KeraNetics

STUDY DEVICE: **KeraStat Cream**
STUDY NUMBER: KSCM-CRD-001
VERSION: 0
EFFECTIVE DATE: **3-1-2018**

PILOT STUDY: KERASTAT™ CREAM FOR RADIATION DERMATITIS

Sponsor: KeraNetics, LLC

KERANETICS SIGNATURE PAGE

Approver(s):	**Signature:**	**Date:**
Luke Burnett, Ph.D. Chief Science Officer		

KERANETICS CLINICAL STUDY PROTOCOL

KeraStat® Cream for Radiation Dermatitis

Study Number: KSCM-CRD-001

NCT03374995

This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with applicable regulatory requirements, this protocol, any future amendments, and with any other study conduct procedures provided by KeraNetics (KN).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the study device(s), as described in this protocol, and any other information provided by the sponsor including, but not limited to, the following: the current directions for use/product labeling or equivalent document, and approved product label (if the product is marketed in this country and the label is not already provided).
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- That I will provide full and unencumbered access to source documents and medical records needed for KN, representatives of KN and regulatory authorities to verify source data and related documentation with respect to this trial.
- To ensure that all persons assisting me with the study are adequately informed about the KN study device(s) and of their study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the Sponsor or the study device, and more generally about his/her financial ties with the Sponsor. KN will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply KN with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
- Agree that KN may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Investigator Name:

_____

_____ _____

Investigator Signature Date

1. SYNOPSIS

Name of Company: KeraNetics, LLC	Name of Product: KeraStat® Cream	Type of Study: Clinical Proof of Concept

Title of Study: Pilot Study: KeraStat® Cream for Radiation Dermatitis

Investigator(s): Karen M. Winkfield, MD, PhD; Doris Brown, MD, PhD

Study Period: Estimated screening expected to start March 2018; Expected completion September 2018

Phase of Development: Design & Development (Phase 3 of Design Control)

Objective(s):
Primary:

- To assess feasibility (compliance of use)
- Collect data for designing a larger future trial evaluating KeraStat Cream

Secondary:

- To assess the safety and tolerability of KeraStat Cream in subjects at risk of radiation dermatitis
- To assess the effectiveness of KeraStat Cream compared to standard of care to manage the symptoms of radiation dermatitis in subjects being treated with radiation therapy
- To estimate amount of KeraStat Cream used per patient and coverage on skin

Methodology: This is a randomized, open label study.

Number of Subjects:
Sufficient subjects will be screened and enrolled such that 24 total subjects, 12 subjects per treatment group, will complete the study through the Follow-Up Visit. With 12 participants in each treatment group, we will be able to calculate a 95% confidence interval around the compliance rate in each group with a maximum margin of error of 0.283. Comparisons between groups for effectiveness will have 80 percent power to detect a difference of 1.2 standard deviations. Results of the current study are intended to provide descriptive endpoint data to inform the design of a future clinical evaluation of product effectiveness.

Study Overview:
Study Periods:
The length of study participation for a subject is about 8-12 weeks, depending on the length of radiation treatment. The study will extend 4-6 weeks beyond the end of radiation therapy. The study will begin with a Screening Visit during treatment planning followed by weekly assessments during radiation therapy, and a follow up visit 4-6 weeks after completion of therapy. There is a total of 5-7 visits.

Study Assessments:
At the Screening/Baseline Visit (Visit 1, Week 0), following informed consent, initial eligibility will be verified per the inclusion/exclusion criteria and demographics and brief medical history will be collected. Subjects will be randomized to receive standard of care or KeraStat Cream. A physical exam and photograph of the area to be irradiated will be obtained, and subjects will complete the Dermatology Life Quality Index.

During the course of radiation therapy (4-6 weeks) and for the duration of the post RT treatment period (4-week follow up), subjects will complete a daily diary detailing symptoms and treatment details. Weekly from week 2 of RT until the end of treatment, study staff will assess the subject for radiation dermatitis by recording the RTOG for Radiation-Induced Acute Skin Toxicity scores and taking photographs. The same evaluation will be performed at the follow up visit after treatment. Subjects will complete the Dermatology Life Quality Index at each visit.

Inclusion Criteria:
Subjects must meet all of the following criteria:

1. Age ≥ 18
2. Female
3. Diagnosis of early stage (stage 0-2) breast cancer and scheduled to receive 4-6 weeks of fractionated radiation therapy as part of breast conserving therapy following lumpectomy

Exclusion Criteria:

Name of Company: KeraNetics, LLC	Name of Product: KeraStat® Cream	Type of Study: Clinical Proof of Concept

To participate in the study, subjects must not meet any of the following criteria:

1. Previous radiation therapy to the area to be treated with radiation therapy
2. Receiving palliative radiation therapy
3. Low dose radiation protocol
4. Unhealed or infected surgical sites in the irradiation area
5. Patients undergoing cytotoxic chemotherapy or concurrent Herceptin as part of overall treatment plan (tamoxifen/aromatase inhibitor allowed)
6. Use of oral corticosteroids or topical corticosteroids in the irradiation area
7. Subjects with an autoimmune disease affecting the skin (e.g., scleroderma, systemic lupus erythematosus, psoriasis) are excluded. A history of other autoimmune disease that does not have direct skin involvement (e.g. rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis) does not exclude participation on the study unless the subject requires active treatment with systemic steroids, immune suppression or biologic agents, or systemic chemotherapeutic agents (methotrexate or cyclophosphamide).
8. Skin disease in target irradiation area
9. Known allergy to the standard of care or any of the ingredients in KeraStat Cream

Test Product(s), Dose, and Mode of Administration:
Investigational: KeraStat® Cream should be applied topically to the irradiation area and 1cm beyond the border of the affected area twice daily. Expel the cream from the tube. Smooth the cream over the target area to cover with a thin layer; do not rub the cream in.
Control: The standard skin care product should be applied topically to the irradiation area and 1cm beyond the border of the affected area twice daily. Smooth the product over the target area to cover with a thin layer; do not rub the product in.

Duration of Treatment:
The length of study participation for a subject is about 8-12 weeks.

Concomitant Medication Restrictions:
Chemotherapy, steroids

Criteria for Evaluation:
Effectiveness Evaluation:
Primary

- Safety and tolerability will be evaluated throughout the study utilizing patient reported outcomes
- Adverse events will be recorded throughout the study.

Secondary

- Maximum severity of radiation dermatitis as assessed by the RTOG Criteria for Radiation-Induced Acute Skin Toxicity.
- Number of subjects with Grade I radiation dermatitis
- Number of subjects with Grade II radiation dermatitis
- Number of subjects with moist desquamation present
- Change from baseline in the Dermatology Life Quality Index

Statistical Methods:
Feasibility:
Feasibility will be determined based on the average number of applications per week for a participant. Participants who average at least 10 applications per week will be classified as compliant. A 95% confidence interval will be calculated for the observed compliance rate. Along with the compliance rate, the number of tubes of KeraStat Cream used and the estimated surface area (bra size used as a surrogate) to be covered for each participant will be used to evaluate the coverage.

Safety:

Name of Company: KeraNetics, LLC	**Name of Product:** KeraStat® Cream	**Type of Study:** Clinical Proof of Concept
All subjects who are randomly assigned to a treatment and receive at least one application of KeraStat Cream or standard of care will be included in the safety and tolerability analysis. Safety will be evaluated by examining the incidence, grade, type of adverse events and changes in clinical laboratory test values, physical examination results, and vital signs measurements from the Screening Period through study completion. Effectiveness: Descriptive statistics will be generated to determine any trends and to support a power calculation for a large follow-up study. Tests comparing the two treatment groups will be done for all outcomes of effectiveness including, skin appearance, the Dermatology Life Quality Index score, and the RTOG skin score. Qualitative assessments of patient-reported skin condition and satisfaction with the intervention will be assessed for themes.		

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
CRF	Case Report Form
CRO	Clinical Research Organization
cGMP	Current Good Manufacturing Practice
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
KRNT	KeraNetics
SAE	Serious Adverse Event
RD	Radiation Dermatitis
SOPs	Standard Operating Procedures
SAP	Statistical Analysis Plan
USP	United States Pharmacopoeia

4. INTRODUCTION

4.1. Background

Radiotherapy (RT) is an effective intervention for treating breast cancer. The primary mechanism of action of RT is to create enough DNA damage within each tumor cell to prevent replication and ultimately induce programmed cell death. This mechanism extends beyond the targeted tumor to normal surrounding tissue. This field effect can be visualized by the effect of RT on the skin within a treatment portal. Approximately 85% of patients undergoing RT experience a moderate-to-severe skin reaction[1]. The disturbance of the cutaneous barrier function can significantly impact both health-related quality of life and the course of treatment[2]. If the skin reaction is severe enough, a treatment break may be recommended[3]. Managing the symptoms associated with skin reactions is important for ensuring completion of RT in a timely manner and increasing patient self-esteem[2]. Current skin care recommendations typically include the use of non-fragrant, hypo-allergenic moisturizers[2].

KeraStat Cream is a non-sterile, non-implantable, emulsion-based wound dressing intended to act as a protective covering in the management of a variety of minor skin wounds and first and second degree (partial thickness) burns as well as skin undergoing radiation treatment. KeraStat Cream uses human hair-derived keratin proteins and is applied topically to the wound surface to absorb exudate, provide a moist environment, and create an environmental barrier supportive of healing.

All ingredients have been used in FDA-approved products. A biological safety profile has been established for the keratin protein ingredient in KeraStat Cream. Biocompatibility studies were chosen and performed in accordance with ISO 10993-1:2007, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." This testing included a full toxicological risk assessment per ISO 10993-17 and 10993-18. Additionally, an FDA-approved hydrogel wound dressing containing the keratin proteins, water, and a preservative, called KeraStat Gel, has been subjected to a human subject Repeat Insult Patch Test (RIPT) to evaluate the irritation/sensitization potential of the product when applied to uncompromised skin. No adverse skin reactions were observed in 50 subjects evaluated in the RIPT study, and KeraStat Gel was considered a non-primary irritant and non-primary sensitizer to the skin. In addition to uncompromised skin, KeraStat Gel was tested in compromised skin to assess human sensitization study, the Skin Prick Test (SPT). The results of the SPT demonstrated that there was no humoral immune response to keratin and supported pre-clinical testing, which determined that the product would not elicit an immune response.

The current study is considered a nonsignificant risk (NSR) device study according to Food and Drug Administration (FDA) guidance and does not require an Investigational Device Exemption (IDE) in advance of study conduct. NSR device studies must follow the abbreviated requirements presented in 21 CFR 812.2(b) related to labeling, Institutional Review Board (IRB) approval, informed consent, monitoring, records, reports, and prohibition against promotion.

4.2. Rationale

Although well tolerated by most patients, about 30% of patients undergoing RT develop a Grade 2 or worse early adverse skin reaction (EASR). One study in Taiwan showed 23% of patients

undergoing chest wall or whole breast irradiation developed moist desquamation based on the RTOG scale[5]. This scale described grade 2 skin toxicity as tender or bright erythema, patchy moist desquamation / moderate erythema; Grade 3 skin toxicity was described as confluent moist desquamation other than skin fold, pitting edema. Both grade 2 and 3 skin toxicities were recorded in the assessment of patients in the Taiwanese study. Another study comparing breast IMRT to conventional tangent fields showed a decrease in moist desquamation, as defined by the NCI CTC version 2, from 48% to 31% of patients, suggesting that even with advanced treatment techniques, a significant number of patients experience skin toxicity[4].

For this study, we will classify grade 2 or 3 skin toxicity (per the RTOG scale) as an EASR. Beyond the discomfort patients may experience, EASRs may result in poor patient outcomes. Severe EASRs can require a "treatment break" which, in some cancers, may result in incomplete tumor control and greater chance of local recurrence and lower survival rates. In addition to the potential impact on cancer outcomes, EASRs may affect patients' self-esteem due to the appearance of their skin and recovery time after treatment. Standard skin regimens often include routine application of creams or lotions in an effort to combat the dryness, prevent interruption of the skin's natural barrier (e.g., cracking or flaking), and reduce the appearance of inflammation. Patients often begin using these creams/lotions at the start of RT. Providing patients with a product that moisturizes and reduces the appearance of inflammation may improve patients' satisfaction with their appearance as they progress through RT treatment.

KeraNetics has determined that this study is a non-significant risk study under 21 CFR 812.3(m). This device is not intended as an implant. It is not for use supporting or sustaining human life. It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health, and it does not otherwise present a serious risk to health, safety, or welfare of a subject. Furthermore, KeraStat Cream is classified as a wound dressing; wound dressings are classified as nonsignificant risk devices in FDA's "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies" published January 2006.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Objectives

The primary objectives of the proposed research are to evaluate the feasibility of the use of KeraStat Cream and collect data to inform a larger future trial.

The secondary objectives are to assess the safety and tolerability of KeraStat Cream in subjects at risk of radiation dermatitis, to assess the effectiveness of KeraStat Cream and how that compares to the current standard of care, and to estimate the amount of KeraStat Cream used per patient and coverage on skin.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a single site, between subject, open-label comparison pilot study to assess the feasibility and effectiveness of KeraStat Cream in managing RT skin toxicity. The length of study participation for a subject is 8-12 weeks depending on when a subject returns for her final follow-up evaluation. The Study Design Schematic is shown below in Figure 1 with the Acceptable Study Windows in Table 2.

Sufficient subjects will be screened such that 24 total subjects will complete the study. Patient compliance is expected to be good, so a target recruitment of 26 subjects is desired.

Once a RT patient is determined to be a candidate for inclusion in this study, they may be approached for consent to participate. A total of 26 breast cancer patients scheduled to receive RT will be recruited and consented.

RT will begin 4 to 10 weeks after surgery; the targeted volume will be the ipsilateral breast with or without regional lymph nodes. Once the patient has consented to participate in the study, their baseline pre-RT assessments can be completed during the radiation treatment-planning process.

Patients are generally treated with RT Monday through Friday, with weekends and holidays off, for approximately 4 to 6 weeks. Patients will be provided with KeraStat Skin Cream for application as often as needed but at least twice daily, morning and evening.

During the course of treatment, the patient sees the radiation oncologist weekly in clinic to review the patient's treatment course, monitor the skin's appearance after application of KeraStat Skin Cream or standard of care, and answer questions. Breaks in the treatment schedule should be avoided whenever possible, but breaks necessitated by RT skin toxicity or for other reasons will be recorded. The radiation oncologist will see each patient in follow-up 4-8 weeks after completing RT to assess the patient for RT-induced skin and other toxicities that may have occurred.

Figure 1: Study Design Schematic

Table 2: Acceptable Study Windows

Visit	Day Visit	Acceptable Visit Window
Screening (Visit 1)	Day 1	None
Baseline (Visit 1)	Day 1	None
First evaluation (Visit 2)	RT Day 8	±2 days
Second evaluation (Visit 3)	RT Day 15	±2 days
Third evaluation (Visit 4)	RT Day 22	±2 days
Fourth evaluation (Visit 5)	RT Day 29	±2 days
Fifth evaluation (Visit 6)	RT Day 36	±2 days
Final evaluation (Visit 7)	Post RT Day 30	±14 days

6.2. Detailed Study Design

6.2.1. Identification of Subjects and Consent

Study personnel will identify potential participants during radiation therapy treatment planning, explain the study, and seek to obtain subject consent. Individuals who express an interest will review and sign an informed consent form with study staff.

6.3. Number of Subjects

Twenty-six subjects are anticipated to be required for screening and enrollment in order to achieve a total of 24 patients participating in this study. Subjects will be randomized to receive either standard of care or KeraStat Cream.

Subjects at screening will be given a sequential subject number starting with 1001, 1002, etc. Subject initials will be collected, but not used as an identifier. The subject number will be used to identify the subject and all study materials associated with each subject.

6.4. Treatment Assignment

All subjects will be randomized to receive one of two test agents: KeraStat Cream or standard of care (physician-directed care).

6.5. Study Procedures

6.5.1. Visit 1

After obtaining consent, ensuring the subject meets study inclusion/exclusion criteria, and randomizing the subject, study personnel will photograph the site to be irradiated. Study personnel will collect vital signs. Subjects will complete the Dermatology Life Quality Index. Study personnel will provide KeraStat Cream to subjects randomized to receive KeraStat Cream. Subjects randomized to standard of care will follow the instructions of their radiation oncologist. Study personnel will provide subjects with a daily diary form where subjects will note symptoms or treatment details of concern.

6.5.2. Weekly Visits through Radiation Therapy

During regular visits with medical staff, study subjects will also meet with study staff. Study staff will obtain photographs of the area of irradiation and collect the daily dairy forms. Study personnel will collect vital signs and the physician's assessment of the presence and quality of radiation dermatitis using the RTOG scale as well as the physician's assessment of skin dryness, appearance of inflammation, and the skin's natural barrier. Any adverse events will be noted and addressed. Subjects will complete the Dermatology Life Quality Index. Study personnel will provide KeraStat Cream, as needed, to subjects randomized to receive KeraStat Cream. Subjects randomized to standard of care will follow the instructions of their radiation oncologist. Study personnel will provide subjects with a daily diary form where subjects will note symptoms or treatment details of concern.

6.5.3. Post-Radiation Therapy/Close-Out Visit

During a final follow up visit with medical staff (estimated at 4 to 6 weeks post radiation therapy termination), or if the subject terminates the study, the study subject will meet with study staff. Study staff will obtain photographs of the area of irradiation and collect the daily dairy forms. Study personnel will collect vital signs and the physician's assessment of the presence and quality of radiation dermatitis using the RTOG scale as well as the physician's assessment of skin dryness, appearance of inflammation, and the skin's natural barrier. Any adverse events will be noted and addressed. Subjects will complete the Dermatology Life Quality Index.

6.6. Criteria for Study Termination

The Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If the Sponsor determines such action is needed, Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, Sponsor will provide advance notification to the Investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform the Investigator and/or institution conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator or KeraNetics/KeraNetics designee, depending on whether the Institutional Review Board (IRB) is a central or local IRB, must inform the IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to Sponsor. In addition, arrangements will be made for all unused study device(s) to be destroyed or returned in accordance with the applicable procedures for the study.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

At the Screening Visit (Visit 1), subjects must meet all of the following criteria:

1. Age ≥ 18
2. Female
3. Diagnosis of breast cancer and scheduled to receive 4 to 6 weeks of radiation therapy (radiation dose of 42 Gy or more)
4. Able and willing to sign protocol consent form
5. Able and willing to document symptoms and treatment details as often as needed, not to exceed daily notes
6. Able and willing to have photographs of the affected area taken regularly

7.2. Subject Exclusion Criteria

To participate in the study, subjects must not meet any of the following criteria:

1. Women who are pregnant, lactating/nursing or plan to become pregnant
2. Previous radiation therapy to the area to be treated with radiation therapy
3. Receiving palliative radiation therapy
4. Unhealed or infected surgical sites in the irradiation area
5. Patients undergoing cytotoxic chemotherapy or concurrent Herceptin as part of overall treatment plan (tamoxifen/aromatase inhibitor allowed)
6. Use of oral corticosteroids or topical corticosteroids in the irradiation area
7. Subjects with an autoimmune disease affecting the skin (e.g., scleroderma, systemic lupus erythematosus, psoriasis) are excluded. A history of other autoimmune disease that does not have direct skin involvement (e.g. rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis) does not exclude participation on the study unless the subject

requires active treatment with systemic steroids, immune suppression or biologic agents, or systemic chemotherapeutic agents (methotrexate or cyclophosphamide).

8. Skin disease in target irradiation area
9. Known allergy to the standard of care or ingredients in KeraStat Cream

7.3. Subject Completion and Withdrawal

7.3.1. Subject Completion

A subject will be considered to have completed the study if they complete the entire study through the final evaluation (Visit 5 or 6).

7.3.2. Patient Withdrawal (Premature Discontinuation from the Study)

A documented effort must be made to determine why a subject fails to return for the necessary visit or is dropped from the study, and the reason for withdrawal must be recorded in the source documents and case report form (CRF). A subject may withdraw or be removed from the study for any of the following reasons and will be treated as considered appropriate by the Investigator:

- Subject request (for any reason)
- In the opinion of the Investigator, continuation is not in the best interest of the subject
- A serious or unexpected AE occurs such that continuation in the study is inappropriate
- Pregnancy
- RT is stopped
- In the opinion of the Sponsor, continuation is not in the best interest of the subject

If a subject is prematurely discontinued from participation in the study for any reason, the Investigator must follow up on all ongoing adverse events (if any).

In the event a subject is prematurely discontinued from the study due to an AE, or unexpected AE or serious adverse event (SAE) (as defined in Section 11.5.1), the procedures stated in Sections 11.3-11.9 must be followed.

7.3.3. Replacement of Patients

Subjects will not be replaced.

8. TREATMENT OF SUBJECTS

8.1. Description of Subject Device

KeraStat Cream is a non-sterile, non-implantable, emollient-based wound dressing intended to act as a protective covering in the management of a variety of skin conditions.

8.2. Concomitant Medications and Therapies

8.2.1. Pharmacological Therapy

Concomitant medications are permitted during this study unless otherwise specified in the Exclusion Criteria.

8.3. Randomization

Patients will be randomized to receive standard of care or KeraStat Cream.

9. STUDY DEVICE MATERIALS AND MANAGEMENT

9.1. Study Device

KeraStat Cream is a non-sterile, non-implantable, emollient-based wound dressing intended to act as a protective covering in the management of a variety of skin conditions. KeraStat Cream is designed to be topically applied to the skin surface. When applied, KeraStat Cream covers the skin or wound, isolating it from the external environment, absorbing excess exudate and facilitating a moist wound environment.

9.2. Study Device Packaging and Labeling

KeraStat Cream will be provided in multiuse tubes. The study device supplies will be maintained at the site under controlled conditions and dispensed by qualified personnel at the study site. The study device labels will contain information to meet the applicable regulatory requirements.

9.3. Study Device Storage

The study device must be stored at room temperature (15 to 30ºC [59-86ºF]). The study device must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive the study device, in accordance with all applicable regulatory requirements. Only authorized site staff may supply the study device.

9.4. Study Device Preparation

KeraStat Cream final product will be manufactured within applicable current Good Manufacturing Practice (cGMP) regulations in accordance with KeraNetics quality system. The product will be supplied in the form of a cream and packaged in a multi-use tube as detailed in Section 9.2.

9.5. Administration

KeraStat Skin Cream has been shown to moisturize the skin and reduce dryness, redness, and the appearance of inflammation. It should be applied **as needed** but **at least twice daily**.

In this study, patients will apply the cream at least twice-daily during the radiation treatments, 7 days per week.

9.6. Study Device Accountability

The Investigator is responsible for the study device accountability and record maintenance.

9.7. Study Device Handling and Disposal

Unused supplies, including the study device, will be disposed of using appropriate documentation according to International Conference on Harmonization-Good Clinical Practice (ICH-GCP), local requirements, applicable Occupational Safety and Health Administration (OSHA) and Environmental Protection Agency (EPA) regulations, and applicable study-specific procedures.

10. SCREENING ASSESSMENTS

The following assessments will be used for screening purposes only and taken after informed consent is obtained.

10.1. Demographics

Basic demographic information will be collected from the subject. This information includes age, gender, and race/ethnicity.

10.2. Medical History

Each subject will provide a brief medical history (e.g. history of allergic reactions to ensure they meet the inclusion/exclusion criteria). Study personnel will review the completed medical history form prior to enrolling the subject in the study. Study personnel may ask the subject for additional information, as necessary.

11. STUDY ENDPOINTS

11.1. Feasibility

Feasibility is the compliance rate, defined as the average number of applications per week. Participants may track applications in their daily diaries to assist in reporting to their physician at the weekly evaluation visit.

11.2. Skin Appearance

The appearance of the skin (including dryness, appearance of inflammation, and the natural barrier) as observed and recorded by study staff as well as the patient's self-report of satisfaction with the appearance of skin during the RT and up to 10 weeks post-RT.

11.3. Quality of Life

Subject quality of life will be measured using the Dermatology Life Quality Index. Subjects will complete the index at each visit. Quality of care will also be assessed qualitatively through examination of daily diary notes.

11.4. Coverage

Coverage will be calculated using the compliance rate, the number of tubes of KeraStat Cream used, and the estimated surface area (bra size).

11.5. Adverse and Serious Adverse Events

EASR will also be assessed at four time points from the start of radiotherapy through 4 weeks of the post radiotherapy follow-up period. The RTOG scale will be used for classification of EASRs related to the skin. The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of a non-serious AE or SAE as provided in this protocol. During the study, as defined from the time of informed consent until completion of study-related procedures, the Investigator or site staff will be responsible for detecting and following AEs and SAEs, as detailed in this section of the protocol. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative). We will also estimate the incidence of EASR of any grade, and for grades 2 and higher. At each time point we will estimate the proportion of women who have RT-induced EASR present and also calculate a 95% confidence interval around this estimate.

11.5.1. Definitions

11.5.1.1. Adverse Event (AE)

An adverse event (AE) is defined as any unfavorable or unintended change in body structure, body function, laboratory result (e.g., chemistry, ECG), or worsening of a pre-existing condition associated temporally with the use of the test product, whether or not considered related to the test product.

11.5.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that occurs irrespective of study treatment assignment, if it satisfies any of these criteria: results in death; is life-threatening; requires inpatient hospitalization or prolongs existing hospitalization; results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions; or if the event results in a congenital anomaly or birth defect. All SAEs should be reported to the study sponsor within 24 hours of the investigator being aware of the event.

11.5.2. Adverse Event Reporting

Subjects will be encouraged to spontaneously report any changes in baseline health from the time the subject enters the study through study completion. Study staff also will inquire about AEs on each visit while the subject is in the research center. All AEs/SAEs will be recorded in the source document and the case report form (CRF).

11.6. Relationship to Study Device

11.6.1. Assessment of Causality

The Investigator is obligated to assess the relationship between study device and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study device will be considered and investigated.

The Investigator will assess causality based on the following definitions:

- **Not Related** (the AE was more likely explained by causes other than the study treatment).
- **Related** (the study treatment and AE were closely related in time and the AE may be explained by exposure to study product: e.g., known adverse effect or recurrence on re-challenge).

11.7. Recording Adverse Events

When an AE occurs, it is the responsibility of the Investigator to review all documentation (e.g., medical progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an AE in the CRF.

The Investigator will attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

11.7.1. Eliciting Adverse Event Reports

At each visit, subjects will be asked about AEs by means of a non-leading question, such as "how have you been since your last visit?" or "how has the treatment been?" In this way, possibly milder, but clinically important, side effects of the study device can be detected. SAEs will be reported promptly to KeraNetics as described in the following table once the Investigator determines that the event meets the protocol definition of a SAE.

11.7.2. Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each AE/SAE recorded in the CRF should be assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

11.8. Reporting Adverse Events

An unexpected event is one that is not consistent with the subject's past medical history and is not evident from previous clinical experience with the test product or reasonably anticipated from information known about the test product. Events that are deemed serious, related, and unexpected involve special handling and reporting requirements to the IRB. All SAEs will be followed until stabilization or improvement.

11.8.1. SAE Reporting Procedures

Once an Investigator becomes aware that a SAE has occurred in a study subject, she/he will report the information as thoroughly as possible with all available details of the event to the Sponsors within 24 hours. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying Sponsor of the event. The information regarding the event will be updated when additional information is received. The Investigator will always provide an assessment of causality at the time of the initial event report as described in Section 11.6.1. An email is the preferred method to transmit this information regarding a SAE to the project contact for SAE receipt. In rare circumstances and in the absence of email equipment, notification by telephone is acceptable, with a copy of the event details sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator to complete the SAE report via email within 24 hours.

11.8.1.1. Regulatory Reporting Requirements for SAEs

Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

11.8.2. Reporting Safety Information to the IRB

The Investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB) / Institutional Ethics Committee (IEC).

11.8.3. Protocol Deviations Due to an Emergency or Adverse Event

Any subject experiencing an emergency or adverse event requiring immediate medical attention will receive appropriate medical management by medical staff at the site and at other clinical sites as indicated. These events will be reported to Sponsor as soon as possible. If the medical management results in departure from the study protocol, the Sponsor will be responsible for granting permission for the subject to continue in the trial if the subject is able to return to study protocol adherence in a timely fashion. If the subject cannot return to the study protocol in a timely fashion, then the subject will be discontinued from the study.

11.9. Follow-up of Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject and provide further information to Sponsor on the subject's condition. All AEs and SAEs documented at a previous visit/contact and designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate CRF entries will be updated.

12. STATISTICS

12.1. Description of Statistical Methods

Descriptive statistics will calculated and used to inform additional device development and to inform a power calculation for a follow on study, if required. The completion rate will be used as a measure of feasibility, with participants with an average of 10 or more applications per week being classified as compliant. A 95% confidence interval will be calculated around the estimate of compliance. After summary statistics are calculated by group, a t-test will be used to compare the two treatment groups for the effectiveness outcomes of DLQI score and RTOG score. A Fisher's exact test will be used to compare skin appearance issues between the groups. The counts for each type of adverse event will be summarized by grade and treatment group. For the KeraStat treatment group, the mean coverage will be calculated per square centimeter.

12.2. Sample Size

Up to 26 subjects will be enrolled on this pilot study to assure completion of at least 24 subjects. The expected accrual rate is four per month with accrual lasting approximately six months. Participants will be randomized equally (n=12 per group) to standard of care or KeraStat Cream. With 12 participants in each treatment group expected to complete the study, we will be able to calculate a 95% confidence interval around the compliance rate in each group with a maximum margin of error of 0.283. Comparisons between groups for effectiveness (RTOG scale and DLQI score) will have 80 percent power to detect a difference of 1.2 standard deviations.

12.3. Analysis of Patients Withdrawing Prematurely from the Study

All information for withdrawing subjects will be included in the analyses. Subjects who withdraw prematurely from the study will have any completed assessments included in the data summary.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

In accordance with applicable regulations, ICH-GCP and procedures covering the study, a monitor will contact the site prior to the subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits at an appropriate frequency to ensure data quality and to ensure the safety and rights of subjects are being protected.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 16.3.

13.2. Audits and Inspections

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, quality assurance audits may occur during the study or after the study is complete. Authorized representatives of KeraNetics, a regulatory authority, or an IRB may visit the site to perform audits or inspections to examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP, and any applicable regulatory requirements.

If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board (IRB)

This study will be conducted in full compliance with the Institutional Review Board (IRB) regulations in 21 CFR 56 and applicable local regulatory guidance.

IRB approval for the investigation must be obtained before the study is initiated. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form, and recruitment materials must be maintained by the Investigator and made available for inspection.

The current study is considered a nonsignificant risk (NSR) device study according to FDA guidance and does not require an Investigational Device Exemption (IDE) in advance of study conduct. NSR device studies must follow the abbreviated requirements presented in 21 CFR 812.2(b) related to labeling, Institutional Review Board (IRB) approval, informed consent, monitoring, records, reports, and prohibition against promotion.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Sponsor (or representative of Sponsor) may conduct a quality assurance audit. Please see Section 13.2 and 16.5 for more details regarding the audit process at any time during the conduct of the study or after study completion.

14.1. Regulatory Authority Approval

Not applicable. This is an NSR device.

14.2. Protocol Modifications

The initial protocol as well as all protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation of the original protocol and any amendment. The Principal Investigator must submit all protocol modifications to the IRB, as applicable for specific Investigators, or applicable local regulatory authority.

Departures from the protocol will be determined as allowable on a case-by-case basis or in event of an emergency involving subject safety. The Investigator or other physician in attendance must contact Sponsor as soon as possible to discuss the circumstances of the emergency. Sponsor, in concurrence with the Investigator, will decide whether the subject should continue to participate in the study. All protocol deviations and the reason for such deviations must be noted on the source document and in the CRF and reported to the IRB as appropriate.

15. ETHICS

15.1. Ethics Review

The Investigator is responsible for ensuring that this protocol, the site's informed consent form (ICF), and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IRB. The Investigator agrees to allow the IRB direct access to all relevant documents. The IRB must be constituted in accordance with all applicable regulatory requirements. Sponsor will provide the Investigator with relevant document(s)/data that are needed for IRB review and approval of the study. The IRB must approve the study and ICF before study device(s) and other study material can be supplied to the site.

If the protocol, the ICF, or any other information that the IRB has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring the IRB reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IRB approval of the amended ICF/other information and the approved amended ICF/other information must be maintained in the regulatory files at the site.

15.2. Ethical Conduct of the Study

This study will be conducted in accordance with ICH-GCP guidelines and all applicable regulatory requirements, including, where applicable, the Declaration of Helsinki.

15.3. Written Informed Consent

This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. The consent form must be reviewed and approved by the Sponsor prior to submission to the IRB. The consent form must be approved by the IRB prior to initiation of the study.

No Investigator may involve a human being as a subject in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An Investigator may seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether to participate and that minimize the possibility of coercion or undue influence. The information given to the subject or the representative must be in a language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the Investigator, the institution, the Sponsor, or its agents from liability for negligence.

An IRB-approved consent form should inform each prospective subject or the legally authorized representative of each prospective subject of the purpose and the nature of the study, its possible hazards and benefits, and the subject's right to withdraw from the study at any time without prejudice to further treatment. Exemptions to the requirement for informed consent in the United States are described in 21 CFR 50.23.

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator is responsible for obtaining written consent (signed and dated ICF) from potential subjects prior to performing any tests or assessments required by the protocol. A copy of the signed consent document will be given to the subject and the original retained by the Investigator.

16. DATA HANDLING AND RECORDKEEPING

16.1. Case Report Form Completion and Source Documentation

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Subject data are collected by the Investigator or designee using source documents that are transferred to a CRF, defined in collaboration with Sponsor. Subject data necessary for analysis and reporting will be entered onto the source documents and then provided to the

Sponsor as an electronic compilation of raw data from source documents via secure file exchange.

All information entered in the CRFs must be consistent with the subject's source documentation (i.e., medical records). The Investigator is responsible for the accuracy of the data transcribed from all source documentation. CRF entries should be made within a reasonable timeframe from the time of a subject's visit. Instances of missing or uninterpretable data will be brought to the attention of the Investigator and/or Sponsor for resolution.

16.2. Data Management

Clinical data management will be performed in accordance with applicable study standards and data cleaning procedures. All data will be collected and stored on-site in REDCap. Database lock will occur when data management quality control procedures are completed.

16.3. Study Site Close-Out

Upon completion of the study, the monitor may conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

1. Resolve data queries.
2. Accountability, reconciliation, and return of unused study device(s).
3. Review of final site study records for completeness.
4. Return all study-specific equipment to Sponsor.

16.4. Retention of Study Documents and Records

Following closure of the study, the Investigator must maintain all site study records in a safe and secure location. All study-related data will be retained by and are the sole property of Sponsor. The Investigator will retain a copy of all source documents and CRF data (i.e., DVD-ROM containing pdf files of data) for the subjects enrolled at the site. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection). Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Sponsor standards/procedures; otherwise, the retention period will default to 5 years.

The Investigator must notify Sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the Investigator leaves the site.

16.5. Inspection of Records

Sponsor (or a representative of Sponsor) will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the storage area, study device stocks, study material accountability records, subject charts and study source documents, and other records relative to study conduct.

17. INVENTION AND PUBLICATION POLICY

In the event of a conflict between the provisions of this section and a written contract regarding the conduct of the study between Sponsor (or a contract research organization) and the site, the Investigator or any person assisting Investigator with the Study, the terms of that contract shall control.

17.1. Ownership

All information provided by or on behalf of Sponsor and all data and information generated by the site, the Investigator or any person assisting Investigator with the study as part of or in connection with the study (other than a subject's medical records), is the sole and exclusive property of Sponsor. All rights, title, and interests in and to any inventions, discoveries or know-how made, conceived, learned or first reduced to practice by the site, Investigator or any person assisting Investigator with the study during the course of, in relation to, or as a result of the study (and any intellectual property rights related thereto) are the sole and exclusive property of the Sponsor, and are hereby assigned to Sponsor.

17.2. Confidentiality

All information provided by Sponsor and all data and information generated by the site as part of or in relation to the study (other than a subject's medical records) will be kept confidential by the Investigator, the site, and any person assisting Investigator with the study. This information and data shall not be used by the site, Investigator, or any person assisting Investigator with the study for any purpose other than conducting the study. These restrictions do not apply to: 1) information which becomes publicly available through no fault of the site, Investigator or any person assisting Investigator with the study; 2) information which it is necessary to disclose in confidence to an IRB solely for the evaluation of the study; 3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or 4) study results which are permitted to be published as described in the next section.

17.3. Publication

Investigator may publish the results of the study only for noncommercial, educational or academic purposes provided that prior to making the publication, or otherwise disclosing the study results, Investigator provides Sponsor with a copy of the proposed publication and allows

Sponsor a reasonable period to review. Proposed publications shall not include Sponsor's confidential information (other than the study results) or personal data with respect to any subject (such as name or initials) and if Sponsor identifies any confidential information in a proposed publication, it shall be removed.

At the request of Sponsor, the submission, publication or other disclosure of a proposed publication will be delayed a sufficient time to allow KeraNetics to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights contained in such proposed publication.

18. LIST OF REFERENCES

1. 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(4):94-112. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2913836&tool=pmcentrez&rendertype=abstract. Accessed July 23, 2014.

2. Bensadoun R-J, Humbert P, Krutman J, et al. Daily baseline skin care in the prevention, treatment, and supportive care of skin toxicity in oncology patients: recommendations from a multinational expert panel. *Cancer Manag Res*. 2013;5:401-408. doi:10.2147/CMAR.S52256.

3. Glover D, Harmer V. Radiotherapy-induced skin reactions: assessment and management. *Br J Nurs*. 23(4):S28, S30-5. http://www.ncbi.nlm.nih.gov/pubmed/24619051. Accessed July 23, 2014.

4. Pignol J-P, Olivotto I, Rakovitch E, et al. A Multicenter Randomized Trial of Breast Intensity-Modulated Radiation Therapy to Reduce Acute Radiation Dermatitis. *J Clin Oncol*. 2008;26(13):2085-2092. doi:10.1200/JCO.2007.15.2488.

5. Chen M-F, Chen W-C, Lai C-H, Hung C-H, Liu K-C, Cheng Y-H. Predictive factors of radiation-induced skin toxicity in breast cancer patients. *BMC Cancer*. 2010;10(1):508. doi:10.1186/1471-2407-10-508.