STUDY DEVICE:	**KeraStat® CREAM**
STUDY NUMBER:	KSCM-CRD-002
VERSION:	01
EFFECTIVE DATE:	**17 JUL 19**

SKIN PRICK TEST OF KERASTAT® CREAM

Sponsor: KeraNetics
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KERANETICS SIGNATURE PAGE

Approver(s):	Signature:	Date:
Luke Burnett, Ph.D. Chief Science Officer		17 Jul 19

KERANETICS CLINICAL STUDY PROTOCOL

Skin Prick Test of KeraStat® Cream

Study Number: KSCM-CRD-002

CONTACT INFORMATION

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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	**Name of Product:** KeraStat® Cream	**Type of Study:** Clinical Safety
Title of Study: Skin Prick Test of KeraStat® Cream		
Investigator(s): Dr. Jonathan Wilson		
Study Period: Estimated FPFV July 2019; Expected LPLVAugust 2019		
Phase of Development: Verification & Validation (Phase 3 of Design Control)		
Objective(s): • To evaluate the potential for a humoral reaction to KeraStat Cream compared to a predicate device		
Methodology: This is a within subject, open-label comparison study.		
Number of Subjects: Sufficient subjects will be screened such that approximately 20 total subjects will complete the study. Sample size for the study is not based on statistical considerations. A total of 20 subjects were deemed sufficient to assess the potential for a humoral response to KeraStat Cream compared to the predicate device in support of establishing substantial equivalence.		
Study Overview: <u>Study Periods</u>: The length of study participation for a subject is about 2-3 days depending on availability for the final site check. There are two skin prick site checks during the course of Day 1 with a final follow up between Days 2 and 3. <u>Study Evaluations:</u> Initial screening (Screening Visit; Visit 1) will be performed on the day of the Skin Prick Test (SPT) administration and will include obtaining demographic information, brief medical history, and abbreviated physical exam. On Day 1 (Visit 1) the SPT will be performed on the infrascapular region of the back to the right of the midline. Test articles will include the subject device (KeraStat Cream), predicate devices (KeraStat Gel, Biafine), positive control (histamine), and negative control (saline). Each test article will have a single administration, only the re-test will utilize a triplicate administration. The SPT will be ready for initial reading after approximately 15 minutes (but no sooner than 10 minutes and no longer than 20 minutes) following the final SPT administration in the series. When reading the test, the investigator will note the presence or absence of a wheal at all five sites and will measure the diameter of each wheal present. In order for the SPT to be valid, the wheal at the positive control site must exceed that at the negative control by 4 mm. If the above criteria are not met, the SPT will be repeated in triplicate on the infrascapular region of the back to the left of the midline, following the same protocol. Following the initial reading, the subject will remain at the testing facility. A second reading will be conducted approximately 6 hours (+/- 15 minutes) after SPT administration on Day 1 (Visit 1). When reading the test, the investigator will note the presence or absence of a wheal at all five sites and will measure the diameter of each wheal present. Subjects are free to leave the clinical site after the second reading. Subjects will be instructed to promptly contact the PI and go to the ER if symptoms of an allergic reaction or shock occur. Subjects will return to the office one to two days after initial administration for a third test reading (Visit 2). When reading the test, the investigator will note the presence or absence of a wheal in all five sites and will measure the diameter of each wheal present.		

Name of Company:	**Name of Product:**	**Type of Study:**
KeraNetics	KeraStat® Cream	Clinical Safety

Each site of test article administration will be measured for a positive reaction. A positive reaction is present when there is a measurable wheal of 3 mm or more, surrounded by a flare. Small wheals are to be confirmed by palpation. A flare alone is disregarded.

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

1. Men and women, age 18-65
2. Able to understand the informed consent and provide written informed consent
3. Healthy, unmarked skin at the test area
4. Agreement to avoid consumption of antihistamines until completion of third test reading (Visit 2)

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. Presence of skin disease, such as widespread urticaria or eczema
3. Diagnosis of infectious disease
4. Receiving corticosteroids, immunosuppressive agents, radiation or chemotherapy, topical growth factors, anxiolytics, imipramine, phenothiazine, dopamine, phenergen, clonidine, montelukast, immunotherapy, UV light therapy, H-2 antagonist, cyclosporine or any other medication the investigator feels will affect the test within the last month
5. Medical history of hypotension, severe hypertension, vasomotor instability, asthma, autoimmune disease, severe cardiac, pulmonary or renal disease
6. Tattoo in the intrascapular test area
7. History of surgical procedure/skin graft in the intrascapular test area
8. Employee or relative of employee of KeraNetics
9. Consumption of an anti-histamine within 7 days of the screening visit
10. History of hypersensitivity to histamine products
11. Any condition the investigator determines will compromise subject safety or prevent the subject from completing the study
12. Participated in an investigational study within 30 days of the screening visit

Name of Company:	**Name of Product:**	**Type of Study:**
KeraNetics	KeraStat® Cream	Clinical Safety

Test Product(s), Dose, and Mode of Administration:

Subject Device: KeraStat® Cream is a non-sterile, non-implantable wound dressing intended to act as a protective covering and provide a moist environment in the management of a variety of partial thickness dermal wounds. KeraStat® Cream is provided in a screw top tube for multiple uses. Each tube contains 1 oz (29.6 mL) of KeraStat® Cream, which contains 5% keratin protein incorporated into a cream base. KeraStat Cream will be provided in its final device form and sourced by the sponsor.

Predicate Devices: KeraStat Gel is a sterile, non-implantable, water-based gelatinous (hydrogel) wound dressing intended to act as a protective covering in the management of a variety of partial thickness dermal wounds. It is provided in a single-use (5 mL), collapsible aluminum tube. KeraStat Gel will be provided in its final device form and sourced by the sponsor.

BIAFINE is a water-based emulsion formulated for the dressing and management of superficial wounds, minor abrasions, dermal ulcers, donor sites, 1st and 2nd degree burns, including sunburns, and radiation dermatitis. Biafine will be provided in its final device form and sourced by the clinical site.

Positive Control: Histamine will be provided as a solution of histamine base (6.0 mg/mL). Histamine will be sourced by the clinical site.

Negative Control: Saline (sterile) will be provided as 0.9% NaCl. Saline will be sourced by the clinical site.

For SPT, the infrascapular region of the back to the right of the midline will be cleaned with alcohol wipes and allowed to air dry. Five marks will be made, at least 4 cm apart, to identify the test sites. These marks will be made in a vertical line. The back will be cleaned again with alcohol wipes and allowed to air dry. A UniTest® PC (Lincoln Diagnostics, Inc) will be used, according to the instructions of use, to administer each test article. If blood is drawn, the test will be repeated for that specific site. The test will be repeated at an additional mark made along the vertical line. One minute after completing the pricks, absorbent tissue will be applied to remove residual extract, and the back will be covered with a shirt or sheet to keep the back warm. The subject will be instructed not to scratch the test area.

Duration of Treatment:

The length of study participation for a subject is 2-3 days.

Concomitant Medication Restrictions:

Corticosteroids, immunosuppressive agents, radiation or chemotherapy, topical growth factors, anxiolytics, imipramine, phenothiazine, dopamine, phenergen, clonidine, montelukast, immunotherapy, UV light therapy, H-2 antagonist, cyclosporine

Criteria for Evaluation:

Skin Reaction:

Primary

- Size of wheal for the subject device and predicate device at 15 minutes post SPT administration

Secondary

- Size of wheal for the subject device and predicate device at 6 hours and 1-2 days post SPT administration

Safety Parameters:

- Safety of the subjects will be monitored and adverse events recorded throughout the study

Statistical Methods:

No formal statistics will be performed to compare the subject device and predicate device. Data will be summarized for each individual subject and time point. The number of subjects that meet criteria for a positive skin reaction to KeraStat Cream and/or a positive skin reaction to the predicate device(s) will be reported.

Safety:

All subjects who participate in the study will be included in the safety analysis. Safety will be evaluated by examining the incidence and type of adverse events from the Screening Visit through study completion.

FIGURE 1: TIME AND EVENTS SCHEDULE

Period	**Skin Prick Test**	
Visits	**Screening Visit / Visit 1 Day 1**	**Follow-Up Visit/ Visit 2 (Day 2-3)**
Screening		
Informed Consent	X	
Demography	X	
Brief Medical History	X	
Inclusion/Exclusion	X	
Safety Procedures		
*Vital Signs	X	
Abbreviated Physical Examination	X	
Adverse Events	X	X
Concomitant Medications	X	X
Study Treatment/General		
Skin Prick Administration	X	
Meal	X	
Assessments		
Evaluation of Response (15 min)	X	
Evaluation of Response (6 hrs)	X	
Evaluation of Response (24-48 hrs)		X

*Vital signs include height, weight, blood pressure, pulse, temperature, and respirations per minute.

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
ER	Emergency Room
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
IDE	Investigational Device Exemption
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
KN	KeraNetics
NSR	Nonsignificant Risk
OSHA	Occupational Safety and Health Administration
PI	Principal Investigator
RIPT	Repeat Insult Patch Test
SAE	Serious Adverse Event
SPT	Skin Prick Test
SOPs	Standard Operating Procedures
SAP	Statistical Analysis Plan
USP	United States Pharmacopoeia
UV	Ultra Violet

4. INTRODUCTION

4.1. Background

Active, healthy individuals are often involved in activities of daily living that put them at risk of sustaining acute skin trauma. Superficial to partial thickness abrasions may be the most common,[1] but other partial thickness injuries such as burns (450,000 burn injuries resulted in medical treatment in 2013)[2] and ulcers are also common. Due to the risk of untreated acute partial thickness wounds and burns becoming more serious chronic wounds or full-thickness burns, there is pressure on the medical community to find a cost-effective and efficacious wound dressing that supports healing.

KeraStat® Cream is a non-sterile, non-implantable wound dressing intended to act as a protective covering and provide a moist environment in the management of a variety of partial thickness dermal wounds. KeraStat® Cream is provided in a screw top tube for multiple uses. Each tube contains 1 oz (29.6 mL) of KeraStat® Cream, which contains 5% keratin protein incorporated into a cream base.

A biological safety profile has been established for 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." Furthermore, KeraStat Cream has been subjected to a human subject Repeat Insult Patch Test (RIPT) to evaluate the irritation/sensitization potential of the medical device when applied to uncompromised skin. No adverse skin reactions were observed in 50 subjects evaluated in the RIPT study and KeraStat Cream was considered a non-primary irritant and non-primary sensitizer to the skin.

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

When applied, KeraStat Cream covers the wound, isolating it from the external environment, absorbing excess exudate and facilitating a moist wound environment for the management of partial thickness wounds. KeraStat Cream contains human hair-derived keratin proteins.

Keratin, like collagen, is a structural, intermediate filament-forming protein.[3] Irrespective of what species they reside in, keratin proteins are functionally important for mechanical stability and integrity and structure of the hair shaft and cells in the epithelium. These proteins are highly conserved between species, with only minor differences in expressed keratin gene sets between species. Human hair and sheep wool in particular are highly similar with equivalent keratin intermediate fibers found in each species.[4] Keratin proteins have been used for multiple applications such as FDA cleared topical wound care products (e.g. Keratec Wound Dressings, KeraStat Gel),[5] and multiple cosmetic and personal care applications that include hair straightening products, shampoos, conditioners, and styling agents, as well as skin care creams and ointments that are sold as cosmetics.

The intended use for KeraStat Cream is as a wound dressing for management of partial thickness wounds where the normal skin barrier function has been disrupted. The keratin proteins in KeraStat Cream are derived from human hair and represent a novel component for use in a wound dressing compared to a legally marketed device (KeraStat® Gel) containing keratin proteins derived using the same manufacturing process. Animal models used for biocompatibility studies may not be fully predictive of the immune, inflammatory, and irritation responses in human subjects. While the RIPT study resulted in no observed skin reactions, the assessment is conducted on intact skin and there is a need to evaluate the potential for a humoral (B-cell mediated) immune response to KeraStat Cream on compromised skin to support its intended use. Therefore, a skin prick test is being conducted to support the continued evaluation of the safety of this product.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Objective

The objective of the present study is to evaluate the potential for a humoral reaction to KeraStat Cream compared to predicate devices.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a single site, within subject, open-label comparison study to assess the humoral reaction KeraStat Cream compared to predicate devices. The length of study participation for a subject is two to three days depending on when a subject returns for their final follow-up evaluation. The Acceptable Study Windows is shown in Table 2.

Sufficient subjects will be screened such that 20 total subjects will complete the study. We expect excellent retention throughout the duration of the study, so we will target recruitment of 22 subjects. The sample size for the study is not based on any statistical considerations. A total of 20 subjects were deemed sufficient to assess the potential for a humoral response to KeraStat Cream compared to the predicate devices in support of establishing substantial equivalence.

Initial screening (Screening Visit; Visit 1) of the subject will take place the day of the SPT administration. The Screening Visit will include collecting demographic information, a brief medical history, and an abbreviated physical exam. If a subject fulfills all the inclusion criteria, none of the exclusion criteria, and gives their informed consent they will be admitted into the study.

The SPT will be performed on Day 1 (Visit 1), after screening and consent is obtained. The test will include five agents: the subject device (KeraStat Cream), predicate devices (KeraStat Gel, Biafine), positive control (histamine), and negative control (saline). The SPT will be administered on the infrascapular region of the back to the right of the midline. The region will be cleaned with alcohol wipes and allowed to air dry. Five marks will be made using a sterile skin marker to identify the test sits. These marks will be at least 4 cm apart and made in a

vertical line. Once the marks are made, the back will be cleaned again with alcohol wipes and allowed to air dry. All subjects will initially receive the agents in the same order, going in descending order from a subjects' head to feet: subject device, predicate device (KeraStat Gel), predicate device (Biafine), positive control, and negative control.

Each agent will be administered once using the UniTest® PC (Lincoln Diagnostics, Inc), following the manufacturer's instructions for use. In brief, all five agents are loaded into a well tray. A UniTest PC touch post is placed into a well, tip-down, to load an agent onto the touch post. Each well contains approximately 250-500 µL. Allow the touch post to sit in the agent for at least 5 seconds. The touch post is removed and placed into contact at the appropriate mark for one second then pressed firmly into the skin. With proper pressure, all test sites should show a circular impression with an indented circle in the center surrounded by six dot indentations. A separate touch post is used for each agent. If blood is drawn, the test is repeated at an additional mark made along the vertical line. One minute after completing the pricks, absorbent tissue is applied to remove residual extract with care taken to avoid cross contamination of sites. When administration of the pricks is completed, the subject's shirt or a sheet will be used to cover the back and keep it warm. The subject will be instructed not to scratch the test area.

The initial evaluation of the sites will be taken after 15 (±5) minutes following the final SPT administration in the series. When reading the test, the investigator will note the presence or absence of a wheal at all five sites and will measure the diameter of each wheal present. In order for the SPT to be valid the wheal at the positive site control must exceed that at the negative site control by 4 mm. If the above criteria are not met, the SPT will be repeated in triplicate on the infrascapular region of the back to left of the midline, following the same protocol. Three vertical lines will be made with all marks at least 4 cm apart. If the triplicate re-administration fails, the subject will be removed from the study.

Following the initial reading, the subject will remain at the testing facility. They will wait with the pricks covered by their shirt or a sheet for a period of approximately 6 hours. The subject will be instructed not to scratch the test area. During this time, the testing facility will provide a meal for the subject.

A second evaluation will be conducted 6 hours (±15 minutes) after SPT administration on Day 1 (Visit 1). Again, the investigator will note the presence or absence of a wheal at each site and measure the diameter of each wheal present. Subjects are free to leave the clinical site after the second reading. Subjects will be instructed to not scratch or irritate the test area and to promptly contact the PI and go to the Emergency Room (ER) if symptoms of an allergic reaction or shock occur.

Subjects will return to the clinical site for a third/final test evaluation (Visit 2) one to two days after the initial test administration. When reading the test, the investigator will note the presence or absence of a wheal in all five sites and will measure the diameter of each wheal present. A subject will have completed the study after the third/final evaluation has been completed.

Table 2: Acceptable Study Windows

Visit	Day Visit	Acceptable Visit Window
Screening (Visit 1)	Day -7 to Day 1	None
SPT Administration (Visit 1)	Day 1	None
First evaluation (Visit 1)	Day 1	15 minutes ±5 minutes after SPT administration
Second evaluation (Visit 1)	Day 1	6 hours ±15 minutes after SPT administration
Third/Final evaluation (Visit 2)	Day 2 – 3	1 – 2 days after SPT administration

6.2. Number of Subjects

Enough subjects will be screened and enrolled such that a total of approximately 20 total subjects will be recruited into the study. All subjects will receive all five test articles.

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 samples associated with each subject.

6.3. Study Endpoints

The primary objective of the study is to assess the humoral response of KeraStat Cream compared to the predicate devices utilizing the following endpoints:

- Size of wheal for the subject device and predicate devices at 15 minutes post SPT administration
- Size of wheal for the subject device and predicate devices at 6 hours and 1 – 2 days post SPT administration
- Safety of the subjects will be monitored and adverse events recorded throughout the duration of the study

6.4. Treatment Assignment

All subjects will receive all five test agents: KeraStat Cream, KeraStat Gel, Biafine, histamine, saline.

6.5. Criteria for Study Termination

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 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.

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, day of the SPT), subjects must meet all of the following criteria:

1. Males or females aged 18 – 65 years.
2. Able to understand the informed consent, and provide written informed consent.
3. Healthy, unmarked skin at the test area (infrascapular regions of the back).
4. Agreement to avoid consumption of antihistamines until completion of the third test reading (Visit 2).

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. Presence of skin disease, such as widespread urticaria or eczema.
3. Diagnosis of infectious disease.
4. Receiving corticosteroids, immunosuppressive agents, radiation or chemotherapy, topical growth factors, anxiolytics, imipramine, phenothiazine, dopamine, phenergen, clonidine, montelukast, immunotherapy, UV light therapy, H-2 antagonist, cyclosporine, or any other medication the investigator feels will affect the test within the last month.
5. Medical history of hypotension, severe hypertension, vasomotor instability, asthma, autoimmune disease, severe cardiac, pulmonary or renal disease.
6. Tattoo in the intrascapular test area.
7. History of surgical procedure/skin graft in the intrascapular test area.
8. Employee or relative of employee of KeraNetics.
9. Consumption of an antihistamine within seven days of study initiation.
10. History of hypersensitivity to histamine products.

11. Any condition the investigator determines will compromise subject safety or prevent the subject from completing the study.
12. Participated in an investigational study within 30 days of the Screening Visit.

7.3. Subject Restrictions and Requirements

7.3.1. Medication and Therapy Restriction

See Section 8.2.

7.3.2. Food, Meals, Beverages and Fluid Intake

Subjects will be instructed to maintain their normal level of food and fluid consumption throughout the trial and therefore they should not alter their fluid intake greatly over the course of the trial. The testing center will provide the subject with a meal between the 15 minute and 6 hour evaluations on Day 1.

7.3.3. Contraception

Women of childbearing potential are defined as premenopausal women who are not surgically sterile. Surgically sterile is defined as women with tubal ligation, hysterectomy and/or bilateral oophorectomy.

Women of childbearing potential must:

1. Self-report that they are not pregnant or plan to become pregnant. This study does not require a negative urine pregnancy test.
2. Not be lactating.

Women of childbearing potential with male partners must:

1. Be willing to use acceptable methods of contraception from screening through follow-up unless the woman is in a monogamous relationship with a sterilized male partner (e.g., vasectomy).
2. Acceptable methods of birth control are systemic contraceptives (contraceptive pills, hormonal implants, contraceptive patches and injectable contraceptives), or intra-uterine devices), double-barrier methods, or as approved by the Investigator.

7.4. Subject Completion and Withdrawal

7.4.1. Subject Completion

A subject will be considered to have completed the study if they complete the entire study through the final evaluation (Day 2 – 3, Visit 2).

7.4.2. 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.
- Test area (infrascapular region of the back) becomes marked or affected so that the Investigator is unable to read the test sites.
- Subject consumes antihistamines during the study.
- Pregnancy
- 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 11.2.1), the procedures stated in Sections 11.2-11.6 must be followed.

7.4.3. Replacement of Patients

Subjects that fail the criteria for positive and negative controls in the triplicate re-administration will not be replaced.

8. TREATMENT OF SUBJECTS

8.1. Description of Subject Device

KeraStat® Cream is a non-sterile, non-implantable wound dressing intended to act as a protective covering and provide a moist environment in the management of a variety of partial thickness dermal wounds. KeraStat® Cream is provided in a screw top tube for multiple uses. Each tube contains 1 oz (29.6 mL) of KeraStat® Cream, which contains 5% keratin protein incorporated into a cream base.

The study device is described below in Table 3.

Table 3: Subject Device

	Subject Device	Predicate Device	Predicate Device	Positive Control	Negative Control
Product Name	KeraStat Cream	KeraStat Gel	Biafine	Histamine	Saline
Manufacturer	KeraNetics	KeraNetics	Johnson and Johnson	HollisterStier, LLC	McKesson
Packaging	Multi-use tube	Single-use tube	Multi-use tube	Multi-use sterile amber vial with dropper	3ml Syringes
Components	5.0% keratin, purified water, glycerin, caprylic/capric triglyceride, dimethicone, mineral oil, sodium stearoyl glutamate, sodium polyacrylate/hydrogenated polydecene/trideceth-6, phenoxyethanol, ethylhexylglycerin, and sodium hydroxide	5.0% keratin; purified water, phenoxyethanol, carbomer, sodium hydroxide, and ethylhexylglycerin	Purified water, liquid paraffin, ethylene glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalane, avocado oil, trolamine/sodium alginate, triethanolamine, cetyl palmitate, methylparaben (sodium salt), sorbic acid (potassium salt), propylparaben (sodium salt), and fragrance	6.0 mg/mL	0.9% NaCl
Route of Administration	Topical	Topical	Topical	Percutaneous	Percutaneous
Physical Description	White to tan cream	Hydrogel	White to tan cream	Clear liquid	Clear liquid

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

All subjects receive the same test agents in the same location (infrascapular region of the back) in the same order. The test agents will be administered going in descending order from a subject's head to feet: subject device, predicate device, positive control, and negative control.

9. STUDY DEVICE MATERIALS AND MANAGEMENT

9.1. Study Device

KeraStat® Cream is a non-sterile, non-implantable wound dressing intended to act as a protective covering and provide a moist environment in the management of a variety of partial thickness dermal wounds. KeraStat® Cream is provided in a screw top tube for multiple uses. Each tube contains 1 oz (29.6 mL) of KeraStat® Cream, which contains 5% keratin protein incorporated into a cream base.

9.2. Study Device Packaging and Labeling

KeraStat Cream will be provided in a multi-use (1 oz), collapsible aluminum tube. Study device supplies will be maintained at the site under controlled conditions and dispensed by qualified personnel at the study site. 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]). 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 or administer the study device.

9.4. Study Device Preparation

KeraStat Cream final product will be manufactured by Dexios for KeraNetics in the form of a cream and packaged in a multi-use tube as detailed in Section 9.2. T

9.5. Administration

During the SPT, the study device (KeraStat Cream) will be administered on the infrascapular region of the back to the right of the midline by qualified personnel. The region will be cleaned with alcohol wipes and allowed to air dry. Five marks will be made using a marker to identify the test sets. These marks will be at least 4 cm apart and made in a vertical line. Once the marks are made, the back will be cleaned again with alcohol wipes and allowed to air dry. All subjects

will initially receive the agents in the same order, going in descending order from a subjects' head to feet: subject device, predicate devices, positive control, and negative control.

Each agent will be administered once using the UniTest® PC (Lincoln Diagnostics, Inc), according to procedures described herein. If blood is drawn, the test is repeated at an additional mark made along the vertical line. One minute after completing the pricks, absorbent tissue is applied to remove residual extract with care taken to avoid cross contamination of sites. When administration of the pricks is completed, the subject's shirt or a sheet will be used to cover the back and keep it warm. The subject will be instructed not to scratch the test area.

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 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. The Investigator will review the completed medical history form prior to enrolling the subject in the study. The Investigator may ask the subject for additional information, as necessary.

10.3. Physical Exam and Vital Signs

An abbreviated physical exam and documentation of vital signs will be conducted by the site following the site's standard policy, prior to enrolling the subject in the study. The abbreviated physical exam includes measuring a subject's height, weight, blood pressure, pulse, temperature, and respiratory rate as well as an examination of the skin prick test region of the back.

11. STUDY ENDPOINTS

11.1. Positive Reactions

During all evaluations, each site will be measured for a positive reaction. A positive reaction is present when there is a measurable wheal of 3 mm or more, surrounded by a flare. In cases where the wheal diameter is non-uniform, the longest wheal diameter should be used for the evaluation of the SPT.[6,7] Small wheals are to be confirmed by the investigator via palpation.

11.2. Adverse and Serious Adverse Events

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).

11.2.1. Definitions

11.2.1.1. 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.

11.2.1.2. 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.

11.2.2. 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).

11.3. Relationship to Study Device

11.3.1. 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).

11.4. 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.

11.4.1. 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 more mild, 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.

11.4.2. 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.

11.5. 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 both serious and unexpected involve special handling and reporting requirements to the IRB and FDA. All SAEs will be followed until stabilization or improvement.

11.5.1. 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 KeraNetics 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 KeraNetics 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 11.3.1. 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.

11.5.1.1. Regulatory Reporting Requirements for SAEs

KeraNetics 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.

11.5.2. 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).

11.5.3. 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 KeraNetics 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.

11.6. 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

This is an observational study only; no formal statistics will be performed.

12.1.1. Baseline Data Summary

Demographic data and subjects' characteristics (e.g. vital signs) at screening will be listed and summarized using descriptive statistics. Any deviations from inclusion/exclusion criteria will be listed.

12.1.2. Responder Summary

The total number of subjects with a positive skin reaction (i.e. wheal diameter > 3mm) will be determined for the subject device and predicate device for each evaluation time point. The proportion of subjects who have a positive response to the subject device will be compared to the proportion of subjects who have a positive response to the predicate device.

12.2. Sample Size

A total of 20 subjects were deemed sufficient to assess the potential for a humoral response to KeraStat Cream compared to the predicate devices in support of establishing substantial equivalence. The sample size for the study is not based on any statistical considerations. Approximately 22 subjects will be enrolled to assure completion of at least 20 subjects.

12.3. Procedure for Accounting for Triplicate Data

In the case that a triplicate re-administration is required, wheal diameter will be averaged for each test agent. A subject will be considered to show a positive reaction to the subject device or predicate device when the average wheal diameter is greater than 3 mm.

12.4. 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, 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 KeraNetics 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, KeraNetics (or representative of KeraNetics) 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.

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 KeraNetics as soon as possible to discuss the circumstances of the emergency. KeraNetics, 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. KeraNetics 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, it's 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 by KeraNetics. 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. A monitor representing the Sponsor will verify the CRF documentation for each subject against the source documents at the study center. 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. 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 KeraNetics.

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 KeraNetics. 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.

KeraNetics 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 KeraNetics standards/procedures; otherwise, the retention period will default to 5 years.

The Investigator must notify KeraNetics 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

KeraNetics (or a representative of KeraNetics) 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 drug 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 KeraNetics 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

If the study is a multi-center study, the first publication or disclosure of study results shall include data from all sites.

Investigator may publish the results of the study only for noncommercial, educational or academic purposes provided that: 1) said publication is made after the multi-center publication; and 2) 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 KeraNetics confidential information (other than the study results) or personal data with respect to any subject (such as name or initials) and if KeraNetics identifies any such KeraNetics confidential information in a proposed publication, it shall be removed.

At the request of KeraNetics, 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

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