# The GEM-1 Study

KB103-001

A Phase II Study of KB103, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)

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| Status: | **Final** |
| Protocol Version: | **Version 4.0** |
| Version Date: | **01-Aug-2019** |
| IND Number: | **18100** |
| Investigational Product: | **KB103** |
| Phase of Development: | **Phase II** |

# Protocol Signature Page

**Sponsor Endorsement**

This protocol has been approved by Krystal Biotech, Inc.

Sponsor's Authorized Officer: Suma Krishnan, M.S., M.B.A.

Chief Operating Officer
Krystal Biotech, Inc.
2100 Wharton Street, Suite 701
Pittsburgh, PA 15203

_____ _____
Signature Date

**Principal Investigator's Agreement**

I have read the Phase II Protocol:

**A Phase II Study of KB103, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)**

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's representative.

I agree to conduct the study as outlined herein and in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), with applicable Food and Drug Administration (FDA) regulations set forth in 21 CFR Parts 50,54, and 312, and all other applicable regulatory requirements.

Principal Investigator Name: _____

_____ _____
Signature Date

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# Abbreviations

Abs..... antibodies
AEs ..... adverse events
AF ..... anchoring fibrils
ALT (SGPT) ..... alanine aminotransferase, included in metabolic panel
AST (SGOT) ..... aspartate aminotransferase, included in metabolic panel
BMZ ..... basement membrane zone
CBC ..... complete blood count
CFR..... Code of Federal Regulations
CLIA..... Clinical Laboratory Improvement Amendments
CM ..... centimetre
COL7..... collagen VII
COL7A1 ..... collagen 7 gene
CRF..... case report form
CTC ..... Common Toxicity Criteria
DEB..... dystrophic epidermolysis bullosa
DNA ..... deoxyribonucleic acid
EB ..... epidermolysis bullosa
eGFP..... enhanced green fluorescent protein
ELISA..... enzyme-linked immunosorbent assay
ELISPOT..... enzyme-linked immunospot
EM..... electron microscopy
ET ..... early termination
FDA..... Food and Drug Administration
GCP ..... Good Clinical Practice
GFP..... green fluorescent protein
GMP..... Good Manufacturing Practice
GRAS..... Generally Regarded As Safe
HCMV ..... human cytomegalovirus
HDF..... Human Dermal Fibroblasts
HEENT..... head, ears, eyes, nose, throat
Hep ..... hepatitis
HIPAA ..... Health Insurance Portability and Accountability Act
HIV ..... human immunodeficiency virus
HK..... human keratinocytes
HSV..... herpes simplex virus

ICF ..... informed consent form
ICP ..... infected cell polypeptide
ID ..... intradermal
IEM..... immunoelectron microscopy
IF ..... immunofluorescence
Ig ..... immunoglobulin
IIF ..... indirect immunofluorescence
IND ..... Investigational New Drug application
IP..... Investigational Product
IRB ..... Institutional Review Board
ITT..... Intent-to-treat
LTFU ..... long-term follow-up
MCH ..... mean corpuscular hemoglobin
MCHC ..... mean corpuscular hemoglobin concentration
MCV ..... mean cell volume
mRNA ..... messenger ribonucleic acid
NC1 ..... noncollagenous 1 domain
NC2 ..... noncollagenous 2 domain
NCI ..... National Cancer Institute
ORF ..... open reading frame
PCR ..... polymerase chain reaction
PFU ..... plaque-forming units
PHI ..... protected health information
PP ..... per protocol
RBC ..... red blood cell count
RCV ..... replication competent virus
RDEB ..... recessive dystrophic epidermolysis bullosa
RDW ..... red blood cell distribution width
SAE ..... serious adverse event
SD ..... standard deviation
SMC ..... safety monitoring committee
SOPs..... standard operating procedures
WBC..... white blood cell

# Protocol Synopsis

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|---|---|
| **Title** | A Phase II Study of KB103, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB) |
| **Objectives** | **Primary**<br>1) To assess wound closure through post-administration imaging:<br>a. Change in surface area of a KB103-administered wound relative to the same wound at baseline and a placebo-administered wound<br>b. Time to wound closure of a KB103-administered wound relative to a placebo-administered wound<br>c. Duration of wound closure of a KB103-administered wound relative to a placebo-administered wound<br>**Secondary**<br>1) To assess change from baseline in the Investigator's Global Assessment score<br>2) To assess change from baseline in PRO scales of severity and pain<br>**Other**<br>1) To evaluate the expression of human collagen VII as determined by immunofluorescence (IF).<br>2) To evaluate the presence of anchoring fibrils as determined by immunoelectron microscopy (IEM) post-administration. |
| **Test Product** | KB103 |
| **# of Subjects** | Up to 14 including Phase 1 and Phase 2. This version of the protocol intends to enroll 3 subjects. |
| **Study Design** | This study is an intrasubject comparison of KB103-administered and placebo-administered wounds. Up to three 50 $cm^2$ areas will be selected for entry: one or two will be selected to receive topical KB103, and one to receive topical placebo.<br>The primary objective of this study is to evaluate clinical efficacy through digital imaging of wounds. Secondary objectives include an evaluation of change in an Investigator's global assessment and change in patient reported outcomes.<br>Patients will be administered Investigation Product (IP) in two cycles. Cycle 1 starts on Day 1. Up to three 50 $cm^2$ areas are administered IP (one or two KB103 and one placebo) every 2 to 3 days (to correspond with bandage changes) until wound closure, or up to 3 months. IP is administered to the entire areas, on the wound(s) and on intact skin.<br>Following this initial dosing period, patients will enter into an observation period in which wounds are monitored at home using a phone imaging app. Upon re-opening and/or expansion of a wound in the KB103 treatment area, patients will be asked to return to clinic or will be treated at home to begin the 2nd cycle of dosing.<br>The 2nd cycle mimics the first. The same 50 $cm^2$ areas are administered IP (one or two KB103 and one placebo) every 2 to 3 days until wound closure or up to 3 months. IP is administered to the entire areas, on the wound(s) and on intact skin. |

After the 2nd cycle of IP administration, patients enter a second observation period. Patients image their wounds at home using a phone app, and return to the clinic at monthly intervals.

Time to wound closure and duration of wound closure will be evaluated after both the 1st and 2nd cycles. Safety will be monitored throughout the study.

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| **Population** | **Inclusion Criteria**<br>1. Clinical diagnosis of the recessive form of dystrophic epidermolysis bullosa.<br>2. Age: 3 subjects age 2 and older<br>3. Willing and able to give consent/assent.<br>4. Confirmation of RDEB diagnosis by genetic testing, IF and EM.<br>5. Confirmed RDEB COL7A1 mutations in subject.<br>6. Two areas of skin up to 50 cm2, with at least 1 wound in each area.<br>7. Subjects who, in the opinion of the Investigator, are able to understand the study, co-operate with the study procedures and are willing to return to the clinic for all the required follow-up visits.<br>**Exclusion Criteria**<br>1. Medical instability limiting ability to travel to the investigative center.<br>2. The presence of medical illness expected to complicate participation and/or compromise the safety of this technique, such as active infection with HIV, hepatitis B or hepatitis C, as determined by hepatitis B surface antigen screening, detection of hepatitis C antibodies, or positive result of hepatitis C PCR analysis.<br>3. Active infection in the area that will undergo administration<br>4. Evidence of systemic infection.<br>5. Known allergy to any of the constituents of the product.<br>6. Current evidence or a history of squamous cell carcinoma in the area that will undergo treatment.<br>7. Active drug or alcohol addiction.<br>8. Hypersensitivity to local anesthesia (lidocaine/prilocaine cream).<br>9. Receipt of chemical or biological study product for the specific treatment of RDEB in the past three months, except for KB103.<br>10. Specific wounds that have previously been administered investigational gene or cell therapy. Wounds previously administered KB103 are not excluded.<br>11. Positive pregnancy test or breast-feeding.<br>12. Clinically significant abnormalities as determined by the investigator. |
| **Test Product and Route of Administration** | Topical KB103 (KB103 formulated with a carrier gel) |

# 1 Background

## 1.1 Disease Background

Dystrophic epidermolysis bullosa (DEB) is a group of heritable skin diseases characterized by skin fragility, blister formation, milia, and scarring (Intong, 2012). Epidermolysis bullosa (EB) affects 1 in 20,000 live births and causes the skin and mucous membranes to blister and erode in response to minor injury or friction, such as scraping, rubbing, or scratching (Varki, et al., 2007). Dystrophic epidermolysis bullosa (DEB) is one of the major forms of EB and is the result of mutations to the COL7A1 gene encoding collagen VII (Varki, et al., 2007), (Uitto & Christiano, 1994).

Severe generalized recessive dystrophic epidermolysis bullosa (RDEB), formerly termed Hallipeau-Siemens, is characterized by extensive blistering and scarring of the skin and mucosal membranes. Blisters and erosions affect skin as well as certain mucosa exposed to disruptive external environment, including oropharynx, esophagus, rectum, genitourinary system and eye. Healing of erosions results in debilitating scarring. Damage to the mouth and esophagus can make it difficult to chew and swallow food, leading to chronic malnutrition and slow growth. Complications from extensive scarring can include fusion of the fingers and toes, joint deformities, and vision impairment. Additionally, patients suffering from RDEB have a high risk of developing squamous cell carcinoma, which is highly aggressive and life-threatening. There is significant mortality associated with RDEB with nearly 10% of the patients dying before age 10, almost 40% by age 20, and 72% die before the age of 30 (Varki, et al., 2007). There is no cure for EB and treatment options are limited. Current care focuses on managing the disease symptoms, including pain/itch medications, antibiotics and surgical treatments of scarring deformities (Fine, 2010).

Given the severity of this disorder and the lack of effective treatment options, there exists a clear need for alternative treatment options that focus on the root cause of the debilitating symptoms and can be administered in a minimally invasive way.

### 1.1.1 RDEB Pain and Patient Reported Outcomes

Pain is clinically meaningful as it is documented as one of the top symptoms affecting quality of life reported by EB patients (van Scheppingen, et al., 2008). As such, this protocol will evaluate pain through the use of pain scales. The pain scales (Wong-Baker Faces Pain Rating Scale, **Appendix 2**) are well established existing questionnaires from the medical literature that have been shown to be both valid and reliable measures of pain in children and adults for a wide range of dermatologic conditions (Morris, et al., 2012) (Garra, et al., 2010). The same scale has been used previously in a Phase 3 EB study (Browning, et al., 2017).

## 1.2 Collagen VII

The mutations cause an absence or reduction of functional COL7 and anchoring fibrils. Anchoring fibrils may be reduced in number and show abnormal morphology (loss of fan-shaped appearance

and central cross-banding) or, in the clinically most severe cases, the anchoring fibrils are barely detectable; where only a few thin structures can be seen (Tidman, 1985).

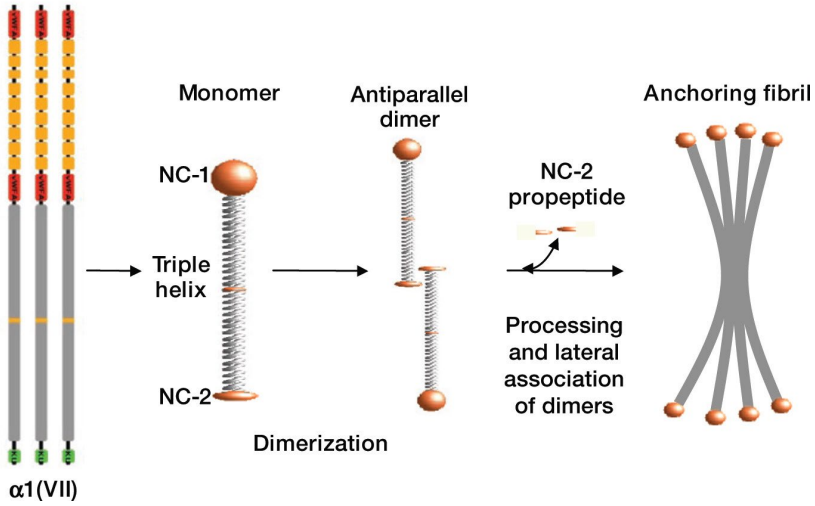
Skin integrity is achieved by interactions between the basal keratinocyte cytoskeleton, hemidesmosome complexes at the dermal-epidermal junction and the underlying anchoring fibrils. Anchoring fibrils are supramolecular structures primarily composed of collagen VII (Jonkman, et al., 2003) that originate and terminate within the basement membrane (Burgeson, 1993) and tether this superstructure to collagen bundles within the dermis (Leigh, et al., 1988).

### 1.2.1 COL7A1 Gene

The COL7A1 gene encodes a 290-kDa alpha chain (Christiano, et al., 1994) and three of the chains form a triple helix (trimer). The trimers form antiparallel dimers, which aggregate laterally to form anchoring fibrils (AFs) within the extracellular space (Burgeson, 1993).

The trimers are characterized by repeating Gly-X-Y amino acid sequences, flanked by a large 145kDa amino-terminal, non-collagenous domain (NC1) and a small 34-kDa carboxyl-terminal non-collagenous domain (NC2). The tail-to-tail dimers that aggregate laterally to form the anchoring fibrils have NC1 domains at both ends. **Figure 1** below schematically represents anchoring fibril formation.

**Figure 1 - Anchoring Fibril Formation**




(Bruckner-Tudorman, 2009)

The NC1 domains interact with various proteins of the extracellular matrix, including fibronectin, laminin-5, type I and IV collagen. This interaction mediates attachment of the basement membrane to the dermis (Burgeson, 1993).

### 1.2.2 NC1 Domains

COL7A1 contains 118 exons composed of a noncollagenous domain 1 (NC1) (exons 1-28), a central collagenous domain with Gly-X-Y region (exons 29-111), and a noncollagenous domain 2 (NC2) (exons 112 – 118) that catalyzes the anchoring fibril assembly. RDEB patients may either express the NC1 amino-terminal fragment of type VII collagen NC1[+] or lack it (NC1[-]). Epitope mapping of autoantibodies in patients with acquired autoimmunity to type VII collagen

(epidermolysis bullosa acquisita) demonstrates that NC1 is the predominant domain targeted by patient autoantibodies. These studies suggest that NC1 is likely the most antigenic portion of the type VII collagen molecule. Subjects whose fibroblasts demonstrate expression of the NC1 domain by Western blot analysis should have a reduced chance of an immune response to the therapeutic gene product, type VII collagen. These subjects' immune systems will have recognized the most antigenic portion of the type VII collagen molecule, the NC1 domain, as self, thus reducing potential immune reactions.

## 1.3 COL7A1 Gene Delivery for DEB

Published studies in animal models have shown that expression of COL7 results in DEB disease correction**.** Immunodeficient mice grafted with RDEB skin were intradermally injected fibroblasts modified to over-express COL7. The injection normalized RDEB disease features, including blistering and anchoring fibril defects (Ortiz-Urda, et al., 2003). In addition, a lentiviral vector expressing COL7 was administered intradermally into immunodeficient mice grafted with RDEB skin. The vector transduced dermal cells, which expressed COL7 into the extracellular space. The COL7 incorporated into the basement membrane zone (BMZ), formed anchoring fibril structures, and reversed the DEB phenotype (Woodley, et al., 2004). Recently, genetically modified fibroblasts were administered to human RDEB skin xenografts on NOD-scid mice and were shown to deposit COL7 and generate anchoring fibrils at the BMZ (Georgiadis, et al., 2016).

This mechanism of action, whereby DEB cells are transduced to express COL7, has also demonstrated efficacy in a clinical trial at Stanford where patients were administered genetically modified keratinocytes via epidermal xenografts. The autologous keratinocyte grafts were modified with a Moloney leukemia virus–derived retroviral vector (LZRSE-COL7A1) (Siprashvili, et al., 2010). Analysis of the modified keratinocytes showed a transduction efficiency of 65 – 80% and demonstrated the COL7 to be functionally indistinguishable from the endogenous wild-type protein. Following administration of the grafts, COL7 expression was detected in 9 of 10 biopsy samples (90%) at 3 months, in 8 of 12 samples (66%) at 6 months, and in 5 of 12 samples (40%) at 12 months. At 3 months, 5 of 7 biopsy samples (71%) showed a morphologically normal appearance and had anchoring fibrils (Siprashvili, et al., 2016). These observations of efficacy validate preclinical evidence suggesting that replacing as little as 30% of normal COL7 levels is sufficient for restoring proper skin function (Fritsch, et al., 2008) (South & Uitto, 2016).

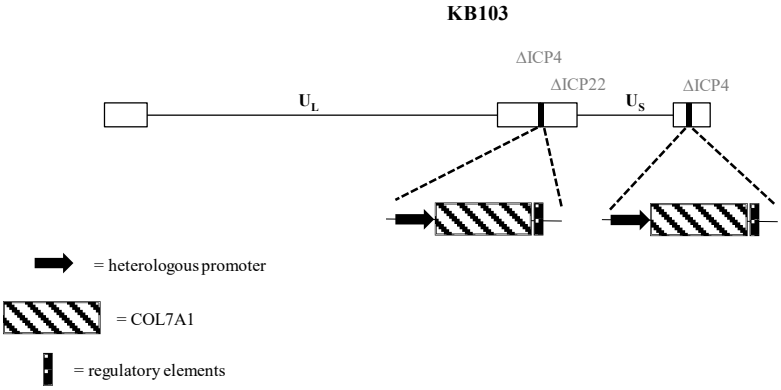
Although successful in achieving durable correction of key disease features, and well-tolerated from a safety perspective, ex vivo gene delivery is expensive, time-consuming (3 to 6 months to manufacture an autologous therapy), and invasive. Manufacturing requires harvesting skin cells from the DEB patient by skin biopsy, growing the cells in tissue culture, correcting the gene defect, expanding the gene-corrected cells, and then transplanting them back onto the patient through surgery or several injections. Drawbacks include high cost, poor graft takes, surgical debridement, complex bandaging and wound care, and potential postsurgical infection. There is a need for a less invasive, non-autologous therapy.

## 1.4 KB103 Background

The vector delivery system, KB103, is a non-integrating, replication-deficient recombinant strain of herpes simplex virus (HSV)-1 engineered to express the COL7A1 transgene encoding COL7 which strengthens and stabilizes the skin. Direct dermal delivery of this vector has the capability of enhancing COL7 expression in target cells including fibroblasts and keratinocytes, thereby strengthening the skin and reducing blistering. It can infect both dividing and non-dividing cells without integrating into the DNA, making it safer relative to integrating vectors. It also provides high transduction efficiency in skin cells in both fibroblasts and keratinocytes.

KB103 is a replication defective HSV-1 modified as follows: 1) complete deletions of the viral ICP4 and ICP22, and (2) insertion of a human cytomegalovirus (HCMV) immediate early promoter that drives human collagen VII expression cassette within both copies of the deleted ICP4 loci. HSV genes are expressed in a sequential, interdependent lytic cycle cascade and the removal of these essential immediate early genes renders the virus replication defective. The KB103 vector is represented schematically in **Figure 2**.

**Figure 2 - KB103 Vector Map**




To summarize the construction strategy, the collagen VII open reading frame (ORF), flanked by the HCMV promoter and a bovine growth hormone polyadenylation sequence, was cloned into a targeting plasmid that contains ICP4 flanking sequences to facilitate recombination with the ICP4 loci within a replication-deficient HSV virus deleted for both copies of ICP4. Both copies of the ICP4 gene within the HSV virus have been replaced by a fluorescent reporter (eGFP). Transfection of the collagen VII targeting plasmid into complementing Vero cells followed by infection with the replication-deficient HSV virus allows for recombination at the ICP4 locus and replacement of eGFP with collagen VII. Positive isolates were selected based on loss of GFP expression and confirmed by quantitative PCR (not shown) and Western blot analysis.

Following selection of positive isolates, a small-scale virus stock was prepared and purified in-house using nine T-175 tissue culture flasks and 1 mL purification columns following established SOPs for HSV production. The final purified product showed good yield (> $1x10^{10}$pfu) and titer ($3.4x10^{9}$pfu/mL) based on an infectious titer plaque assay, confirmed positive for collagen VII expression by Western Blot analysis, and negative in a Replication-Competent Virus (RCV) screen. Purified KB103 was evaluated for expression and functionality in 2-D and 3-D cell-based assays using normal and RDEB patient-derived fibroblasts (HDF) and keratinocytes (HK).

## 1.5 KB103-001, Results from Subjects 01 and 02

KB103 (HSV-COL7) was evaluated in two adult subjects taking part in this protocol. The therapy was well-tolerated and there were no serious or KB103-related adverse events. Wound images demonstrate wound closure post-administration and immunofluorescence and immune electron microscopy data demonstrate molecular and structural correction.

The primary objectives of Version 1.0 of the study were to evaluate safety through the incidence of adverse events (AEs) associated with KB103 post-administration, to evaluate the expression of human collagen VII as determined by immunofluorescence (IF), and to evaluate the presence of anchoring fibrils as determined by immunoelectron microscopy (IEM) post-administration. Secondary objectives included an assessment of change in surface area of a treated wound area through imaging, and safety through an evaluation of laboratory values and physical exam.

Eligible subjects were at least 18 years old, had the recessive form of DEB, and were NC1+. Each subject was on-study for approximately three months. Prior to administration, two wounds per subject < $10cm^2$ in surface area were selected to be randomized to receive either KB103 or placebo. KB103 was administered at least 4 times between Day 0 and Day 30, both topically and intradermally.

### 1.5.1 Safety

Prior to the study, real-time qPCR assays for the detection of viral vector were validated at Charles River Laboratories for the purpose of analyzing viral shedding study samples. Blood and urine were collected during the study per protocol. All of the samples were either negative or below the limit of detection. No treatment-related adverse events were observed or reported. No patient showed systemic autoimmune symptoms or increased blistering around the sites of administration.There were no abnormal laboratory findings.

### 1.5.2 Efficacy

Analysis of biopsies by immunofluorescence from KB103-treated intact skin and wounds revealed clearly detectable and correctly localized (at the BMZ) COL7 expression. Analysis of biopsies by immunoelectron microscopy showed initiation of anchoring fibril (AF) formation along the BMZ with closely localized COL7 staining at Weeks 2 and 4. By Day 80 mature NC2-positive AFs were observed demonstrating the presence of functional full-length COL7. The biopsy analyses correlated to an observed efficacy signal of wound closure. Relative to baseline, wound imaging for both subjects revealed complete wound closure for KB103-treated wounds by Week 4 and sustained closure through the End of Study visit and beyond (about 5 months of closure for Subject 01 and 4 months for Subject 02 as of the date of this protocol).

### 1.5.3 Summary

In summary, the clinical data obtained from the first two subjects showed that KB103 has a favorable benefit-to-risk profile, having demonstrated wound healing associated with molecular and structural correction, and no drug-related adverse events.

## 1.6 Rationale for Protocol Amendments

Four subjects were enrolled onto version 2 of the Phase 2 portion of the protocol. Three subjects (1 adult and 2 children) were administered 3e8 per wound daily for 5 days. One adult was administered 6e8 daily for 5 days. There were no signs of immunogenicity, no KB103-related adverse events and the data indicate that 3e8 per wound per administration was an effective dose for wounds 20 $cm^2$ or less.

Post-dose imaging from these patients clearly indicated that wound morphology and size is a major factor in wound healing as a result of KB103 administration. Wounds that were chronic but recurring based on natural history tended to heal and close completely within 7 to 10 days of KB103 administration. Chronic wounds that were open for a few years showed signs of healing following an initial five consecutive applications but the wound healing process appears to stagnate. These wounds would likely benefit from additional administrations to obtain full closure. Caregivers of the patients currently on trial have requested additional administrations to wounds that have clearly benefited but have not achieved complete wound closure.

Therefore, version 3.1 of the protocol incorporated dosing every 2 to 3 days for two weeks at 2e8 PFU with the option of at-home KB103 administrations, at the discretion of the Investigator.

Five patients were enrolled onto version 3.1 of the protocol. KB103 continues to be well tolerated and wound healing is observed in KB103 administered wounds. Wound healing results of the KB103 treated wounds evaluated to-date continues to show improvement. There is also empirical evidence that repeat administration on the chronic wounds that were retreated in patients that rolled over from the previous portion of the study showed improved healing with complete closure of the wound observed. Therefore, version 4.0 incorporates a 2-cycle approach to KB103 administration with greater flexibility given regarding the number of administrations within each cycle to understand the duration of treatment prior to moving into the Phase 3 Clinical trial.

# 2 Objectives

## 2.1 Primary

1) To assess wound closure through post-administration imaging:
    a. Change in surface area of a KB103-administered wound relative to the same wound at baseline and the placebo administered wound
    b. Time to wound closure of a KB103-administered wound relative to a placebo-administered wound
    c. Duration of wound closure of a KB103-administered wound relative to a placebo-administered wound

## 2.2 Secondary

1) To assess change from baseline in the Investigator's Global Assessment score
2) To assess change from baseline in PRO scales of severity and pain

## 2.3 Other

1) To evaluate the expression of human collagen VII as determined by immunofluorescence (IF).
2) To evaluate the presence of anchoring fibrils as determined by immunoelectron microscopy (IEM) post-administration.

# 3 Selection of Patients

Investigators are expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g. gender, age, race) and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

## 3.1 Inclusion Criteria

To be eligible for inclusion, each subject must fulfill each of the following criteria:

1. Clinical diagnosis of the recessive form of dystrophic epidermolysis bullosa.
2. Age: 3 subjects age 2 and older
3. Willing and able to give consent/assent.
4. Confirmation of RDEB diagnosis by genetic testing, IF and EM.
5. Confirmed RDEB COL7A1 mutations in subject.
6. Two areas of skin up to 50 $cm^2$, with at least 1 wound in each area.
7. Subjects who, in the opinion of the Investigator, are able to understand the study, co-operate with the study procedures and are willing to return to the clinic for all the required follow-up visits.

## 3.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria are met:

1. Medical instability limiting ability to travel to the investigative center.
2. The presence of medical illness expected to complicate participation and/or compromise the safety of this technique, such as active infection with HIV, hepatitis B or hepatitis C, as determined by hepatitis B surface antigen screening, detection of hepatitis C antibodies, or positive result of hepatitis C PCR analysis.
3. Active infection in the area that will undergo administration
4. Evidence of systemic infection.
5. Known allergy to any of the constituents of the product.
6. Current evidence or a history of squamous cell carcinoma in the area that will undergo treatment.
7. Active drug or alcohol addiction.
8. Hypersensitivity to local anesthesia (lidocaine/prilocaine cream).
9. Receipt of chemical or biological study product for the specific treatment of RDEB in the past three months, except for KB103.

10. Specific wounds that have previously been administered investigational gene or cell therapy. Wounds previously administered KB103 are not excluded.
11. Positive pregnancy test or breast-feeding.
12. Clinically significant abnormalities as determined by the investigator.

# 4 Study Design

## 4.1 Study Overview

This study is an intrasubject comparison of KB103-administered and placebo-administered wounds. Up to three 50 $cm^2$ areas will be selected for entry: one or two will be selected to receive topical KB103, and one to receive topical placebo.

The primary objective of this study is to evaluate clinical efficacy through digital imaging of wounds. Secondary objectives include an evaluation of change in an Investigator's global assessment and change in patient reported outcomes.

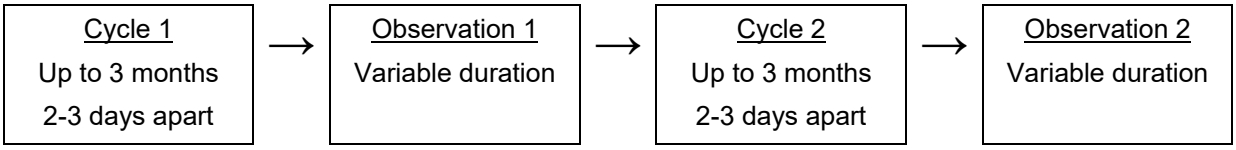
Patients will be administered Investigation Product (IP) in two cycles. Cycle 1 starts on Day 1. Up to three 50 $cm^2$ areas are administered IP (one or two KB103 and one placebo) every 2 to 3 days (to correspond with bandage changes) until wound closure, or up to 3 months. IP is administered to the entire areas, on the wound(s) and on intact skin.

Following this initial dosing period, patients will enter into an observation period in which wounds are monitored at home using a phone imaging app. Upon re-opening and/or expansion of a wound in the KB103 treatment area, patients will be asked to return to clinic or will be treated at home to begin the 2nd cycle of dosing.

The 2nd cycle mimics the first. The same 50 $cm^2$ areas are administered IP (one or two KB103 and one placebo) every 2 to 3 days until wound closure or up to 3 months. IP is administered to the entire areas, on the wound(s) and on intact skin.

After the 2nd cycle of IP administration, patients enter a second observation period. Patients image their wounds at home using a phone app, and return to the clinic at monthly intervals.

Time to wound closure and duration of wound closure will be evaluated after both the 1st and 2nd cycles. Safety will be monitored throughout the study.




Three additional new patients age 2 and older will be enrolled under this version. Patients from this protocol will be allowed to roll over into Phase 3 study of KB103.

## 4.2 Sites and Trial Duration

One (1) investigative site is planned for this study.

The trial duration is variable depending on the duration of response following the first and second administration cycles. It is estimated that trial participants will be on study for 6 months to a year. Additional time for recruitment and screening is anticipated to take 1 month. Safety data is to be

collected by clinic visit or telephone contact approximately every 1 year for up to 5 years after the subject completes the final on-site or at-home visit as part of this protocol.

## 4.3 Concomitant Therapy and Skin Care

Stanford is a major epidermolysis bullosa center and has an established multidisciplinary epidermolysis bullosa team. Subjects will have full access to the care provided by this team throughout participation in this study.

The Investigator is encouraged to restrict topical administration of any EB therapy to a wound that receives KB103 or placebo for a minimum of 72 hours following administration. Any therapy administered to the target wound should also be applied to the control wound. Throughout the study, any concomitant medications or treatments deemed necessary to provide adequate supportive care may be prescribed. In particular, medication should be considered during and after any biopsies to treat pain and/or anxiety (i.e. lidocaine, lorazepam, etc.). Routine skin care for DEB patients continues throughout the study. Though not anticipated due to the non-replicating nature of KB103, active herpes should be treated with an antiviral at the discretion of the Investigator.

Conscious sedation to anesthetize pain associated with biopsies is acceptable at the discretion of the Investigator.

## 4.4 Subject Enrollment and Withdrawal

Written protocol and informed consent approval are required from the IRB prior to enrollment. Assent form approval is required from the IRB prior to enrolling subjects below the age of consent. All subjects or their respective legal guardians must personally sign and date the relevant consent and/or assent form before enrollment.

### 4.4.1 Subject Identification and Number Assignment

Subjects who sign the informed consent form are assigned a 3-digit subject identification number. Subject identification numbers begin with 001. This number identifies the subject throughout the study and must be used on all study documentation related to that subject.

### 4.4.2 Withdrawal of Subjects

A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety or for other reasons. Criteria for withdrawal include:

1. Consent/assent is withdrawn.
2. The subject refuses treatment and/or procedures/observations.
3. Occurrence of unmanageable adverse events or pregnancy.
4. For other reasons (e.g., significant protocol violation, non-compliance).

The Sponsor may be contacted if clarification is required. The primary reason for withdrawal must be recorded on the CRF. Comments or complaints made by the subject must also be recorded on the CRF. Withdrawal should be discussed with the medical monitor prior to withdrawal when possible. Subjects who wish to discontinue treatment or study procedures after receipt of KB103 are asked to continue in the Long-Term Follow-Up Period. Subjects who withdraw prior to the first KB103 administration are considered a screen failure and are replaced. The Sponsor reserves the right to terminate the study.

## 4.5 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) comprised of an independent DEB specialist, enrolling PIs, and Sponsor representatives and/or designee(s) hold periodic teleconferences to evaluate subject safety and treatment status. An SMC charter dictates procedure, responsibilities, membership, data requirements and meeting timing. A written summary documenting the results and recommendations of each review is provided to the investigator(s) and maintained on file with the Sponsor. Additional sub-investigators and scientific personnel may participate in reviews, as appropriate. The SMC provides recommendations about stopping or continuing the trial and has the authority to recommend dose or regimen modifications for safety concerns. The SMC may also make recommendations regarding the selection or retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control.

## 4.6 Subject Companions

Subjects are permitted to bring a companion to study visits. Costs associated with travel to the Investigative Site, including those of a companion, are reimbursed by the sponsor.

# 5 Study Procedures

## 5.1 Stopping Criteria

**Table 1** provides the stopping criteria. Occurrence of any of these observations triggers a temporary suspension of KB103 administration pending a safety investigation.

**Table 1 - KB103-001 Stopping Criteria**

| Event | Severity | Number of Events |
|---|---|---|
| A treatment emergent serious adverse event that is definitely or suspected to be related to KB103. | Any | 1 |
| An AE associated with HSV infection in combination with a positive RCV qPCR assay result. | Any | 1 |
| An immune response determined by the Investigator to be possibly, probably or definitely related to investigational product or a procedure. | Severe | 1 |
| Any treatment emergent systemic infection designated as possibly, probably or definitely related to investigational product or a procedure. | Moderate or higher | 2 or more |
| A treatment emergent uncontrolled bacterial, viral, or fungal infection in an area administered investigational product where product sterility testing results reported post injection were positive for contamination. | Mild or higher | 1 |

For subject safety, subjects should be followed in accordance with the study visits and procedures as outlined in the protocol. An occurrence of any of these safety observations is shared with the SMC and the appropriate authorities. The SMC reviews the results of the safety investigation and may request any additional data needed to assess the safety of restarting product administration. The SMC determines if the suspension can be lifted or if the trial terminates based on their review of the safety investigation.

## 5.2 Study Schedule

Study visit procedures are performed only after a signed informed consent / assent is obtained. During the study, every effort should be made to adhere to the visit schedule provided in the Schedule of Events (**Table 2**). Visit windows for each visit are described below.

Patients visit the clinic at baseline and as needed after baseline for the Cycle 1 and Cycle 2 dose administrations. After the first dose administration of each cycle, patients can either return to the clinic for additional administrations or the administrations can occur at home by a trained professional. During the on-site dose administration periods, patients will stay in lodging near the clinical site. Following the 2nd cycle, patients will return home and visit the clinic at least monthly for 3 months. Interim unscheduled visits may occur in between the monthly visits depending on the patient's ability and willingness to travel.

**Table 2 - Schedule of Events**

| | | Cycle #1 | | OP[1] #1 | Cycle #2 | | OP #2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Dosing every 2-3 days | | Home images | Dosing every 2-3 days | | At-home monitoring and monthly on-site visits | | | |
| | | ≤ 3 months | | Variable | ≤ 3 months | | 3 months after C2[2] | | | |
| **Procedures** | **Screen/ BL** | **Dose days** | **Last dose** | **OP 1** | **Dose days** | **Last dose** | **C2 +1mo** | **C2 +2mo** | **C2 +3mo** | **LTFU** |
| Urine Pregnancy Test | X | | | | | | | | | |
| HIV, Hep B, Hep C Testing | X | | | | | | | | | |
| Hematology & Chemistry[3] | X | | X | | | X | X | X | X | |
| COL7 Antibody Assay | X | | X | | | X | X | X | X | |
| HSV Antibody Assay | X | | X | | | X | X | X | X | |
| Wound Area Assignment | X | | | | | | | | | |
| Pre-dose Tattoos | X | | | | | | | | | |
| Concomitant Medications | X | X | X | | X | X | X | X | X | X |
| Adverse Events | X | X | X | | X | X | X | X | X | X |
| Viral shedding (skin swab) | X | X | X | | X | X | X | X | X | |
| Viral shedding (blood and urine) | X | | X | | | X | X | X | X | |
| Physical Exam | X | | | | | | | | X | |
| PRO Assessment | X | X | X | | X | X | X | X | X | |
| Global Wound Assessment | X | X | X | | X | X | X | X | X | |
| Vital Signs | X | X | X | | X | X | X | X | X | |
| At-home wound imaging[4] | | X | X | X | X | X | X | X | X | |
| On-site wound imaging | X | X | X | | X | X | X | X | X | |
| Wound stenciling | X | X | X | | X | X | X | X | X | |
| IP Administration | X | X | X | | X | X | X | X | X | |
| Wound biopsy[5] | X | | X | | | X | X | X | X | |

[1] OP = Observation Period
[2] Visit windows for the OP2 visits are +/- 1 week
[3] After screening/baseline, performed only as clinically indicated to minimize blood draws
[4] At-home wound imaging occurs throughout the study during bandage changes
[5] Biopsies are performed at the discretion of the Investigator and Sponsor.

## 5.3 Screening and Baseline

For well-characterized subjects that meet criteria, the procedures for screening and baseline will be conducted during the same visit to the investigative site as the first day of Cycle 1. Subjects that are not well-characterized may be screened well in advance (about 2 months) of the planned baseline to allow time for genetic testing.

### 5.3.1 Informed Consent

The Investigator is responsible for obtaining an ICF signed by the subject or legally authorized representative from every subject prior to his/her participation in the study, in accordance with the Code of Federal Regulations (CFR), Title 21, Part 50.20. For subjects between the ages of 7 and 17 (inclusive), the Investigator is responsible for obtaining assent from the subject and consent from both parents or legal guardians. For subjects that are 5 or 6 years old, the Investigator is responsible for obtaining parental/legal guardian consent (no assent is required).

The ICF/Assent that is used must be the current version and must be approved by both the reviewing IRB and by the Sponsor. Informed consent/assent is obtained from the subject after a full explanation of the purpose of the study, risks and discomforts involved, potential benefits, etc. have been provided by the Investigator both verbally and in writing. The original signed copy of the informed consent/assent must be maintained in the institution's records, and is subject to inspection by a Sponsor representative.

### 5.3.2 Phone Screening

A phone screen is utilized to minimize subject travel. An Investigator or designee will prescreen medical histories of RDEB patients for potential inclusion into this study. Potential subjects or parent or guardian are contacted by phone. An Investigator or designee provides a study overview, key inclusion/exclusion criteria, information about the recruitment process, and addresses questions. If the potential subject remains interested in participating in the study, a copy of the informed consent is sent to the potential subject to review.

Medical information reviewed may include the following and is dependent upon the Investigative Site's receipt of prior authorizations to access the data:

- NC1 and LH24 antibody results
- Genetic testing results, including COL7A1 genotype of the subject
- COL7 antibody history
- IF and EM/IEM results
- Medical history

The Investigator may request additional personal health information disclosure authorizations from the potential subject to assist with Screening.

### 5.3.3 Screening and Baseline Procedures

The following procedures are performed on or the day before the first planned administration day.

- Review and signature of informed consent form
- The following evaluations are required only if RDEB diagnosis documentation is not available to support entry into this protocol. If these are needed, the screening visit may occur several weeks prior to the baseline visit:
    - Collection of a biopsy for EM/IEM
    - Collection of a biopsy for IF
    - Collection of blood for genetic testing
- Collection of demographic data (e.g. sex, age, race, and ethnicity)
- Inclusion/exclusion criteria
- Medical history and medication history
- Collection of blood (approximately 15 mL) for clinical laboratory tests:
    - Serum chemistry
    - Hematology
    - HIV, Hep B, Hep C
    - Baseline viral shedding
    - Baseline HSV and COLVII autoantibodies
- Collection of urine
    - For a pregnancy test, if applicable
    - For baseline viral shedding
- Physical and skin exam
- Vital signs: blood pressure, heart rate, respiratory rate, temperature
- Collection of a baseline skin swab for viral shedding analysis
- Bacterial culturing of target wounds (if clinical evaluation is indicative of infection)
- Digital imaging of target areas
- Collection of a biopsy from intact skin for IF and IEM analyses. This collection can occur at a later visit at the discretion of the Investigator.
- Patient reported outcomes (PRO) questionnaire
- Investigator's global assessment

## 5.4 Cycle 1

The patient will visit the Investigative site for the first dose of Cycle 1. Additional Cycle 1 doses can occur on-site or at-home at the discretion of the Investigator. Unless the patient requires disease characterization, Day 1 of Cycle 1 is the same day as the Screening/Baseline visit. For Cycle 1, KB103 and placebo are administered topically every 2 to 3 days to correspond with bandage changes, up to 3 months.

### 5.4.1 On-Site Dosing Day Procedures

For visits that occur at the clinic, the following procedures may be performed:

- Adverse events
- Concomitant medications
- Vital signs
- Viral shedding skin swab collection
- Digital imaging of target wound areas
- PRO assessment
- Investigator's global assessment
- Wound stenciling
- Topical administration of KB103 and placebo to the target areas

### 5.4.2 At-home Procedures

After the first administration of each cycle, KB103 may be administered at home by a caretaker every 2 to 3 days until wound closure, a stopping criterion is met, 3 months have elapsed, or until directed to discontinue by the Investigator.

Appendix 1 provides administration instructions. Wound closure is monitored through remote imaging.

### 5.4.3 Last Dosing Day of Cycle 1

The patient will visit the Investigative site on or near the final Cycle 1 administration day, in which the following procedures will be performed:

- Collection of blood (approximately 10 mL) for clinical laboratory tests:
  - Serum chemistry
  - Hematology
  - Viral shedding
  - HSV and COLVII autoantibodies
- Collection of urine for viral shedding
- Optional: biopsy collection from a wound area
- Wound stenciling
- Topical administration of KB103 and placebo to the target areas

## 5.5 Observation Period (OP) 1

Following Cycle 1 wound closure and/or 3 months, the patient returns home. Wound areas are imaged every 2 to 3 days at home with a phone app.

The duration of OP 1 varies. If complete wound closure is obtained during Cycle 1, OP 1 ends when the wound(s) re-open. If complete closure is not obtained during Cycle 1, OP 1 ends when the wound surface area increases relative to size of the wound at the last Cycle 1 administration.

## 5.6 Cycle 2

The patient will visit the Investigative site for the first dose of Cycle 2. Additional Cycle 2 doses can occur on-site or at-home at the discretion of the Investigator. For Cycle 2, KB103 and placebo are administered topically every 2 to 3 days to correspond with bandage changes, up to 3 months.

### 5.6.1 On-site Dosing Day Procedures

For visits that occur at the clinic, the following procedures may be performed:

- Adverse events
- Concomitant medications
- Vital signs
- Viral shedding skin swab collection
- Digital imaging of target wound areas
- PRO assessment
- Investigator's global assessment
- Wound stenciling
- Topical administration of KB103 and placebo to the target areas

### 5.6.2 At-home Procedures

After the first administration of each cycle, KB103 may be administered at home by a caretaker every 2 to 3 days until wound closure, a stopping criterion is met, 3 months have elapsed, or until directed to discontinue by the Investigator.

Appendix 1 provides administration instructions. Wound closure is monitored through remote imaging.

### 5.6.3 Last Dosing Day of Cycle 2

In addition to the procedures above, the following additional procedures should occur on or near the final Cycle 1 administration day:

- Collection of blood (approximately 10 mL) for clinical laboratory tests:
  - Serum chemistry
  - Hematology
  - Viral shedding
  - HSV and COLVII autoantibodies

- Collection of urine for viral shedding
- Optional: biopsy collection from a wound area
- Wound stenciling
- Topical administration of KB103 and placebo to the target areas

## 5.7 Observation Period (OP) 2

Following Cycle 2 wound closure and/or 3 months, wound areas are imaged remotely every 2 to 3 days at home with a phone app.

OP 2 also consists of monthly visits to the clinic.

### 5.7.1 OP 2 Monthly Visits

At 30-day intervals (+/- 7 days) after the last administration of Cycle 2, the patient returns to the clinic for follow-up procedures:

- Adverse events
- Concomitant medications
- Vital signs
- Digital imaging of wounds
- PRO assessment
- Investigator's global assessment
- Collection of blood (approximately 10 mL) for clinical laboratory tests:
    - Serum chemistry
    - Hematology
    - Viral shedding
    - HSV and COLVII autoantibodies
- Collection of a skin swab for viral shedding analysis
- Collection of urine for viral shedding
- Month 3 only: physical exam
- Optional: Biopsy from a wound administered KB103 or placebo
- Wound stenciling
- If a target wound is open: Topical administration of KB103 and placebo to the target areas.

## 5.8 Unscheduled Visits

Subjects may visit the clinic for unscheduled visits as deemed appropriate by the Investigator. Any or all of the monthly visit procedures may be performed during unscheduled visits.

## 5.9 Long-Term Follow-Up Period

Upon completion of the End of Study / Early Termination Visit, subjects will enter into a Long-Term Follow-Up Period.

At a minimum, subjects will be contacted yearly for at least 5 years. Subjects will be contacted by phone. In addition, the subject's primary care provider will be asked to contact the Investigator regarding any unexpected or serious adverse events. Telephone contact reports will document the discussions and the information obtained will be captured on case report forms. The following activities will occur at the one-year follow-up intervals:

- Recording of exposures to mutagenic agents and other medicinal products
- Recording of any new serious adverse events, hospitalizations, or illnesses (including new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, new incidence of a hematologic disorder).
- Discussion with primary care provider regarding medication and medical history.
- If a skin cancer occurs in the region of the KB103 administration, attempts will be made to collect samples of the skin cancer to evaluate cells for the presence of viral vector.

# 6 Investigational Product

Subjects are administered topical KB103 to one or two wound areas, and topical placebo to a second wound area. Wound areas have a surface area of up to 50 $cm^2$.

During Cycles 1 and 2, topical KB103 and placebo are administered every two to three days to coincide with bandage changes. Administrations continue until the wound closes, a stopping criterion occurs or at the discretion of the Investigator, not to exceed 3 months per cycle. After the first administration of each cycle, administrations can be administered at home by a trained caretaker at the discretion of the Investigator. These are referred to as "At-Home Topical Administrations" below. During visits to the Investigative site, KB103 may be administered topically by the Investigator. KB103 is prepared according to the pharmacy manual prior to administration.

## 6.1 At-Home Topical Administrations

At the discretion of the Investigator, KB103 may be administered at home. The Investigator will use at-home imaging to make remote dosing decisions, for example, if at-home dosing should discontinue due to wound closure.

Trained caretakers may administer KB103 or trained personnel may travel to the subject to administer KB103. Training will be documented and will consist of administration, containment, and disposal procedures. At-home administration and disposal instructions are provided to the subjects and are in Appendix 1.

## 6.2 Dose Level

Each topical KB103 dose is 6e8 PFU per wound area per day.

## 6.3 Wound Area Selection

Up to three wound areas are selected to be part of the study: one or two to receive KB103, and one to receive placebo. Final selection of the wound areas occurs at baseline. The following is considered when selecting target wound areas:

- **Wound areas can consist of one wound, or multiple wounds, and can include intact skin.**
- **The size of the wound area.** Target wound areas have a surface area up to 50 $cm^2$.
- **The location of the wound area.** Appropriate sites are on the anterior and/or lateral trunk and/or upper and/or lower extremities in areas protected from frequent trauma or injury. Excluded areas include the face, and areas close to mucous membranes (genitourinary, oral or anal mucosa).

- **The appearance of the wound.** Wounds should appear clean with adequate granulation tissue, excellent vascularization, and not appear infected.
- **Historical consistency in size of the wound.** A wound with a historically more consistent surface area is chosen over a less consistently sized wound.
- **The similarity of the wounds.** To the extent possible, similarity in location on the body should be considered.
- Wounds that have previously been administered investigational gene or cell therapy (except for previous KB103 administration) are not eligible for KB103 and placebo administration.

The Investigator will first selection two areas; one for KB103 and one for placebo. If another area meets the criteria above, it will be considered for inclusion in the study to receive KB103.

## 6.4 KB103 Administration

At-home topical administration of KB103 and placebo is performed as outlined in Appendix 1.

KB103 will be administered only if a target wound is visibly open. An opening as the result of biopsy will be considered visibly open wound. KB103 is compounded into a gel per the pharmacy manual.

On-site administration is performed as follows:

1. Unpackage the Mepitel One, Mepiform, Vaseline, and Kerlix Gauze dressings and place them nearby. Prepare the wound for KB103 administration by unbandaging the area. Cut a hole in the Mepitel One to the size of the wound to be treated and place the cut Mepitel on the patient's skin around the wound surface.
2. To apply KB103, while wearing gloves, apply the compounded product directly to the patient's skin by depressing the syringe plunger very slowly to cover the surface of the wound with KB103. Ensure that the KB103 is contained to the wound without any spillage.
3. If necessary, open a new syringe, connect the spreader and use it to spread the product on the patient's skin.
    a. Any spillage on hard surfaces should be immediately wiped up with 10% bleach wipes, and any used wipes should be disposed of as a biohazard per standard operating procedure of the clinical site.
4. Let the KB103 sit for 5 minutes prior to placing any covering over the wound. Keep the area clean and do not touch the wound during the 5-minute period.
5. After applying KB103, remove the gloves, discard them in the biohazard container, and put on a new pair of gloves.
6. Cover the wound using the non-adherent side of the Mepiform above the wound and then cut to the full size of Mepitel dressings.

7. Thoroughly wrap the dressing in Vaseline Kerlix Gauze and further dress per standard of care.

## 6.5 Placebo Administration

A wound area is selected to serve as the control at baseline. Topical placebo is administered on the days in which KB103 is administered. If KB103 is not administered to both of the KB103-selected wound areas on any dosing day, then placebo will not be administered. The dressings applied to the wound area that is administered the placebo gel mimic those applied to wound area administered KB103.

## 6.6 Peri- and Post-procedural Safety Monitoring

Throughout the study, subjects will have full access to the care provided by Stanford's EB team. During visits to the clinic, subjects will be within 3 miles of the site. Throughout the study, subjects will have direct access to the PI via the PI's cell phone.

## 6.7 Post-Dose Procedures

Following dosing, all empty or partially used vials will be destroyed per Stanford standard operating procedures. During the period in which KB103 and placebo is administered to the skin, patients should avoid touching, scratching, or tampering with the administration sites or their dressings. Following removal of KB103 and placebo, patients should minimize contact with the area. Bandages removed at home should be disposed of as outlined in Appendix 1.

# 7 Efficacy Evaluations

## 7.1 Wound Measurement

Prior to the first administration of IP, small tattoos are placed on non-blistered skin near the target wound for the purpose of locating the wound areas at subsequent visits.

### 7.1.1 Imaging

Target wounds are measured at each visit to the clinic using a phone camera app. Investigators use the camera's software to define wound surface area and other measurements.

Target wounds are also monitored at home using the phone camera app. Subjects are instructed to image the target wounds during bandage changes (approximately twice per week).

### 7.1.2 Stenciling

Stencils are used to trace wound areas at each visit.

1. Place the stencil directly over the wound area
2. Trace all wounds within the 50 $cm^2$ area
3. After the tracing, place the stencil dirty-side down on a flat, disposal surface
4. Use a clean, pre-labeled stencil to re-trace the wounds
5. Dispose of the dirty stencil
6. Make a photocopy of the clean stencil and place the photocopy in the study file
7. Place the clean stencil inside of an envelope in the study file

## 7.2 Biopsy Evaluation

There are 2 evaluations that require a tissue sample on this study: COL7 analysis by IF and AF analysis by IEM.

Throughout the study, the collection of biopsies is optional, and performed at the discretion of the Investigator and Sponsor. If a biopsy is not collected it will not be considered a protocol deviation. The biopsy schedule is outlined in **Table 2 - Schedule of Events**.

IF biopsies are processed at Stanford per Stanford standard operating procedures.

IEM biopsies are to be collected on Monday or Tuesday and shipped to Shriners Hospital to the address below for overnight or same-day delivery. Collection on Thursday or Friday should be avoided.

Douglas R. Keene
Assistant Investigator
Micro-Imaging Center

Shriners Hospital for Children
3101 SW Sam Jackson Park Road
Portland, Oregon 97239

## 7.3 Investigator's Global Assessment Score

Areas administered topical KB103 and placebo will be clinically evaluated at baseline and at Days 15, 30, 45, 60, 90, and unscheduled visits with an IGA score of: 1) complete closure (i.e., 100% healed), 2) <100% to 75% healed, 3) 74% to 50% healed, 4) 49% to 0% healed, 5) unable to determine, or 6) not assessed. The IGA score is used to provide a snapshot of overall disease severity in dermatologic clinical studies, (Langley, et al., 2015) including EB (Tabolli, et al., 2009). Results to date in a Phase 1/2a keratinocyte graft study suggest that wound measurements from imaging and IGA score are supportive and well correlated (Dutt-Singkh, et al., 2018).

## 7.4 Patient-Reported Outcome Measures

A PRO instrument will be used to evaluate secondary endpoints of change in pain and severity at individual wound areas treated with KB103 compared to intra-subject placebo wound areas. At each time point, subjects will be instructed to rate pain symptoms within the last 24 hours for each wound area. Subject global impression of change will be assessed at baseline, and at Days 15, 30, 45, 60 (for adults only), and 90 and unscheduled visits. All study personnel will be trained to on how to administer PROs.

The PRO instrument will be paper-based and collected in person by the treating EB or Principal Investigator. If the EB physician or the Principal Investigator administer the PROs, they will not be able to perform the IGA.

## 7.5 Voice Memo Qualitative Data

Assistive technology is of utility in the RDEB patient population due to the debilitating nature of the disease. During this study, voice memos will be used to capture qualitative data. Throughout the study subjects and caretakers will be encouraged to record voice memos while at home in between the site visits.

Patients and caretakers are encouraged to record:

- Wound observations, positive and negative
- Questions that they want to ask their doctor at their next visit
- Observations about at-home procedures, including imaging and at-home KB103 administration (if applicable)

Adverse events should be reported immediately by phone as stated in the Adverse Event section below.

Recordings will be downloaded and transcribed for inclusion in the source documentation.

# 8 Safety Assessments

Timing of safety assessments must be performed per the Schedule of Events. Safety assessments include evaluation of medical and medication history, physical / skin examination, vital signs, AEs, and laboratory evaluations. AEs are captured between visits through verbal communication with the site staff. Post-administration changes in these assessments that are deemed to be clinically significant by an Investigator or Sub-Investigator are assessed as AEs.

## 8.1 Viral Shedding

Viral shedding will be analyzed through the collection of blood, urine and skin swabs at a wound areas administered KB103. Swabs will be collected per the schedule of events.

## 8.2 Medical and Medication History

The Investigator or delegated staff performs a complete medical history at Screening, including a medication history. The Investigator or staff must record all clinically or medically relevant information. Medical and medication history are reviewed and updated at baseline. The medical history includes respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric and other diseases.

## 8.3 Physical / Skin Examination

A qualified individual performs a full physical examination. Body systems evaluated include:

- General appearance
- HEENT (Head, Ears, Eyes, Nose, Throat)
- Respiratory
- Abdomen
- Musculoskeletal
- Skin
- Spine/Neck/Thyroid
- Cardiovascular
- Nervous System

Abnormalities or changes in severity noted during the exam should be reported in the source document and in the eCRF. If a new clinically relevant finding occurs (not noted prior to KB103 administration), an adverse event form must be completed. In addition, resolution of any abnormal findings during the study are noted in the source document and appropriate CRF if clinically significant. If at any point in the study a skin cancer occurs in the region of the KB103 administration, attempts are made to collect samples of the skin cancer to evaluate cells for the presence of viral vector.

## 8.4 Vital Signs

Vital sign measurements include systolic and diastolic blood pressure, pulse, and respiratory rate as well as temperature. Blood pressure, pulse, and respiratory rate are taken after subjects are

in a rested state. Blood pressure determined by cuff (manual or automated) is acceptable although the same method should be used throughout the study. Temperature, oral or tympanic, is acceptable although the same method should be used throughout the study.

## 8.5 Laboratory Evaluations

### 8.5.1 Serum Chemistry and Hematology

The amount of blood collected should be minimized. Reference ranges are used to assess the laboratory data for clinical significance. Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated as feasible until confirmed, explained or resolved. Changes from baseline are recorded as an AE if deemed clinically relevant by the Investigator or qualified designee. The following evaluations are conducted:

Serum Chemistry / Metabolic Panel

- Albumin
- Alkaline Phosphatase Total
- Anion Gap
- ALT (SGPT)
- AST (SGOT)
- Urea Nitrogen
- Calcium
- Chloride
- Bilirubin, direct & indirect
- CO2
- Creatinine
- Glucose
- Globulin
- Potassium
- Sodium
- Total Bilirubin
- Total Protein

Hematology / Complete Blood Count with Differential

- WBC
- Hemoglobin
- Hematocrit
- Platelet Count
- MCV RDW
- RBC MCH
- MCHC
- Neutrophils, % and abs
- Lymphocytes, % and abs
- Monocytes, % and abs
- Eosinophils, % and abs
- Basophils, % and abs

### 8.5.2 Urine Pregnancy Test

A urine pregnancy test is performed at baseline for women of childbearing potential.

### 8.5.3 HSV Antibody Assay

Collect serum at baseline and Day 30 for the purpose of conducting an HSV antibody assay.

### 8.5.4 Collagen VII Antibody Assay

Collect serum at baseline and Day 30 for the purpose of conducting a collagen VII antibody assay. Using the subject's serum, COL7 antibodies are assayed by linear BMZ staining for IgM, IgG, IgA or serum IgG antibodies binding to the epithelium of monkey esophagus with a basement membrane or superficial dermal pattern by indirect immunofluorescence (IIF) microscopy. A non-CLIA western blot assay is also used to assay for COL7 antibodies as a confirmatory assay.

# 9 Adverse Events

Throughout the course of the study (from the date of informed consent), all adverse events (AEs) will be monitored and reported on the AE case report form. If an adverse event occurs, the first concern will be the safety of the study participants. All AEs occurring after administration will be followed throughout the study. All AEs related to study treatments or procedures will be followed until resolved or stabilized or until follow-up is no longer possible.

In general, even when not participating in a clinical trial, the study subjects and their caretakers communicate with their EB doctor on a regular basis via phone. Study subjects and their caretakers will be instructed to report via phone any adverse events that occur during the study while off-site. The events will then be transcribed to the AE CRF.

## 9.1 Definitions

### 9.1.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (investigational) product.

Subjects should be asked a non-leading question in order to avoid bias in eliciting AEs; such as “How are you feeling?” It is important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made then each symptom should be listed individually.

Each AE requires a complete description including date of onset and corrective actions taken. The intensity of the AE and its relationship to the investigational product, as well as its outcome, must be recorded in the CRF.

Symptoms of the disease under study/lack of efficacy should not be considered as AEs, as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.

A change in the value of a safety laboratory evaluation can represent an AE if the change is clinically relevant (as determined by the Investigator) or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, should be taken into consideration. The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter represents an AE. For

pathological laboratory values that were not present at baseline, follow-up laboratory evaluations should be performed until the values return to within reference range or until a plausible explanation is found.

AEs should be recorded, starting from subject enrollment (date of signature on informed consent) per the Schedule of Events, until the end of the Long-Term Follow-Up Period, and are to be recorded on the appropriate AE pages in the CRF and in source documents. Where possible, all AEs should be followed to resolution, or an outcome is reached. Medical tests and examinations are performed, as appropriate, to document resolution of event(s).

### 9.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Is fatal.
- Is life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Is a persistent or significant disability/incapacity, or
- Is a congenital abnormality/birth defect.

A hospitalization meeting the regulatory requirement for the “serious” criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility.

Any event that does not exactly meet this definition yet, in the investigator’s opinion represents a significant hazard can be assigned the “other significant hazard” regulatory reporting serious criteria.

Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

SAEs are collected and reported throughout the study duration beginning with enrollment through the end of the Long-Term Follow-Up period. If early termination of study treatment occurs, SAEs continue to be collected until the event resolves.

### 9.1.3 Immune Response Adverse Events

Observation of a severe immune response determined by the Investigator to be possibly, probably or definitely related to investigational product or a procedure is a stopping criterion.

## 9.2 Severity

Definitions for classification of severity appear below. The Investigator will review these definitions with the Subject. The Investigator will determine the severity classification based on these definitions, his/her clinical experience with DEB patients, and/or the Subject’s description of the event.

[Note: A “severe” AE is not the same as an “SAE” (serious adverse event), which is defined above.]

**Mild:** Symptoms are barely noticeable or do not make the Subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

**Moderate:** Symptoms are of sufficient severity to make the Subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.

**Severe:** Symptoms are of sufficient severity to cause the Subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

## 9.3 Relationship

The Investigator will determine whether the Subject’s symptom or problem is most likely unrelated to the study treatment or is possibly/probably related to the anesthesia employed, the study device, or the injection procedure.

## 9.4 Reporting Procedures

All adverse events occurring after KB103 administration observed by the investigator or reported by the subject (whether or not attributed to investigational product), are reported on the case report form.

Medically significant adverse events considered related to the investigational product by the investigator or the sponsor are followed until resolved or considered stable. The investigator must assign the following attributes: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The investigator may be asked to provide follow-up information.

All deaths occurring on study must be reported to Krystal. These include deaths during the Long-Term Follow-Up period. For all deaths, available autopsy reports and relevant medical reports may be requested.

The investigator should notify the IRB of serious adverse events occurring at the site and other adverse event reports received from the sponsor, in accordance with local procedures.

It is left to the investigator’s clinical judgment whether or not an adverse event is of sufficient severity to require the subject’s removal from study. A subject may also voluntarily withdraw from study due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject is asked to undergo an early termination assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If the subject was permanently withdrawn from the study due to a serious adverse event, this information must be included in either the initial or follow-up Serious Adverse Event Report Form, and in the End of Study Case Report Form.

### 9.4.1 Post-KB103 Administration Adverse Event Monitoring

The Investigator must monitor the subject's treated and paired, non-treated wounds closely for additional blister formation and expansion of the border.

### 9.4.2 SAE Reporting Procedures

All Serious Adverse Events (SAEs) that occur after the time of informed consent must be reported to Krystal and the IRB. All subjects with an SAE must be followed and the outcomes reported. The Investigator should supply the Sponsor and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy reports and terminal medical reports). The Sponsor shall evaluate all SAEs and determine if they meet FDA reporting requirements. In the event of an SAE, the Investigator must:

1. Notify Krystal within 24 hours of the Investigator's awareness of the event.
2. Obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3. Provide Krystal with a complete, written case history, including copies of supporting reports (e.g., progress notes, laboratory reports) and a statement from the Investigator as to whether or not the event was related to the use of the investigational product.
4. Promptly inform the governing IRB of the event, if it is related. For other SAEs, notify the governing IRB as required by the IRB, local regulations, and the governing health authorities.

# 10 Statistical Considerations

Post-screening procedures occur as outlined in the Schedule of Events. The end-of-treatment (or treatment endpoint) is also defined as the last assessment time point for efficacy evaluations in order to handle the issue of missing data that is caused by incomplete data collection or early terminations.

## 10.1 Number of Subjects

A formal sample size calculation was not performed for this study. The sample size is based on what was considered an adequate number of subjects for a pilot study to obtain sufficient information on the safety and effectiveness of KB103.

## 10.2 Data Management

An electronic case report form (eCRF) is used to collect information for safety and proof of mechanism analyses. A clinical database is managed by a sponsor's representative for this study. The database is constructed based on the CRF data entry plus laboratory data information. Data queries are generated and resolved. In addition, range checks of the CRF fields, plausibility and consistency checks across CRF pages will be performed to assess consistency, accuracy and completeness of the data collected and entered into the CRF. Standard SAS datasets are generated and provided for analysis.

## 10.3 Study Populations

The primary population for an analysis of the proof of mechanism is the intent-to-treat (ITT) population. Study populations are defined in the following sections.

### 10.3.1 Safety Population

This population is defined as all subjects who were administered KB103.

### 10.3.2 Intent-to-Treat Population

The intent-to-treat (ITT) population includes subjects who were administered KB103 who have had at least one paired assessment of the target wound area post-administration, i.e., at least one KB103 target wound and one placebo target wound.

### 10.3.3 Per-Protocol Population

The per-protocol (PP) population is defined as all subjects in the ITT population who have had at least one paired assessment of the target wound area post-administration, and completed the protocol as planned.

## 10.4 Demographic and Baseline Characteristics

The descriptive summaries of subjects' demographic and baseline characteristics are presented by treatment group for the safety, ITT, and PP populations. A detailed description of subject disposition is provided.

Subject characteristics include a summary of the following:

- Subject demographics.
- Baseline disease characteristics as determined at screening.
- Pre-existing medical conditions.

Continuous variables are summarized using number of observations, mean and standard deviation, median, and minimum and maximum values. Categorical values are summarized using number of observations and percentages.

## 10.5 Proof of Mechanism Analyses

### 10.5.1 Expression of Collagen VII

Biopsies collected for the purpose of IF are evaluated for expression of collagen VII by a qualified reader.

### 10.5.2 Production of Anchoring Fibrils

Biopsies collected for the purpose of IEM are evaluated for the presence of anchoring fibrils by a qualified reader.

### 10.5.3 Target Wound Area

Target wound surface area is obtained through on-site and at-home imaging of target areas. Change in area from baseline is evaluated for using a paired t-test for each KB103 target wound vs. control wound.

Time to closure and durability of closure will be assessed after each cycle of administrations.

### 10.5.4 Investigator's Global Assessment

Investigator's Global Assessment (IGA) score on the target wound is obtained at baseline and post-baseline visits as outlined in the schedule of events. IGA scores will be evaluated at baseline and for post-baseline visits, using a paired t-test for each KB103 target wound vs. control wound.

### 10.5.5 Patient Reported Outcome

Patient reported outcome (PRO) in terms of pain and severity of the target wound is obtained at baseline and post-baseline visits as outlined in the schedule of events, using Wong-Baker Faces Pain Rating scale. Change in the pain ratings will be evaluated at baseline and at post-baseline visits, using a paired t-test for each KB103 target wound vs. control wound.

## 10.6 Safety Analyses

All continuous parameters are summarized using standard summary statistics as appropriate (n, mean, standard deviation (SD), median, minimum, maximum, 25th percentile, and 75th percentile). Summary statistics for categorical variables include frequency counts and percentages.

Patient demographics and relevant baseline data is analyzed descriptively. Inclusion and exclusion criteria ensure that participants are suitable for the study. Premature termination data is tabulated and summarized.

### 10.6.1 Adverse Events

Adverse events are coded using the MedDRA adverse event dictionary. Safety evaluations are based on occurred adverse events, laboratory values, vital signs and appearance of collagen VII antibodies, and RCV. Severities of toxicities is described using the NCI Common Toxicity Criteria (CTC) grades.

Adverse events are grouped into pre-treatment adverse events and treatment-emergent adverse events and are tabulated by preferred terminology and by body system for each study phase. The number of adverse event entries, as well as the number of patients are reported. Analyses include tabulation of adverse event type, relationship to KB103, seriousness, and severity of adverse events according to CTCAE.

### 10.6.2 Physical Examinations

Physical examinations at screening and subsequent follow-up visits are displayed in tabular format displaying number of subjects examined and number and percentage of subjects with abnormalities by physical examination category.

### 10.6.3 Vital Signs

Vital signs are listed and summarized by mean and SD.

### 10.6.4 Laboratory Tests

Laboratory test values are presented in shift tables and by display of changes to baseline. Evaluations of collagen VII antibodies and RCV will be done descriptively.

## 10.7 Handling of Missing and Incomplete Data

For efficacy evaluation, the treatment endpoint is defined as one assessment time point, which includes the last measurement obtained during the study for a variable. No other imputation of values for missing data is performed. Standard clinical monitoring and data management practices are used to ensure the integrity of data.

# 11 Regulatory Obligations

## 11.1 Informed Consent

Before a subject's participation in the trial, the investigator (or designee) is responsible for obtaining written informed consent from the subject or legally acceptable representative (see note below) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject or legally acceptable representative and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

## 11.2 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material including the information letters must be submitted to the IRB for written approval. A copy of the written approval of the protocol, informed consent form, and advertising material must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent changes to the above-named documents. The investigator should notify the IRB of important deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the sponsor, in accordance with IRB procedures.

The investigator is responsible for obtaining IRB approval/renewal throughout the duration of the study at the frequency specified by the IRB. Copies of the investigator's reports and the IRB's written continuance of approval must be sent to the sponsor.

## 11.3 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to the sponsor for review before study initiation from the sponsor can occur:

- Signed and dated protocol signature page (Investigator's Agreement).
- Copy of approved informed consent form and assent form (for phase II).
- Copy of the IRB approval of the protocol, information letter, consent form, and assent form.
- Up-to-date curricula vitae of principal investigator and all co/subinvestigators.
- The IRB composition and/or written statement that IRB is in compliance with regulations.
- Laboratory normal ranges and documentation of laboratory certification (or equivalent).
- Current subject/investigator indemnity insurance.
- Signed study contract.
- Completed FDA form 1572. Laboratories providing primary and secondary endpoint data and any central laboratories for the study must be listed on the form.
- For studies covered under 21 CFR Part 54.2(e), "Financial Disclosure," completed Financial Disclosure statements for the principal investigator, all sub-investigators, and their spouses (legal partners) and dependent children.

## 11.4 Subject Confidentiality

The investigator must take all reasonable measures to ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the study sponsor and those working with the study sponsor, subjects should be identified by their initials and a subject study number only. Documents that are not for submission to the study sponsor and those working with the study sponsor should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, the Investigator and Institution shall permit authorized representatives of the sponsor and companies that work with the sponsor, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

# 12 Administrative and Legal Obligations

## 12.1 Protocol Amendments and Study Termination

Protocol amendments must be made only with the prior approval of the sponsor. Agreement from the sponsor must be obtained for all protocol amendments and amendments to the informed consent document. The IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The investigator must send a copy of the approval letter from the IRB to the sponsor.

The sponsor reserves the right to terminate the study, according to the study contract. The investigator should notify the IRB in writing of the trial's completion or early termination and send a copy of the notification to the sponsor.

## 12.2 Study Documentation and Storage

### 12.2.1 Delegation Log

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on case report forms are included on the Delegation of Authority Form.

### 12.2.2 Source Documents

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

### 12.2.3 Study File

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, in a complete, accurate, and legible manner, suitable for inspection at any time by representatives from the sponsor, companies that work for and with the sponsor, and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation.
- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation, and all correspondence to and from the IRB and the sponsor.
- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed, moved to another location, or assigned to another party without prior written consent of the sponsor.

## 12.3 Study Monitoring and Data Collection

The sponsor monitor is responsible for inspecting the case report forms at regular intervals to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are timely resolved.

## 12.4 Publication Policy

The information provided in support of or generated as a result of this study is confidential. Any use or reproduction thereof, including but not limited to publications or presentations by the Investigator or his associates, must be submitted to the Sponsor for review and approval prior to publication or presentation in any form. All publications must acknowledge the sponsorship.

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# 14 Appendix 1 – KB103 Administration and Removal Instructions

## At-Home Administration Instructions

1. Open the compounding, dressing, cleaning and handling kits.
2. Put on the gloves provided with the cleaning and handling kit.
3. You will receive two KB103 vials for each wound to be treated. The vials are shipped on dry ice and stored in an ultra-low temperature freezer at the patient's home. Open the ultra-low temperature freezer and remove four KB103 vials. Inspect the vials for signs of leakage. If leakage as occurred, take a picture of the leakage and dispose of the vial in the provided red biohazard bag.
4. Place the KB103 vials on the blue towel provided in the cleaning and handling kit and let them sit for 20 to 30 minutes to allow the KB103 to warm to room temperature. ***Do not let the vials sit for more than 40 minutes prior to use.***
5. The study team will tell you which of the wounds should be given KB103. If you are unsure, contact your study doctor or study coordinator.
6. Unpackage Mepitel One, Mepiform, Vaseline, and Kerlix Gauze dressings that were provided with the dressing kit and place them nearby. Prepare the wound for KB103 administration by unbandaging the area. Cut a hole in Mepitel One to the size of the wound to be treated and place the cut Mepitel on the patient's skin around the wound surface.
7. To compound KB103 with the gel, take one syringe and attached an 18G needle to it. Open a vial of KB103 and draw the product entirely into the syringe (each vial contains 200uL of KB103). Repeat the same procedure to draw the same volume of gel into a second syringe.
8. Activate safety cover of the needles and removes needles from syringes. Discard the needles in the sharp needle's container.
9. Join the two syringes using the guarded Luer lock connector.
10. To mix KB103 and gel (1:1 dilution), place the syringes in a vertical position and keep the syringe containing KB103 on top. Slowly dispense the syringe containing KB103 while drawing on the syringe containing the gel until all KB103 is mixed with the gel. Invert the syringes and repeat this operation twice.

11. Disconnect the syringes, keep the syringe containing the compounded product and apply directly to the patient's skin depressing the syringe plunger very slowly to cover the surface of the wound with KB103. Ensure that the KB103 is contained to the wound without any spillage.

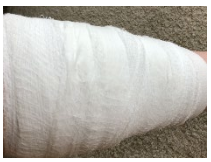
12. If necessary, open a new syringe, connect the spreader and use it to spread the product on the patient's skin.

    a. Any spillage on hard surfaces should be immediately wiped up with the provided 10% bleach wipes, and any used wipes should be placed in the provided biohazard container.

    b. If KB103 spills on an absorbent material such as carpet, while wearing gloves, use a paper towel to absorb any visible KB103. Discard the towel. Spray with Lysol and use a provided 10% bleach wipe to vigorously blot the area.

13. Let the KB103 sit for 5 minutes prior to placing any covering over the wound. Keep the area clean and do not touch the wound during the 5-minute period.

14. After applying KB103, remove the gloves, discard them in the biohazard container, and put on a new pair of gloves.



15. Cover the wound using the non-adherent side of Mepiform on above the wound and then cut to the full size of Mepitel dressings.

16. Thoroughly wrap the dressing in Vaseline Kerlix Gauze and further dress as normally done.

17. All used materials are to be discarded into a biohazard container. Prior to disposal, thoroughly spray the material (bandages, gloves, syringe, etc) with the provided Lysol spray. Store the biohazard container in a safe place out of reach of pets and children until the day of bandage removal and dressing change.

18. Leave KB103 on the wound for at least 24 to 72 hours.

### 14.1.2 Bandage Removal and Disposal

When removing bandages:

- Avoid direct contact between the treatment site and dressings.
- Wear gloves while removing dressings.
- Keep the treatment sites covered with the bandages until the time of removal.
- When it is time to remove the dressings, place the used dressings and cleaning materials in the provided biohazard container. Thoroughly spray the bandages with Lysol and securely close the container.

- Following removal of the dressing, while wearing gloves, clean the area with the subject's standard mild cleanser solution (saline, or mild soap and water).
- Avoid touching or scratching the treatment sites following removal of the bandages.
- Dress the wound as per the usual routine.

### 14.1.3 Dry Ice Disposal

Leave the dry ice in the container in which it was shipped and set it outside, out of reach of pets and children. Do not seal the container. Allow the dry ice to sublimate (convert to carbon dioxide gas), then dispose of the container.

**DO NOT:**

- Place the dry ice in the red biohazard bucket or attempt to ship it for any other reason.
- Attempt to dump dry ice in a sink, tub or toilet. The extreme cold will harm plumbing parts and pipes.
- Dispose of dry ice in garbage receptacles or garbage chutes.
- Leave dry ice in an unventilated room to evaporate. It will release a build-up of carbon dioxide into the air that can cause rapid suffocation.
- Place dry ice on a tile or laminate countertop. Instead, use a solid surface - a wood cutting board or piece of plywood is best. Dry ice is sometimes used in tile removal and may destroy the bonding agent holding the tile or laminated material in place.
- Store dry ice in a glass or air-tight container. Pressure will build up inside and could cause the container to explode.

# 15 Appendix 2 – PRO Scale