Protocol Number R16-017

A Clinical Evaluation of a Manuka-Honey Impregnated Dressing at Removing Necrotic Tissue from Chronic Foot and Ankle Wounds

October 17, 2018

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PRINCIPAL INVESTIGATOR ACKNOWLEDGMENT SIGNATURE

- I agree to conduct the study in accordance with the relevant, current protocol and will make changes in the protocol only after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct and supervise the investigation as described within.
- I agree to inform all subjects that the device is being used for the purposes of an investigational study.
- I will ensure that requirements relating to obtaining informed consent in the guidelines for Good Clinical Practices, and 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- I agree to report to the Sponsor, IRB and/or Ethics Committee, according to the protocol, adverse experiences that occur during the course of the investigation in accordance with guidelines for Good Clinical Practices, and 21 CFR 812.
- I have read and understand the information in the protocol, including the potential risks.
- I agree to maintain adequate and accurate records in accordance with guidelines for Good Clinical Practices and 21 CFR 812.140 and to make those records available for inspection.
- I will ensure that an IRB compliant with the requirements of guidelines for Good Clinical Practices and 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in the guidelines for Good Clinical Practices, and the Code of Federal Regulations.

I have received and reviewed this Investigational Plan. I will conduct the study as described.

_____ _____

Principal Investigator's Signature Date

DOCUMENT HISTORY

VERSION	DATE	DESCRIPTION
Version 1.0	05-Dec-2017	Initial Protocol
Version 2.0	17-Oct-2018	Amendments to study personnel, study equipment, adverse event reporting, and sample size

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1. STUDY TEAM

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2. INTRODUCTION

2.1. BACKGROUND AND RATIONALE

Wound healing is known to be assisted by the removal of necrotic tissue.[1] Healing of these wounds may not occur at an optimal rate due to the presence of such necrotic tissue. Honey has been known to be an important adjunctive therapy in the field of wound care for centuries.[2,3] Honey impregnated wound dressings serve as autolytic debridement agents that promote removal of necrotic tissue from wounds, while maintaining a moist healing environment in subjects with chronic wounds.

The purpose of this study is to evaluate the effectiveness of a honey-impregnated wound dressing (TheraHoney® Foam Flex, Medline Industries, Inc.) at removing necrotic tissue in subjects with chronic foot or ankle wounds. The study will also evaluate the ability to promote granulation and re-epithelialization when using this type of dressing, as well as collect safety and ease of use data on the product.

2.2. INVESTIGATIONAL PRODUCT: THERAHONEY® FOAM FLEX

The investigational product being examined, TheraHoney® Foam Flex, contains 100% Manuka honey and is ideal for difficult to dress wounds. The dressing provides a moist wound environment to help promote autolytic debridement. TheraHoney® Foam Flex is ideal for partial or full thickness wounds with moderate-to-heavy drainage. The honey in the product is carefully filtered, irradiated, and tested in a laboratory.

Suitable secondary dressings are indicated for use when necessary. Contraindications include third-degree burns and lesions with active vasculitis. More information on the product, including labeling, is provided in Appendix A.

2.3 STUDY POPULATION AND DURATION

Participants in this study will be patients with chronic foot or ankle wounds who are under the care of a physician (the Principal Investigator or a Co-Investigator; collectively an “Investigator” or “the Investigators”). Further information on study population can be found in section 4.2. Following initial screening, this study protocol calls for a 4-week period that encompasses initial application of wound dressing, weekly follow-up visits, and a final assessment at approximately 4 weeks. In the event a patient’s wound heals sooner than 4-weeks and he/she no longer needs medical care, all necessary data to complete the study will be collected at the visit where an Investigator deems the patient to be healed, and he/she will not continue through 4-weeks. Therefore, study duration period may vary based on individual wound response and discretion of an Investigator, but will not exceed 4-weeks plus screening time.

2.4 STUDY RISKS AND BENEFITS

This study presents minimal risk to the participant sample, given that this is a currently marketed medical device with FDA cleared 510(k) pre-market submission that will be used in accordance with the product's labeling. Participants may experience some discomfort when applying or removing the dressing, but this should be minimal and not exceed what they would feel through the normal use of the product. Participants may directly benefit from their participation in this study, as the TheraHoney® Foam Flex dressing may provide better debridement and healing of their wound than their previous therapies, though this is not guaranteed and a comparison to other therapies is not part of this study's scope. Participation in this study may allow for scientists and healthcare professionals to better understand the clinical utility of honey impregnated dressings, thereby informing future clinical practice.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

To evaluate the ability of TheraHoney® Foam Flex wound dressing to remove necrotic tissue in patients with chronic foot or ankle wounds.

3.2. SECONDARY OBJECTIVES

To evaluate the efficacy of TheraHoney® Foam Flex in the promotion of granulation and re-epithelialization in chronic wounds.

To evaluate the safety and ease of use of TheraHoney® Foam Flex when applied to chronic wounds.

4. STUDY DESIGN

4.1. DESIGN

A single-center, open-label, observational study involving 20 evaluable subjects with qualified chronic foot or ankle wounds (as judged by an Investigator, in reference to the product labeling and inclusion criteria listed below) on which treatment with Therahoney® Foam Flex will be administered in order to evaluate product efficacy, safety, and ease of use.

4.2. SUBJECT SELECTION

4.2.1. Inclusion Criteria

Subjects MUST MEET ALL of the following criteria prior to enrollment:

- Male or female ≥18 years of age
- Written consent must be obtained from the subject and/or their legally-authorized representative.
- Subject has a qualified chronic foot or ankle wound, sized 1 cm^2 to 25 cm^2, for ≥ 4 weeks in duration.
- Must have necrotic tissue at least 20% of wound area
- The wound type matches one of the indicated wounds listed on the product labeling:
    - Leg ulcers
    - Pressure ulcers
    - Diabetic foot ulcers
    - First and second degree burns
    - Surgical wounds
    - Trauma wounds
- Subject has adequate circulation as demonstrated by biphasic or triphasic Doppler waveform, consistent with adequate blood flow, within 3 months prior to study enrollment. If monophasic on exam, then non-invasive tests must display Ankle Brachial Index over 0.8 and no worse than mild disease on segmental pressures.
- Subject is likely to be compliant with instructions for care, such as following institutional standard of care directions, offloading, and keeping the wound area protected from environmental contaminants
- Type I/II diabetic subjects that meet the following criteria:
    - Random blood glucose is less than 450 mg/dL within 30 days of the screening visit

4.2.2. Exclusion Criteria

Subjects MUST NOT MEET ANY of the following criteria prior to enrollment:

- Subject has a known sensitivity or allergy to honey based products, bee venom, or other ingredients in product
- The subject is breastfeeding, pregnant, or has intentions of becoming pregnant during the course of their study participation.
- Wound duration ≥ 52 weeks

- The subject has a prognosis that indicates unlikely survival past the study period.
- The subject is currently receiving dialysis.
- Gangrene is present in the target wound.
- Patient's wound is infected
- The subject's diagnosis indicates third degree burns.
- The subject has received any treatment prior to study enrollment that may, in the opinion of an Investigator, affect the outcome of the study.
- In the opinion of an Investigator, the subject is otherwise not suitable for study participation, such as the subject is likely to be non-compliant with study requirements.

5. STUDY PROCEDURES

5.1. RECRUITMENT

Subjects will be recruited from the Northern Illinois Foot and Ankle practice of the Principal Investigator (PI) or co-Investigators. All interested subjects will undergo informed consent and screening to ensure they meet the inclusion/exclusion criteria listed in Sections 4.2.1 and 4.2.2 of this protocol.

5.2. SCREENING VISIT (DAY 0)

5.2.1. Informed Consent

Written consent must be obtained from all participating subjects and documented on an informed consent form (ICF) that has received approved by an IRB/Ethics Committee. The ICF must be written in adherence to Good Clinical Practice (GCP) and comply with all elements required by FDA CFR 50.25 and ICH 4.8, state and local regulations, and additional elements relevant to specific study situations, (including a statement that Medline Industries, Inc. and authorities have access to subject records).

5.2.2. Demographics

Subject age, gender, and race will be captured.

5.2.3. Medical History and Concomitant Medication

During initial consideration to determine eligibility, a generalized medical history must be obtained from the subject in order to determine whether any previous or current co-morbidities, chronic wounds (if known) and/or treatments that may, in the opinion of an Investigator, adversely affect subject safety and/or the outcome of study data (reference exclusion criteria listed in section 4.2.2.).

A record of relevant medications (prescription and over the counter) that are administered to the subject throughout the duration of their study participation should be noted, such as antibiotic use and any ongoing adjunct wound therapies. Careful consideration should be made to investigate and document medication use that may be related to Adverse Event occurrences. Additional information regarding Adverse Event reporting may be found in Section 7.

5.2.4. Vascular Ankle Assessment

Doppler Ultrasound (biphasic or triphasic wave form) will be used to assess vascular supply. In the event the potential subject does not have a reading within the past 90 days prior to the screening visit, the assessment will take place at the screening visit using a SONOTRAX Basic ultrasonic pocket Doppler by Edan Industries Inc. If exam result is monophasic, subject can still be enrolled in study if non-invasive tests display an Ankle Brachial Index over 0.8 and no worse than mild disease on segmental pressures.

5.2.5. Diabetic Assessments

Subjects with diabetes (type I or II) will be allowed to participate in the study, provided that their glucose level results are less than 450 mg/dL. In the event the potential subject does not have a blood glucose reading within the past 30 days, a measurement will be conducted at the screening visit using an EVENCARE G3 blood glucose monitoring system.

5.2.6. Wound Screening Evaluation

The type of wound will be diagnosed and receive a diagnostic code based on type of wound at initial presentation (e.g., venous, diabetic, pressure, etc.). A history of the wound will be collected to determine that it has been present for greater than four weeks, but less than 52 weeks. Further, every attempt should be made to document the types of dressings previously used in the treatment of the wound in question, up to six months prior to enrollment. An image of the wound will be taken with the eKare inSight® wound assessment camera, which will calculate wound size and tissue composition of the wound. The Investigator will analyze the wound and the image of the wound to confirm wound size and percent necrotic tissue in order to verify the wound meets the inclusion criteria stated above.

5.2.7. Confirmation of Eligibility

The subject is confirmed as meeting all required inclusion criteria, as listed in section 4.2.1.

The subject is confirmed as not meeting any of the exclusion criteria, as listed in section 4.2.2.

5.3. INITIAL VISIT (DAY 1) AND WEEKLY INTERIM VISITS

Please note that the Initial Visit (Day 1) may be combined with the Screening Visit (Day 0) for pragmatic purposes. In the event this occurs, all Screening Visit activities will precede any Initial Visit activities.

5.3.1. Wound Evaluation

Wound evaluation for data collection purposes will begin at the initial visit and thereafter during each visit at the outpatient centers where this study is going to be conducted. Wound Evaluation will include the following parameters (please also see sample Case Report Form (CRF) in Appendix D which will be used at each visit):

- Wound size (length, width and depth)
- Evaluation of Odor. Investigator assessment of wound odor will be captured via a 4-point categorical scale after each application.
- Percent of Necrotic Tissue. The percent of necrotic tissue will be assessed based on photos taken of the wound with eKare inSight® and visual confirmation from the Investigator to determine the percent covered with the necrotic tissue versus the total area of the wound. This will be entered in question six of the Bates-Jensen Wound Assessment Tool, as described in Appendix C.
- Pain Assessments. Pain will be assessed by the subject after the application (or re-application, for interim visits) of the dressing. Pain will be based on a 10-point Pain Score.
- Site Infections. Any infections at the wound site will be documented. In the event a participant develops an infection his/her participation in the study will discontinue, and the physician will implement appropriate treatment measurements.
- Bates-Jensen Wound Assessment Tool (BWAT). The BWAT will be administered to further characterize the wound. Please see Appendix C for BWAT.

5.3.2. Photographing the Wound

In order to obtain an accurate assessment of the wound, photographs of the wound and surrounding skin must be obtained using the eKare inSight® wound assessment camera. Photographs taken with the eKare device will include a visible label containing the following information subject number and date.

5.3.3. Secondary Dressing Notation

All wounds following treatment will be covered with a suitable secondary dressing where Investigators judge that a wound dressing with debridement or moisture control will be appropriate. The secondary dressings used will be noted during each visit. Medline Industries, Inc. will provide Optifoam® Gentle Super Absorbent silicone dressings for use as secondary dressings.

5.3.4. Debridement

Mechanical debridement should only be performed per normal standard of care. If mechanical debridement occurs at a visit, it will be noted on the CRF.

5.3.5. TheraHoney® Foam Flex Application

The application of TheraHoney® Foam Flex will be performed according to the product labeling during the Initial Visit (Day 1) and subsequent Interim Visits. Dressing changes will take place daily, with the Investigator instructing participants on how to change the dressing at home on days when they do not visit the clinic. The use of secondary dressings will also be done at the discretion of an Investigator. At the discretion of an Investigator, use of TheraHoney® Foam Flex should be discontinued due to adverse events or lack of wound closure response.

5.4. FINAL VISIT

The Final Visit will be scheduled to take place approximately 4 weeks following the Initial Visit. In the event that during a weekly Interim Visit, an Investigator judges the wound to be 100% healed and medical care is no longer necessary, that Interim Visit will be deemed the Final Visit.

5.4.1. Data collection

All activities listed in section 5.3.1 and 5.3.2 will take place in the Final Visit in order to complete data collection. Notations on dressings and debridement will not be documented at this visit, though they may of course occur based on an Investigator's judgment.

5.4.2. Physician Questionnaire

Product ease of use will be evaluated using on the Investigator Questionnaire (Appendix E) at the end of subject's study participation.

TABLE 5.1 TIME AND EVENTS SCHEDULE

REQUIRED ASSESSMENTS	SCREENING VISIT Day 0 (May be combined with first interim visit, Day 1)	INITIAL VISIT Day 1	INTERIM VISITS Approx. Every 7 Days	FINAL VISIT[5] Approx. 28 days after Day 1 visit
Informed Consent	**X**			
Demographics	**X**			
Medical History	**X**			
Concomitant Medication	**X**			
Physical Examination	**X**			
Doppler Assessment	**X**[1,3]			
Blood Glucose Assessment	**X**[1, 2, 4]			
Wound Screening Evaluation	**X**			
Confirmation of Eligibility	**X**	**X**	**X**	
Adverse Event Assessment	**X**	**X**	**X**	**X**
Wound Evaluation		**X**	**X**	**X**
Wound Photograph		**X**	**X**	**X**
TheraHoney® Foam Flex		**X**	**X**	
Secondary Dressing Notation		**X**[1]	**X**[1]	
Mechanical debridement noted		**X**[1]	**X**[1]	
Investigator Questionnaire				**X**

[1] If required
[2] Within 30 days of screening visit or at screening visit
[3] Within 90 days of screening visit or at screening visit
[4] Diabetic subjects only
[5] Final visit may be an interim visit in the event patient heals fully before 4 weeks and no longer requires treatment

6. CLINICAL SUPPLIES AND PRODUCT AVAILABILITY

Medline Industries, Inc. will provide the Investigators with supplies of TheraHoney® Foam Flex dressings and Optifoam® Gentle Super Absorbent silicone dressings (to be used as a secondary dressing if required) for the duration of the study.

Storage conditions for these materials will be maintained in accordance with the guidelines set forth in the product labeling. A record of the study-related materials supplied by the Sponsor, Medline Industries Inc., will be maintained by the Investigators at both clinic locations. Dispensing of these supplies will also be noted.

All unused investigation product will be disposed of properly by the investigational site, in accordance with their standard destruction procedures.

Medline Industries, Inc. will provide the eKare inSight® wound assessment camera, the ultrasonic pocket Doppler (SONOTRAX Basic), and glucose monitor (EVENCARE G3) for the period of the study. This equipment is to be stored securely throughout the study and will be returned to Medline Industries, Inc. upon completion of the study.

7. ADVERSE EVENTS

All Adverse Events (AE) are defined as set forth in the International Conference on Harmonization (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for expedited Reporting E2A (R1) and the Food and Drug Administration Code of Federal Regulations Title 21, part 812, as appropriate.

AEs will be collected throughout the study and documented in the subject's medical record and on the appropriate AE form.

All events will be followed until the event has been resolved or, in the case of permanent impairment, until the event stabilizes.

Information regarding any AEs occurring during the study will be recorded on the appropriate AE form. Such information will include, at a minimum, the date of the event, severity, outcome, and the relation (if any) to the investigational product.

7.1. Adverse Event Reporting

Beginning at enrollment and proceeding throughout the duration of the follow-up period, the PI will closely monitor each subject for the development of adverse events.

An AE is any new untoward medical occurrence (sign, symptom, or laboratory finding) in a clinical investigation subject, who was administered an Investigational Product that does not necessarily have a causal relationship with the Investigational Product.

The severity of all adverse events will be graded on a scale of one through five according to the most recent version of the Common Terminology Criteria for Adverse Events

guideline, where each grade represents a unique clinical description based on this general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting activities of daily living involving self-care.
- **Grade 4:** Life threatening consequences; urgent intervention indicated
- **Grade 5:** Death related to AE

The PI will categorize the relationship of the event to the Investigational Product as follows:

- **Unrelated:** This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)
- **Possible:** This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the Investigational Product administration appears unlikely but cannot be ruled out with certainty.
- **Probable:** This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the Investigational Product.
- **Definite:** This category applies to those adverse events which, after careful consideration, are clearly and incontrovertibly due to the Investigational Product.

Any AE will be documented on the AE Report Form (Appendix F).

7.2. Serious Adverse Event Reporting

Beginning at enrollment and proceeding throughout the duration of the follow-up period, the PI will closely monitor each subject for the development of serious adverse events (SAEs).

An SAE is defined as any adverse experience that results in any of the following outcomes:

- Fatal
- Life-threatening
- Requires or prolongs inpatient hospitalization

- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event or requires medical intervention to prevent one of the above outcomes

Any SAE occurrences (whether or not considered to be related to the Investigation Product) must be reported immediately, within 48 hours of awareness to Medline Industries, Inc. on the SAE Report Form (Appendix G) and be documented on the AE Report Form (Appendix F).

7.3. Unanticipated Adverse Event Reporting

An unanticipated AE is defined as any AE caused by, or associated with, an Investigational Product whose nature or severity is not consistent with the applicable product information.

Reports which add significant information on specificity or severity of a known, already documented serious AE constitute unexpected events.

All serious unanticipated AE that occur throughout the study duration are to be reported to Medline Industries, Inc., as well as to the respective IRB, as soon as possible and no later than 48 hours following acknowledgement.

For questions regarding this process or the event, you may contact your Medline clinical designee or the Medline Clinical Associate Director:

Name: Kara Cassady
Office: 847-643-3809
Fax: 866-758-4660
E-mail: KCassady@medline.com

8. DATA MONITORING AND STATISTICS

All information and data concerning subjects or their participation in this study will be considered confidential. Only authorized personnel will have access to these confidential files. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject. No personal subject identification information should be included in any data submitted for the study.

8.1. DATA COLLECTION

All required data for this study will be collected on standardized CRFs (Appendix D). Qualified site personnel will perform primary data collection, drawn from the initial, interim, and final visits. Study monitors and/or designees will perform ongoing verification of source documentation via periodic on-site visits and remote monitoring. During this time, information will be reviewed for completeness and accuracy. Queries

may be generated for the site to resolve any issues identified. Data from the CRFs will be transferred to a secure electronic database maintained by Medline Industries, Inc. and stored on a secure server.

8.2. SAMPLE SIZE JUSTIFICATION

This is an observational study without a comparison group; therefore a formal power analysis is not feasible. Rather, the study will aim to collect data from 20 patients with evaluable data. The key analysis for the study is providing a quantitative estimate of debridement of necrotic tissue. To this end, a 95% confidence interval centered on the sample mean for necrotic tissue reduction will be created using the critical *t* value for this analysis; this will provide the best point estimate for debridement, as well as a measure of uncertainty, which will takes the sample size into account.

8.3. ANALYSIS OF EFFICACY DATA

8.3.1. Primary Endpoint

Percent reduction in necrotic tissue will serve as the primary endpoint. The Investigator will analyze wound photographs and visually inspect the wound in order to calculate percent necrotic tissue and enter a value of 1-5, corresponding to:

- 1 = No necrotic tissue
- 2 = 0% - 25%
- 3 = 26% - 50%
- 4 = 51% - 75%
- 5 = 76% - 100%

The 95% confidence interval for the mean reduction in necrotic tissue across the study period will be evaluated to determine if the lower bound is positive, which would be an indication of significant reduction in necrotic tissue.

8.3.2. Secondary Endpoints

- Percent patients with 100% wound closure in each group
- Number of new infections in wound site
- Change in wound volume over time, measured similarly to percent necrotic tissue; analyzed by providing the 95% confidence interval for the mean
- Mean odor score between groups; analyzed by providing the 95% confidence interval for the mean
- Mean pain score between groups; analyzed by providing the 95% confidence interval for the mean
- Mean BWAT score between groups; analyzed by providing the 95% confidence interval for the mea

8.3.3. Evaluable Dataset

An evaluable dataset will be used to conduct the efficacy assessments. This dataset will be defined as subjects who have at least a valid measurement for necrotic tissue from the Day 1 visit and their Final Visit, given that this will make up the measurement of the primary endpoint.

8.4 ANALYSIS OF SAFETY DATA

Subject withdrawal and the incidence and nature of AEs will be summarized in safety data assessments. All treated subjects, defined as the safety population, will be the basis for all safety analyses.

9. REFERENCES

1. Schultz GS, Sibbald RG, Falanga V, et al. Wound Bed Preparation: a systemic approach to wound management. Wound Rep Regen 2003; 11 (Suppl 1): S1-28.
2. Keast-Butler J. Honey for necrotic malignant breast ulcers. Lancet 1980; 2(8198): 809.
3. Subrahmanyam M. Topical application of honey in treatment of burns. Br J Surg 1991; 78(4): 497-8.
4. Auerbach A, Katzper M. Assessment of visual analog versus categorical scale for the measurement of osteoarthritis pain. J. Clin Pharmacol. April 2004; 44:368-372.
5. Wound Zoom
6. Robson V, Dodd S, Thomas S. Standardized antibacterial honey (Medihoney TM) with standard therapy in wound care: randomized clinical trial. *J Adv Nurs*. 2009;65(3):565-575.
7. Jull A, Walker N, Parag V, Molan P, Rodgers A. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg*. 2008;95(2):175-182.

10. APPENDICES

APPENDIX A: Therahoney® Foam Flex Product Information

APPENDIX B: Subject Eligibility Questionnaire

APPENDIX C: Bates-Jenson Wound Assessment Scale

APPENDIX D: Case Report Form

APPENDIX E: Subject-Specific Investigator Questionnaire

APPENDIX F: Adverse Event (AE) Report Form

APPENDIX G: Serious Adverse Event (SAE) Report Form

10.1 APPENDIX A: Therahoney® Product Labeling

MEDLINE

MANUKA HONEY

ADVANCED
WOUND CARE

THERAHONEY® FOAM FLEX is ideal for moderate to heavily exudating wounds.

- With 100% Leptospermum Scoparium honey from New Zealand
- Maintains moist wound healing environment that allows autolytic debridement of necrotic tissue

INSTRUCTIONS FOR USE:

1 Remove dressing from package. Remove one piece of the release liner. Note: Use a dressing large enough to cover the wound and surrounding skin.

2 Place dressing on the wound and remove the other release liner.

3 Secure in place using tape or a secondary dressing.

ADDITIONAL CONSIDERATIONS: For Large wounds use additional dressings placed side by side. Dressings may be cut to size if needed.

INDICATIONS FOR USE: Therahoney® Foam Flex dressings are for use in moist wound management of: leg ulcers, pressure ulcers, 1st and 2nd degree burns, diabetic foot ulcers, surgical wounds, trauma wounds. A moist environment allows autolytic debridement of necrotic tissue.

CHANGE FREQUENCY: Therahoney® Foam Flex dressings may require a daily application depending on wound exudate, any surrounding interstitial fluid, edema, and dressing protocol.

STORAGE: Protect from freezing, avoid excessive heat.

CONTRAINDICATIONS: There is no record of increased blood sugar levels in patients with diabetes due to the use of honey dressings however it is advisable to monitor the levels during use of Therahoney® Foam Flex. Temporary increased pain may be experienced due to osmotic action and/or low pH of honey. If pain persists, discontinue use of the dressing and gently irrigate the wound with sterile saline solution. Do not reuse.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician or properly licensed healthcare professional.

Sterile in unopened, undamaged package. Single use only.

10.2 APPENDIX B: Subject Eligibility Questionnaire

Subject Eligibility Questionnaire

Subject #: 16017- __ __ __	Age: _____ (yrs)	
Gender (please check on): ☐ Male ☐ Female	**Yes**	**No**
Does the subject have a known sensitivity or allergy to honey based products, bee venom, or foam dressings?	☐	☐
Is the subject pregnant. breast feeding, or intending to become pregnant during the duration of the study?	☐	☐
Does the subject have any allergies? If so, what are they? _____	☐	☐
Preliminary Wound Analysis		
1. Is the chronic wound between 1 cm^2 to 25 cm^2 and been present for at least 4 weeks?	☐	☐
2. Is the subject's wound duration less than 52 weeks old?	☐	☐
3. Does the target wound meet the indication criteria listed in the product's labeling?	☐	☐
4. Does the subject have adequate circulation as demonstrated by biphasic or triphasic Doppler waveform, measured within 3 months of study enrollment? Or, if monophasic on exam, does subject have an Ankle-Brachial Index greater than 0.8 and no worse than mild disease on segmental pressures, measured within 3 months of study enrollment?	☐	☐
5. Does the subject have either type I/II diabetes? If so, has the subject's random blood glucose been less than 450 mg/dL within 30 days of the screening visit?	☐ ☐	☐ ☐
6. Does the target wound have at least 20% necrotic tissue	☐	☐
7. Is the subject currently receiving dialysis?	☐	☐
8. Does the subject's prognosis indicate an unlikely survival past the study period?	☐	☐
9. Does the subject have third degree burns?	☐	☐
10. Does the subject's target wound present with gangrene or signs of infection?	☐	☐
11. Is the subject likely to be compliant with instructions for care and daily dressing changes?	☐	☐
12. Has the subject received any treatment prior to the study that may affect the outcome of the study?	☐	☐

This subject is: ☐ continuing in the study ☐ dismissed

If Subject is dismissed, please document reason.
Subject did not meet qualification criteria: ☐ explain: _____ _____
Initials: _____ Date: _____

Approved by: _____ Date: _____

10.3 APPENDIX C: Bates-Jenson Wound Assessment Scale

BATES-JENSEN WOUND ASSESSMENT TOOL

Instructions for use

General Guidelines:

Fill out the attached rating sheet to assess a wound's status after reading the definitions and methods of assessment described below. Evaluate once a week and whenever a change occurs in the wound. Rate according to each item by picking the response that best describes the wound and entering that score in the item score column for the appropriate date. When you have rated the wound on all items, determine the total score by adding together the 13-item scores. The HIGHER the total score, the more severe the wound status is. Plot total score on the Wound Status Continuum to determine progress. If the wound has healed/resolved, score items 1, 2, 3 and 4 as =0.

Specific Instructions:

1. **Size**: Use ruler to measure the longest and widest aspect of the wound surface in centimeters; multiply length x width. Score as = 0 if wound healed/resolved.

2. **Depth**: Pick the depth, thickness, most appropriate to the wound using these additional descriptions, score as
   0 = if wound healed/resolved:
   1 = tissues damaged but no break in skin surface.
   2 = superficial, abrasion, blister or shallow crater. Even with, &/or elevated above skin surface (e.g., hyperplasia).
   3 = deep crater with or without undermining of adjacent tissue. 4 = visualization of tissue layers not possible due to necrosis. 5 = supporting structures include tendon, joint capsule.

3. **Edges**: Score as = 0 if wound healed/resolved. Use this guide:

Indistinct, diffuse	=	unable to clearly distinguish wound outline.
Attached	=	even or flush with wound base, no sides or walls present; flat.
Not attached	=	sides or walls are present; floor or base of wound is deeper than edge.
Rolled under, thickened	=	soft to firm and flexible to touch.
Hyperkeratosis	=	callous-like tissue formation around wound & at edges.
Fibrotic, scarred	=	hard, rigid to touch.

4. **Undermining**: Score as = 0 if wound healed/resolved. Assess by inserting a cotton tipped applicator under the wound edge; advance it as far as it will go without using undue force; raise the tip of the applicator so it may be seen or felt on the surface of the skin; mark the surface with a pen; measure the distance from the mark on the skin to the edge of the wound. Continue process around the wound. Then use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine percent of wound involved.

5. **Necrotic Tissue Type**: Pick the type of necrotic tissue that is predominant in the wound according to color, consistency and adherence using this guide:

White/gray non-viable tissue	=	may appear prior to wound opening; skin surface is white or gray.
Non-adherent, yellow slough	=	thin, mucinous substance; scattered throughout wound bed; easily separated from wound tissue.
Loosely adherent, yellow slough	=	thick, stringy, clumps of debris; attached to wound tissue.
Adherent, soft, black eschar	=	soggy tissue; strongly attached to tissue in center or base of wound.
Firmly adherent, hard/black eschar	=	firm, crusty tissue; strongly attached to wound base and edges (like a hard scab).

6. **Necrotic Tissue Amount**: Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine percent of wound involved.

7. **Exudate Type**: Some dressings interact with wound drainage to produce a gel or trap liquid. Before assessing exudate type, gently cleanse wound with normal saline or water. Pick the exudate type that is predominant in the wound according to color and consistency, using this guide:

Bloody	=	thin, bright red
Serosanguineous	=	thin, watery pale red to pink
Serous	=	thin, watery, clear
Purulent	=	thin or thick, opaque tan to yellow or green may have offensive odor

8. **Exudate Amount**: Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie- shaped quadrants to determine percent of dressing involved with exudate. Use this guide:

None	=	wound tissues dry.
Scant	=	wound tissues moist; no measurable exudate.
Small	=	wound tissues wet; moisture evenly distributed in wound; drainage involves ≤ 25% dressing.
Moderate	=	wound tissues saturated; drainage may or may not be evenly distributed in wound; drainage involves > 25% to ≤ 75% dressing.
Large	=	wound tissues bathed in fluid; drainage freely expressed; may or may not be evenly distributed in wound; drainage involves > 75% of dressing.

9. **Skin Color Surrounding Wound**: Assess tissues within 4cm of wound edge. Dark-skinned persons show the colors "bright red" and "dark red" as a deepening of normal ethnic skin color or a purple hue. As healing occurs in dark-skinned persons, the new skin is pink and may never darken.

10. **Peripheral Tissue Edema & Induration**: Assess tissues within 4cm of wound edge. Non-pitting edema appears as skin that is shiny and taut. Identify pitting edema by firmly pressing a finger down into the tissues and waiting for 5 seconds, on release of pressure, tissues fail to resume previous position and an indentation appears. Induration is abnormal firmness of tissues with margins. Assess by gently pinching the tissues. Induration results in an inability to pinch the tissues. Use a transparent metric measuring guide to determine how far edema or induration extends beyond wound.

11. **Granulation Tissue**: Granulation tissue is the growth of small blood vessels and connective tissue to fill in full thickness wounds. Tissue is healthy when bright, beefy red, shiny and granular with a velvety appearance. Poor vascular supply appears as pale pink or blanched to dull, dusky red color.

12. **Epithelialization**: Epithelialization is the process of epidermal resurfacing and appears as pink or red skin. In partial thickness wounds it can occur throughout the wound bed as well as from the wound edges. In full thickness wounds it occurs from the edges only. Use a transparent metric measuring guide with concentric circles divided into 4 (25%) pie-shaped quadrants to help determine percent of wound involved and to measure the distance the epithelial tissue extends into the wound.

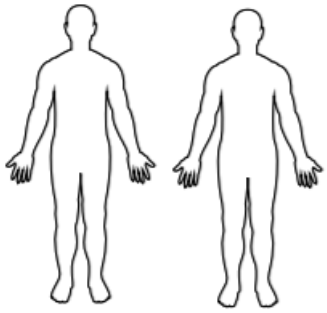
BATES-JENSEN WOUND ASSESSMENT TOOL

Subject Number:

Complete the rating sheet to assess wound status. Evaluate each item by picking the response that best describes the wound and entering the score in the item score column for the appropriate date. If the wound has healed/resolved, score items 1,2,3, & 4 as =0.

Location: Anatomic site. Circle, identify right **(R)** or left **(L)** and use **"X"** to mark site on body diagrams:

Sacrum & coccyx	Lateral ankle
Trochanter	Medial ankle
Ischial tuberosity	Heel
Buttock	Other site:



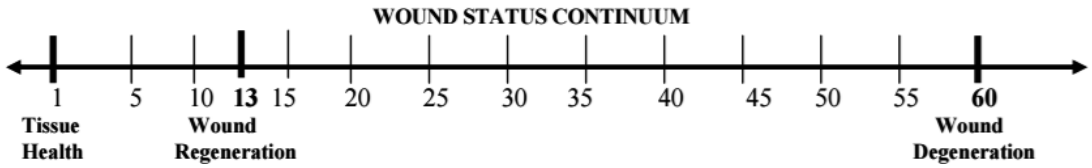
Shape: Overall wound pattern; assess by observing perimeter and depth.

Circle and date appropriate description:

Irregular	Linear or elongated	
Round/oval	Bowl/boat	
Square/rectangle	Butterfly	Other Shape

Item	Asses	Date Score	Date Score	Date Score
1. Size*	*0 = Healed, resolved wound 1 = Length x width <4 sq cm 2 = Length x width 4--≤16 sq cm 3 = Length x width 16.1--≤36 sq cm 4 = Length x width 36.1--≤80 sq cm 5 = Length x width >80 sq cm			
2. Depth*	*0 = Healed, resolved wound 1 = Non-blanchable erythema on intact skin 2 = Partial thickness skin loss involving epidermis &/or dermis 3 = Full thickness skin loss involving damage or necrosis of subcutaneous tissue; may extend down to but not through underlying fascia; &/or mixed partial & full thickness &/or tissue layers obscured by granulation tissue 4 = Obscured by necrosis 5 = Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures			
3. Edges*	*0 = Healed, resolved wound 1 = Indistinct, diffuse, none clearly visible 2 = Distinct, outline clearly visible, attached, even with wound base 3 = Well-defined, not attached to wound base 4 = Well-defined, not attached to base, rolled under, thickened 5 = Well-defined, fibrotic, scarred or hyperkeratotic			
4. Under-mining*	*0 = Healed, resolved wound 1 = None present 2 =Undermining < 2 cm in any area 3 = Undermining 2-4 cm involving < 50% wound margins 4 = Undermining 2-4 cm involving > 50% wound margins 5 = Undermining > 4 cm or Tunneling in any area			
5. Necrotic Tissue Type	1 = None visible 2 = White/grey non-viable tissue &/or non-adherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar			

6. Necrotic Tissue Amount	1 = None visible 2 = < 25% of wound bed covered 3 = 25% to 50% of wound covered 4 = > 50% and < 75% of wound covered 5 = 75% to 100% of wound covered			
7. Exudate Type	1 = None 2 = Bloody 3 = Serosanguineous: thin, water, pale red/pink 4 = Serous: think, watery, clear 5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor			
8. Exudate Amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Large			
9. Skin Color Surrounding Wound	1= Pink or normal for ethnic group 2 = Bright red &/or blanches to touch 3 = White or grey pallor or hypopigmented 4 = Dark red or purple &/or non-blanchable 5 = Black or hyperpigmented			
10. Peripheral Tissue Edema	1 = No swelling or edema 2 = Non-pitting edema extends < 4cm around wound 3 = Non-pitting edema extends ≥ 4cm around wound 4 = Pitting edema extends < 4cm around wound 5 = Pitting edema extends ≥ 4cm around wound			
11. Peripheral Tissue Induration	1 = None present 2 = Induration < 2cm around wound 3 = Induration 2-4cm extending <50% around wound 4 = Induration 2-4cm extending ≥50% around wound 5 = Induration > 4cm in any area around wound			
12. Granulation Tissue	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth 3 = Bright, beefy red; <75% & >25% of wound filled 4 = Pink, &/or dull, dusky red &/or fills ≤25% of wound 5 = No granulation tissue present			
13. Epithelialization	1 = 100% wound covered, surface intact 2 = 75% to < 100% wound covered &/or epithelial tissue extends > 0.5cm into wound bed 3= 50% to < 75% wound covered &/or epithelial tissue extends < 0.5cm into wound bed 4 = 25% to < 50% wound covered 5 = < 25% wound covered			
Total Score				
Signature: _____ Date: _____				



Plot the total score on the Wound Status Continuum by putting an **"X"** on the line and the date beneath the line. Plot multiple scores with their dates to see-at-a-glance regeneration or degeneration of the wound.

10.4 APPENDIX D: Case Report Form

Case Report Form (R16-017)

Subject Number: | **Visit Date:** | **Visit Time:** AM PM | **Visit Type and Number:**

Height (inches): **Weight (lbs):** **Age:**

Sex: ☐ Male ☐ Female

Race: ☐ White ☐ Black ☐ Hispanic or Latino ☐ Asian ☐ Other/Mixed Race ☐ Native American

Was mechanical debridement used? ☐ Yes ☐ No

Was a secondary dressing used? ☐ Yes ☐ No If yes, what kind? _____

Wound Assessment

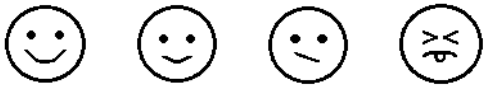
Physical Examination and Wound Zoom Analysis

Diagnosis: _____

What is the percent of necrotic tissue? _____ %

Wound size (cm): Width_____ x Length _____ x Depth _____

Evaluation of odor: _____



1 2 3 4

VAS Pain scale score within 10 minutes following dressing change: ____

0 1 2 3 4 5 6 7 8 9 10

Site Infection: Yes No

If yes, discontinue subject and note steps taken:

_____

Bates – Jensen Wound Assessment Tool (BWAT)

1. **Skin:** ____
2. **Depth:** ____
3. **Edges:** ____
4. **Undermining:** ____
5. **Necrotic Tissue Type:** ____
6. **Necrotic Tissue Amount:** ____
7. **Exudate Type:** _____
8. **Exudate Amount:** ____
9. **Skin Color Surrounding Wound:** ____
10. **Peripheral Tissue Edema:** _____
11. **Peripheral Tissue Induration:** ____
12. **Granulation Tissue:** ____
13. **Epithelialization:** _____

TOTAL BWAT SCORE: _____

Place photograph of the wound from the Wound Zoom camera below:

Subject #: _____ Date: _____

*Please note that the information in the picture should match the above information.

Signature _____ Date _____

10.5 APPENDIX E: Subject-Specific Investigator Questionnaire

Subject-Specific Investigator Questionnaire

Subject #: 16017- __ __ __

1. In your opinion, was the product effective in healing the wound? ☐ Yes* ☐ No*

   *Comment:

   ____

   ____

2. In your opinion, was the product effective in decreasing the subject's exudate? ☐ Yes* ☐ No*

   *Comment:

   ____

   ____

3. In your opinion, did the product help promote autolytic debridement? ☐ Yes* ☐ No*

   *Comment:

   ____

   ____

4. How would you rate ease of use for the product on the wound?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Very bad ← - →Very Good										

*Comment:

____

____

5. How would you rate the performance of the product on the wound?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Very bad ← - →Very Good										

*Comment:

____

____

6. When selecting wound care products to treat a similar wounds in the future, how likely are you to choose the product?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Very Unlikely ← - →Very Likely										

*Comment:

____

____

Signature ______________________________ **Date** ____________________

10.6 APPENDIX F: Adverse Event (AE) Report Form

Site/Subject Information	
Study Sponsor: Medline Industries, Inc.	Protocol Number: R16-017
Site Number:	Principal Investigator:
Subject Number:	Subject Initials:

Adverse Event Information

#	Adverse Event:		Start Date: DD-MMM-YYYY	Stop Date: DD-MMM-YYYY	Ongoing:	Frequency:	Severity:	Outcome:	IP Lot #:	Relation-ship to IP:	Action Taken with IP:	SAE Status:	Comment:
		☐ Expected			☐ Yes							☐ Yes*	
		☐ Unexpected			☐ No							☐ No	
		☐ Expected			☐ Yes							☐ Yes*	
		☐ Unexpected			☐ No							☐ No	
		☐ Expected			☐ Yes							☐ Yes*	
		☐ Unexpected			☐ No							☐ No	
		☐ Expected			☐ Yes							☐ Yes*	
		☐ Unexpected			☐ No							☐ No	
		☐ Expected			☐ Yes							☐ Yes*	
		☐ Unexpected			☐ No							☐ No	

Frequency:	Severity:	Outcome:	Relationship to IP:	Action Taken with IP:	SAE Status
1 = Isolated 2 = Intermittent 3 = Continuous	1 = Grade 1; mild 2 = Grade 2; moderate 3 = Grade 3; severe 4 = Grade 4; life-threatening 5 = Grade 5; death	1 = Resolved, with no sequelae 2 = Resolved, with sequelae 3 = Unresolved 4 = Death 5 = Unknown	1 = Not Related 2 = Possible 3 = Probable 4 = Definite	1 = None 2 = Modified 3 = Interrupted 4 = Discontinued	Death, life-threatening, prolonged hospitalization, significant disability/anomaly, medical intervention to prevent a serious outcome

***In the event of a Serious Adverse Event, please complete the Serious Adverse Event Report form and send to Medline Industries, Inc. within 48 hours of awareness**

Initials: ___________________ Date: _______________________

Approval: ___________________ Date: _______________________

10.7 APPENDIX G: Serious Adverse Event (SAE) Report Form

Site Information		
Study Sponsor: Medline Industries Inc.	Protocol Number: R16-017	
Site Number:	Principal Investigator:	
Site Address:	Report Type:	☐ Initial
		☐ Follow-up
		☐ Final
Form Completed By:	Title:	
Telephone:	E-mail:	

Serious Adverse Event Information			
Subject Number:			
Age:	Gender:	☐ Male	☐ Female
Investigational Product:			
Event Description: (Please include a detailed description of the event in question, including the results of any laboratory/diagnostic imagery testing)			
Site Notification	Date Notified:	Time Notified:	
of the Event:	Method of Notification:		
Event Start/Stop:	Start Date:	Stop Date: ☐ Ongoing	
Event Qualifiers: (Check all that apply)	☐ Death	☐ Intervention to Prevent Impairment	
	☐ Life-Threatening	☐ Disability/Permanent Damage	
	☐ Initial or Prolonged Hospitalization	☐ Congenital Anomaly	
	☐ Other:		

Relevant Medical History:	
Concomitant Medication/Device History: (Please include historical information such as medication/device name, dosage, frequency, route, start date, etc.)	
Relationship to Investigational Product (IP):	☐ Not Related (event definitely not related to IP, as judged by the Principal Investigator)
	☐ Possibly Related (event maybe related to IP, as judged by the Principal Investigator)
	☐ Related (event definitely related to IP, as judged by the Principal Investigator)
Action Taken with Investigational Product:	☐ Discontinued- Please Provide Date:
	☐ Interrupted- Please Provide Date:
	☐ None
Comments:	
Initials: _____ Date: _____	
Approval: _____ Date: _____	

Confirmation of Receipt: **SECTION TO BE COMPLETED BY MEDLINE INDUSTRIES INC.**	
Date Received:	Time Received:
Received By:	Title: