitoring plan

The study will be monitored on a regular basis by the CRO's adequately qualified and trained clinical Monitors throughout the study period to ensure the proper conduct of the clinical Investigation.

The purposes of study monitoring are to verify that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete and verifiable against the source documents, and that the study is conducted in accordance with the current clinical investigation plan, Good Clinical Practice guideline (UNI EN ISO 14155) and applicable regulatory requirements.

During the monitoring visits, Monitors will verify the following including but not limited to: subject informed consent, subject's eligibility, safety data and reporting, quality of source documents and CRF data against subject's medical records. If inconsistencies are identified, the corresponding corrections to the CRF data will have to be made by the Investigator or designated person. Monitors will also check subject compliance, accrual, study product handling, including dispensing procedures and accountability logs, delegation of responsibilities within the Investigator's team, relevant communications with family doctors, if any, ancillary equipment and facilities, including refrigerators and freezers, local labs, etc. The Investigator and other site staff involved in the study must allocate enough time to the Monitor at these visits.

Upon request by the Sponsor, on-site study audits may be conducted in order to ensure the study is in compliance with GCP, applicable regulatory requirements, and the clinical investigation plan. The auditing activities may also be conducted after study completion.

The Investigator agrees to allow Sponsor/auditors/CRO monitors to have direct access to his/her study records for review, being understood that they are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

Regulatory Authorities may wish to conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator must inform the Sponsor and CRO immediately. The Investigator will make all efforts to facilitate the conduct of the audits and inspections giving access to all necessary facilities, data and documents.

Any result or information arising from the inspection will be immediately communicated by the Investigator to the Sponsor. The Investigator will take all appropriate measures required by the Sponsor to implement corrective actions for all problems found during audits or inspections.

# 7. Statistical considerations

This section summarizes the statistical principles and methods planned to analyze the data for this clinical investigation.

## 7.1 Sample Size Determination

In a previous observational study[11], 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 using Xonrid® *(Iacovelli et al. 2016, submitted*), 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 will have 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 will be enrolled in each treatment group.

As two cancer sites will be investigated, to assess the treatment effect within each site, 80 patients will be enrolled: 40 patients with breast cancer and 40 patients with head and neck cancer.

## 7.2 Definition of Study Populations for Analysis

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.

## 7.3 Statistical Analysis

Descriptive statistics of all relevant variables will be performed. Continuous variables will be summarized by the number of patients (N), mean, standard deviation, median, minimum, maximum. Where appropriate, 95% confidence intervals for the target variables will be estimated. Categorical variables will be summarized by the number (N) and the proportion of patients (%).

The significance level of statistical tests will be set at 0.05. Details of statistical analysis are provided in the following paragraphs.

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

### 7.3.1 Missing Data

Missing values will not be replaced unless specified otherwise. Missing safety data will not be replaced.

### 7.3.2 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.

### 7.3.3 Covariates, Interactions and Subgroups

Due to the limited number of patients to be enrolled, covariates and subgroup analyses, if any, will be performed only with exploratory purposes.

### 7.3.4 Analysis of Demographics and Baseline Variables

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.

### 7.3.5 Efficacy analysis

#### *7.3.5.1 Primary endpoint*

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. Logistic regression will be used to obtain Odds Ratio (OR), with 95% Confidence Interval (95% CI), and to eventually adjust for covariates.

#### *7.3.5.2 Secondary 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.

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 worst skin toxicity during treatment and until 2 weeks after the last radiation will be compared between treatment groups using ANOVA.

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

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.

### 7.3.6 Safety analysis

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

Adverse events will be 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.

Physical Examination data will be listed only, excepting baseline data, which will be summarized in terms of proportion of normal/abnormal findings.

### 7.4 Planned Interim Analysis(es)

No interim analysis is planned.

## 8. Data management

During each study visit, the study Investigator (or designee) will collect and report study data in the relevant patient's chart, documenting all significant observations.

Any contact with the patient via telephone or other means that provides significant clinical information shall be documented in the source data.

An Electronic Case Report Form (e-CRF) will be used to record patient's study data.

The Investigator will maintain a list of all persons authorized to make entries and/or corrections on the CRFs. Each authorized person will be provided with a user-specific ID protected by a renewable password. Data entries and corrections will be made only by the authorized persons. The e-CRF system will record date and time of any entry and /or correction and the user ID of the person making the entry/correction. The system will keep track of all old and new values (audit trail). It is the responsibility of the Investigator to ensure that the CRFs are properly and completely filled in. The CRFs must be completed for all subjects who have been included in the study. The Investigator will review all CRFs and electronically sign and date them for each subject, verifying that the information is complete, true and correct. All fields on the CRF must be completed as applicable.

Subjects will be provided with paper questionnaires. Such documents will be filled by the subjects during the study visits, to record data concerning their skin condition.

It is responsibility of the Investigators to instruct the study participants on how to fill in questionnaires in a clear way and preferably in black ball-point pen. The questionnaires will be anonymous, each subject is identified through the subject screening number. A copy of all questionnaires will be stored in patient's chart. It is responsibility of the Investigators to correctly enter the data collected on the questionnaires in the relevant sections of the e-CRF. Questionnaires will be considered source data.

Checks to assist during the data entry and to assess the appropriateness and consistency of data will be developed on the e-CRF system. E-CRF pages will be reviewed both on site by the monitor of the center and remotely, by the data management staff of the CRO. Data Clarification Forms (DCF) will be generated through the e-CRF system, both automatically, through edit checks, and manually, by CRAs and/or data

managers, and the Investigator will have to check and solve them. Occasionally, paper DCF can be sent to the site for resolution. The Investigator is responsible for the review and approval of all query resolutions.

# 9. Amendments to the CIP

Changes to the clinical investigation plan may only be made by means of a written amendment, which has to be approved and signed by the authorized representatives of the Sponsor, and by the Investigator. Exhaustive justifications that motivate the amendment to the clinical investigation plan should clearly be addressed in the document.

All substantial Clinical Investigation Plan amendments must be submitted to IEC and to Regulatory Authority (if applicable) for review and approval unless it covers administrative issues only. In this case the IEC and the Regulatory Authority (when applicable) will be notified of the amendment without the request to review and approve it.

The Investigator, the Sponsor and IEC, separately or together, should decide whether the subject's informed consent form needs to be changed.

# 10. Deviations from clinical investigation plan

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.

# 11. Device accountability

The Investigator is responsible of ensuring accountability of the study product, including reconciliation of study product and maintenance of records.

Upon receipt of the study product, the Investigator (or designee) will check the contents and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained in the Investigator File.

The dispensing of the study product will be carefully recorded on the appropriate accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Study Monitor at each monitoring visit.

Study product accountability records will include:

- Confirmation of study product receipt at the clinical site.
- The inventory at the site of study product provided by the Sponsor.
- The bottles delivery to each subject.
- The return to the Sponsor or alternative disposition of unused study product.

The Investigator should maintain records that adequately document:

- That the subjects were provided the doses specified by the Clinical Investigation Plan/amendment(s), and
- That all study products provided by the Sponsor were fully reconciled.

Unused study product must not be discarded or used for any purpose other than the present study. Study product that has been dispensed to a subject must not be re-dispensed to a different subject.

The Study Monitor will periodically collect the study product accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the clinical site.

# 12. Statement of compliance

The study will be conducted in compliance with the current version of the Declaration of Helsinki, with the clinical investigation plan, the ISO 14155:2012, the Italian laws in force and the principles of the Good Clinical Practice.

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

# 13. Informed consent process

The Investigator is responsible for and will obtain informed consent from each subject in the study, in accordance with the ICH-GCP Guidelines, and the current version of the Declaration of Helsinki.
All subjects invited to participate in the study are entitled to make their voluntary decision based on all current available information provided to them by the Investigator/designee. In addition, they will be given a document in native language written in clear concise lay language for review and consideration. The document will previously have been approved by the relevant independent Ethics Committee (IEC) and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the study.
The subject must be made aware that he/she may refuse to join the study or may withdraw his/her consent at any time without prejudicing further medical care and that he/she is covered by the Sponsor's indemnity insurance in the event of a study related injury. Subjects must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by Regulatory Authority and IEC and that personal information will be collected and retained in a confidential database. Consent will always be given in writing after the subject has had adequate time to review the information and ask questions, if need be. The signed form will be reviewed by the study Monitor.

# 14. Adverse events, adverse device effects and devices deficiencies

## 14.1 Definitions

***Adverse Event (AE)***

Any undesirable experience occurring to a subject, whether or not it is considered causally related to the investigational medical device. An AE may be a clinical finding, a clinical laboratory abnormality or a symptomatic complaint which is considered by the Investigator to be outside the normal variation for that parameter.

***Adverse Device Effect (ADE)***

Any untoward and unintended response to a medical device. This includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of a user error.

***Device Deficiency***

Inadequacy of a medical device with respect to its identity, quality, durability, safety or performance (included malfunctions, use errors and inadequate labelling).

***Serious Adverse Event (SAE)***

A serious adverse event (SAE) could be any event that suggests a significant hazard, contraindication, side effect, or precaution. The seriousness of an AE relates to its clinical significance and its potential impact on health.

An AE will be considered as serious when:

Lead to death

Lead to serious deterioration in the health of the subject, that either results in:

a. a life-threatening illness or injury, or
b. a permanent impairment of a body structure or a body function, or
c. in-patient or prolonged hospitalization, or
d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function

Lead to foetal distress, foetal death or a congenital abnormality or birth defect.

***Serious Adverse Device Effect (SADE)***

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

***Unanticipated Serious Adverse Device Effect (USADE)***

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

## 14.2 Adverse Event Intensity/Causality

The Investigator, based on his direct observation or on subjects' report, will record the event according to the current version of CTCAE:

**Grade 1 (Mild):** asymptomatic or mild symptoms; clinical or diagnostic observations only;

intervention not indicated.

**Grade 2 (Moderate)**: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental daily life activities.

**Grade 3** (**Severe):** medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self -care daily life activities.

**Grade 4 (Life-threatening consequences)**: urgent intervention indicated.

**Grade 5:** Death related to AE.

The relationship of any AE to the product will be classified by the Investigator as follows:

| **Description** | **Definition** |
|---|---|
| Certain | The AE is clearly related to the study product |
| Probable | The AE is likely related to the study product |
| Possible | The AE may be related to the study product |
| Unlikely | The AE is unlikely related to the study product |
| None | The AE is clearly not related to the study product |
| Unknown | Causality is not assessable, for one reason or another, e.g. because of insufficient evidence, conflicting data or poor documentation |

## 14.3 Adverse Event, Device Deficiency, Adverse Device Effect reporting

The investigator will report to the Sponsor any AEs, Device Deficiencies and ADEs concerning the medical device occurring during the study. He/She will also co-operate with the Sponsor in connection with the reporting of any SADE to the Competent Authority and to the Independent EC, if applicable.

All AEs regardless of severity occurring between recruitment and completion of the study by a subject must be recorded on the AE form provided with the CRF.

If there is a significant worsening of a medical condition that was present before starting the study, this should be considered as a new AE and a complete evaluation recorded.

Signs and symptoms considered as lack of efficacy and occurring during the study will not be recorded on the AEs Section of the CRF except on the condition that, in the Investigator's opinion, these signs and symptoms are caused by any reason different from lack of efficacy of the study product or meet the definition of serious AE.

**In the event of a SADE/SAE the Investigator has to:**

- Complete the relevant CRF pages and a reporting form with the all available initial information,
- Immediately inform the CRO by telephone,
- Fax the completed report form to the contact person at the CRO or to the Sponsor as soon as possible.

SAE/SADE reporting contacts are on page 4 of this Clinical Investigation Plan.

The Investigator is responsible for ensuring the follow-up of any subject who experiences an SAE/SADE during the study. The investigator must re-examine the subject at regular intervals until the symptoms have completely disappeared or stabilized.

# 15. Vulnerable population

This section is not applicable, since no subject belonging to any vulnerable population will be recruited for participating in this study.

# 16. Suspension or premature termination of the clinical investigation

Unless premature interruption occurs, the end of the study will be the closure visit at the clinical site.

## 16.1 Study Discontinuation

Subjects may be discontinued at any time from the study for any of the following reasons:

- Grade ≥ 3 skin toxicity develops
- An AE occurs that, in the opinion of the Investigator, makes it unsafe for the subject to continue in the study, included laboratory test abnormalities evaluation
- Lack of compliance of the subject to the study treatment or assessments
- The subject is lost to follow-up
- The subject dies
- The subject withdraws consent

- The Investigator, for any reason, terminates the entire study, or terminates the study for that subject or the attending physician requests that the subject be withdrawn for any medical reason
- The Sponsor or the Regulatory Authority or the Ethics Committee, for any reason, terminates the entire study or terminates the study for this site or this particular subject.

If a subject is discontinued from the study, the Investigator will, as far as possible, complete the end of study visit (visit 9 or 10) CRF pages. The Investigator should try to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights.

### 16.2 Study Interruption

The Sponsor may consider study closure at the clinical site if the following occurs:

- serious and/or persistent non-compliance with the Clinical Investigation Plan
- inadequate collaboration of site personnel with CRO/Sponsor
- administrative reasons
- non-compliance with GCP, SOPs or regulatory requirements
- lack of confidentiality and/or non-compliance with the contract spread with the Sponsor.

## 17. Publication policy

All information obtained as a result of the study will be regarded as confidential.

The results of the clinical study will be documented in an integrated clinical study report according to ISO 14155.

The Sponsor and the Investigator(s) agree that no publications presenting or discussing data and/or results from clinical study sponsored by Helsinn Healthcare SA will take place until the participating center has completed the study, the data have been interpreted, and the final report has been issued.

As a rule, the Sponsor is free to use the data collected in the sponsored study for world-wide scientific product documentation, and for publication.

In general, the Sponsor has no objections if the Investigator publishes the results of the study sponsored by Helsinn Healthcare SA. However, the Investigator is requested to provide the Sponsor with a copy of the manuscript for review before submitting it to the publisher with a cover letter informing the Sponsor about the intention to publish the study results. When permission for presentation or for publication is granted, Investigators, prior to submission of a manuscript or abstract to the publisher, shall forward a copy of said manuscript or abstract to the Sponsor who shall have 45 days to request any reasonable amendment thereto, which shall be taken into due account and consideration by the Investigator.

The Sponsor is entitled to include as authors of the publication all Sponsor's personnel who contributed substantially to the theoretical or experimental work and also to take part in the decision that establishes the order in which the authors' names will be given. Costs for publication must be regulated by written agreement between the parties.

For multicenter studies, the Investigators who will be quoted as authors of the publication(s) should be agreed upon with the Sponsor. If publication of the results of the study, either in part or in full, is prepared by the Sponsor, the Investigator(s) will be provided with a copy of the manuscript before the submission to the publisher and asked to give approval of the document. Investigators will be asked in writing if he/she accepts to be included as author of the publication. Answers should be sent in writing to the Sponsor within a reasonable time limit (30 days). If no answer is received, it is assumed that the Investigator agrees to the Sponsor's proposal.

# 18. Bibliography

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. 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.

12. Carrara M, Tomatis S, Bono A, et al. Automated segmentation of pigmented skin lesions in multispectral imaging . Phys Med Biol. 2005; 21;N345-57.

13. 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.

14. 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.

# Appendix 1

## List of abbreviations

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| CI | Confidence Interval |
| CIP | Clinical Investigation Plan CRA |
| | Contract Research Associate |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCF | Data Clarification Form |
| EC | European Community |
| ECOG | Eastern Cooperative Oncology Group |
| e-CRF | Electronic Case Report Form |
| g/m²h | grams per square meter per hour |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| Gy | Gray |
| ICH | International Conference on Harmonization |
| IEC | Indipendent Ethics Committee |
| ITA | Individual Typological Angle |
| MASCC | Multinational Association for Supportive Care in Cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OR | Odds Ratio |
| PRO | Patient-Reported Outcome |
| PT | Preferred Term |
| ml | milliliters |
| nm | nanometers |
| RS | Reflectance Spectrometry |
| RT | Radiotherapy |

| | |
|---|---|
| RTOG | Radiation Therapy Oncology Group |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SOC | Standard Of Care |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TEWL | Trans Epidermal Water Loss |
| USADE | Unanticipated Serious Adverse Device Effect |

# Appendix 2

*Study Flow-Chart for head & neck cancer subjects*

| **Phase of the study** | Screening | RT & treatment start | RT (expected 33-35 sessions) | | | | | | RT end | 2 weeks treatment without RT |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| **Week** | - | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 |
| **Time (Days) ± 2 days** | -3 to 0 | 1 | 7 | 14 | 21 | 28 | 35 | 42 | 49 | 63 |
| Informed consent signature | X | | | | | | | | | |
| Inclusion/Exclusion criteria | X | X | | | | | | | | |
| Patient randomization | | X | | | | | | | | |
| Socio-demographic data | X | | | | | | | | | |
| Medical and surgical history collection | X | | | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications and therapies | X | X | X | X | X | X | X | X | X | X |
| ECOG performance status | X | | | | | | | | | |
| Erythema assessment | X | X | X | X | X | X | X | X | X | X |
| Skindex-16 questionnaire | X | X | X | X | X | X | X | X | X | X |
| Spettrophotometry & TEWL | | X | X | X | X | X | X | X | X | X |
| Study treatment dispensation to patient | | X | | | | | | | X | |
| Study treatment return and accountability | | | | | | | | | X | X |
| Patient diary dispensation | | X | | | | | | | X | |
| Patient diary collection | | | | | | | | | X | X |
| Patient Global Satisfaction score | | | | | | | | | X | X |
| Adverse events | | X | X | X | X | X | X | X | X | X |

*Study Flow-Chart for breast cancer subjects*

| **Phase of the study** | Screening | RT & treatment start | RT (expected 30 sessions) | | | | | RT end | 2 weeks treatment without RT |
|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Week** | - | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 8 |
| **Time (Days) ± 2 days** | -3 to 0 | 1 | 7 | 14 | 21 | 28 | 35 | 42 | 56 |
| Informed consent signature | X | | | | | | | | |
| Inclusion/Exclusion criteria | X | X | | | | | | | |
| Patient randomization | | X | | | | | | | |
| Socio-demographic data | X | | | | | | | | |
| Medical and surgical history collection | X | | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X | X |
| Concomitant medications and therapies | X | X | X | X | X | X | X | X | X |
| ECOG performance status | X | | | | | | | | |
| Erythema assessment | X | X | X | X | X | X | X | X | X |
| Skindex-16 questionnaire | X | X | X | X | X | X | X | X | X |
| S Spettrophotometry & TEWL | | X | X | X | X | X | X | X | X |
| Study treatment dispensation to patient | | X | | | | | | X | |
| Study treatment return and accountability | | | | | | | | X | X |
| Patient diary dispensation | | X | | | | | | X | |
| Patient diary collection | | | | | | | | X | X |
| Patient Global Satisfaction score | | | | | | | | X | X |
| Adverse events | | X | X | X | X | X | X | X | X |

## Appendix 3: SKINDEX-16 Questionnaire

# QUESTIONARIO DERMATOLOGICO

Questo questionario riguarda il problema di pelle che le ha dato più fastidio negli ultimi 7 giorni.

Skindex-16_Italian/Italy_Mapi Research Institute
ID2251_Skindex16_AU2.0_ita-IT.doc

Skindex-16
©MMChren,1997

**QUESTE DOMANDE RIGUARDANO IL PROBLEMA DI PELLE CHE LE HA DATO PIÙ FASTIDIO NEGLI ULTIMI 7 GIORNI**

| **Negli ultimi 7 giorni, quanto spesso le ha/hanno dato fastidio:** | Non mi ha mai dato fastidio ↓ | | | | | | Mi ha sempre dato fastidio ↓ |
|---|---|---|---|---|---|---|---|
| 1. Il **prurito** dovuto al suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 2. Il **bruciore** o il **pizzicore** dovuti al suo problema di pelle. | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 3. Il **dolore** dovuto al suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 4. L'**irritazione** dovuta al suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 5. La **persistenza/ricomparsa** del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 6. La **preoccupazione** per via del suo problema di pelle (Per es. che si possa estendere, peggiorare, lasciare segni, essere imprevedibile, ecc.) | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 7. L'**aspetto** del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 8. La **frustrazione** per via del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 9. L'**imbarazzo** per via del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 10. **Essere seccato/a** per via del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 11. **Sentirsi depresso/a** per via del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 12. Le conseguenze del suo problema di pelle sui suoi **rapporti con gli altri** (Per es.: rapporti con famigliari, amici, rapporti intimi, ecc.) | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 13. Le conseguenze del suo problema di pelle sul suo **desiderio di stare con gli altri** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 14. La difficoltà di **manifestare il suo affetto** a causa del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 15. Le conseguenze del suo problema di pelle sulle sue **attività quotidiane** | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |
| 16. La difficoltà di **lavorare o fare quello che le piace** a causa del suo problema di pelle | ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |

**Ha risposto a tutte le domande? Sì ☐ No ☐**

Skindex-16_Italian/Italy_Mapi Research Institute
ID2251_Skindex16_AU2.0_ita-IT.doc

# Appendix 4: Helsinki Declaration

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**
**Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

**Preamble**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

**General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions

(methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

**Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with

foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

**Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

**Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

**Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence

and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

**Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

**Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote

the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

**Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

**Post-Trial Provisions**

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

**Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.