A clinical evaluation of an esterified hyaluronic acid matrix on preparing wounds in burn patients for split-thickness skin grafting

Protocol Number MED-2018-DIV31-006

8-July-2020
Version 2.0

Prepared by:

Medline Industries
Three Lakes Drive
Northfield, IL 60093

Prepared by (Signature) Date

Reviewed by (Signature) Date

Contents

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 (Print):	
Principal Investigator (Signature):	Date (MM-DD-YYYY):

DOCUMENT HISTORY

VERSION	DATE	DESCRIPTION
Version 1.0	12-Sep-2018	Initial Release

Version 2.0	8-July-2020	Following protocol edits were made: 1. The “Investigator Acknowledgement Signature” page was modified. 2. The economic outcomes were removed from the secondary objectives. 3. Secondary endpoints were modified in order to obtain a more comprehensive study design. 4. The “Study Population” section was modified to also include patients with electrical burns. 5. Inclusion and exclusion criteria were added in the synopsis. 6. Inclusion and exclusion criteria were modified in order to further streamline the screening process. 7. The “post-market” phase was added in the synopsis. 8. The “Participant Duration” section of synopsis was modified to provide more clarity to the “End of study definition” section of the protocol. 9. The “Schedule of Activities” section was modified to align with the study procedures and assessments. 10. The “Assessment of potential risk/benefit profile” section was modified in order to show a favorable risk-benefit profile of this study. 11. The “Study procedures and assessments” section was modified to align with the changes in the study design. 12. The language in the “Adverse Events” section was updated to reflect the new grading system. 13. The language in the “Serious Adverse Events” section was modified, in order to align with the current updated processes.

		14. The title of Kara Cassady was changed from Associate Director of Clinical Operations to Director of Clinical Operations. 15. The "Key roles and Study Governance" section was removed. 16. The language in "Clinical Monitoring" section was modified to provide a more realistic monitoring activity by the Clinical Research Associate(s). 17. The "Confidentiality and Privacy" section was modified to include paper files, in addition to electronic database. 18. The statistical analysis system was updated in the "Data handing and record keeping" section. 19. The "Study closeout" section was modified such that now Medline Industries, Inc. (sponsor) is not required to share with the site(s) the final analysis of data for study completed at the site(s). 20. Updated instructions for use (IFU) document was added. 21. Screening form, case report forms, AE form, and SAE form were removed from the protocol. They will be provided by Medline Industries, Inc. but will go as a separate document.

1. PROTOCOL SUMMARY

1.1. Synopsis

Title: A clinical evaluation of an esterified hyaluronic acid matrix on preparing post-escharectomy wounds for split-thickness skin grafting in burn patients.

Study Description:

Hyaluronic acid is a major component of the extracellular matrix. During the wound healing process, hyaluronic acid impacts several stages of healing by modulating inflammation, cellular proliferation, and migration. Consequently, matrices composed of hyaluronic acid may accelerate the wound healing process and lead to improved patient outcomes. This multisite case series will evaluate the impact of a specific matrix composed of esterified hyaluronic acid (Hyalomatrix® Wound Device) on the management of wounds in burn patients. Study participants will have wounds that are clinically suitable to be managed by the use of a regenerative matrix followed by final wound closure with split thickness skin graft (STSG).

Objectives:

Primary Objective: Evaluate the capability of a hyaluronic acid wound matrix to prepare a post-escharectomy wound, in burn patients, to receive an STSG.

Secondary Objectives: Evaluate clinical and health outcomes relating to the wound and STSG.

Endpoints:

Primary Endpoint: Number of days from initial application of Hyalomatrix® Wound Device to approval of wound to receive an STSG.

Secondary Endpoints: (1a) Change in wound volume from the time prior to application of the Hyalomatrix® Wound Device to the time before the application of STSG and after STSG, (1b) Length-of-stay in inpatient unit, (1c) Patient pain rating, (1d) Proportion of STSG take for the wound at 28 days, per clinician judgement, (1e) Proportion of patients who develop an infection of the target wound at any time, per confirmation with culture, (2a) Length-of-stay as inpatient, (2b) Discharge destination.

Study Population:

Twenty thermal or electrical burn patients (18-85 years old) who have a wound with a total body surface area (TBSA) between 0.5% and 20%, and the wound (per the investigator) requires treatment in an inpatient setting. The admission need not be the initial presentation of the burn. Patients must have a wound from a thermal or electrical burn that has undergone escharectomy and likely requires an STSG to heal. All patients must meet treatment indications for Hyalomatrix® Wound Device.

Inclusion Criteria

Patients will be eligible to participate in the study if they satisfy *ALL* of the inclusion criteria below:

- Patients who are 18-85 years old
- Patient with a wound originating from a thermal or electrical burn
- Total burn area is less than 20% of TBSA
- Target burn wound is greater than 0.5% of TBSA
- Patient has undergone escharectomy procedure or will undergo escharectomy on the target wound before application of Hyalomatrix® Wound Device, and resulting wound will likely need an STSG, but wound site is not immediately ready for grafting.
- For patients with diabetes, an A1C hemoglobin level below 11 percent (taken within 90 days).

Exclusion Criteria

A participant is ineligible for the study if he or she meets *ANY* of the criteria below:

- Current active diagnosis of substance abuse, per the Investigator
- Patient currently taking non-inhaled corticosteroids
- Patient needs or is likely to need Negative Pressure Wound Therapy (NPWT) of the target wound after application of Hyalomatrix® Wound Device
- Patient is pregnant, planning to become pregnant during study period, or breastfeeding
- Unstable medical condition as determined by the site investigator or sub-investigator
- Patients with known sensitivities to hyaluronan, hyaluronan derivatives, silicone, or any other ingredients of the Hyalomatrix® Wound Device

Description of Sites/Facilities Enrolling Participants:	Multiple burn centers within acute care facilities.
Phase	Post-market
Description of Study Intervention:	This is a case series, in which burn patients meeting all of the inclusion criteria and none of the exclusion criteria will receive Hyalomatrix® Wound Device as a matrix for their wound, in conjunction with the standard-of-care for managing these types of wounds. The study will be divided into two phases. Phase I will entail intervention with the Hyalomatrix® Wound Device and will continue until one of the following occurs, (1) sufficient granulation has occurred and the patient can receive an STSG and proceed to Phase II, (2) the patient's physician determines an STSG is no longer necessary, or (3) two applications with the Hyalomatrix® Wound Deviceoccur and no STSG is approved. Phase II will begin following the STSG procedure. In this phase the wound will be monitored and proportion of STSG take will be evaluated, but no application of the Hyalomatrix® Wound Devicewill take place. This phase will continue for 28 days or if the physician deems the patient no longer needs regular care to monitor the wound, whichever occurs earlier.
Participant Duration:	Participant duration will begin upon obtaining informed consent and will end when one of the following occurs: (1) The patient completes Phase II, (2) the patient's physician determines an STSG is no longer necessary, (3) the patient is unwilling or clinically inappropriate, per determination by the Investigator, to receive a second application of Hyalomatrix® Wound Device or STSG. The silicone backing should be removed at 21 days but the decision to reapply the Hyalomatrix® Wound Device or schedule the STSG may happen up to three days thereafter, (4) the patient is not ready to receive an STSG after two applications with the Hyalomatrix® Wound Device. The silicone backing should be removed 21 days after the second application of Hyalomatrix® Wound Device but the decision to schedule the STSG may happen up to three days thereafter,, (5) the patient develops an infection of the target wound at any time, (6) the patient needs NPWT of the target wound after application of the Hyalomatrix® Wound Device.

Overall time will be variable depending on the patient's wound and condition; however, typical time for a wound to be ready for grafting following the use of the Hyalomatrix® Wound Device is 14-21 days after initial matrix application. Time to heal after STSG application is typically two weeks, but the patient will remain in the Phase II portion of the study while the wound is still open, up to a maximum period of 28 days post STSG.

1.2. Schedule of Activities (SOA)

REQUIRED ASSESSMENTS & ACTIVITIES	SCREENING VISIT Day 0	PHASE I: INITIAL VISIT Day 1	PHASE I: ASSESSMENT VISITS Days 7, 14, 21, 28, 35, 42[b]	PHASE II: ASSESSMENT VISITS Days 7, 14, 21, 28[c], post-Phase I completion
Informed consent	X			
Wound assessment for eligibility	X			
Review of medical history to determine eligibility	X			
A1C test [a]	X			
Demographics, comorbidities, wound history & medication(s)		X		
Wound photograph, infection evaluation, & pain assessment		X	X	
Application of Hyalomatrix® Wound Device and secondary dressing		X		
Record analgesic use		X	X	X

Wound assessment for STSG eligibility			X	
Wound photograph and STSG take assessment				X
Adverse event assessment		X----------X		

a Only for diabetic patients who do not have an A1C reading within the past 90 days

b Days must be +/- two days within target day. In most cases, Phase I will end by 21 days. In the event Phase I extends beyond 21 days, a second application of the Hyalomatrix® Wound Device will occur c Days must be +/- two days within target day. Phase II may end earlier depending on participants wound progress.

2. INTRODUCTION

2.1. Background & Rationale

The wound healing process following burn wounds takes a coordinated biological effort involving inflammation, tissue proliferation, and tissue remodeling, amongst other biological processes.[1] Given the extensive damage typically occurring in burn wounds, cellular and/or tissue-based products, which are applied to the wound to aid in tissue regeneration, are often prescribed to facilitate tissue granulation and healing. A variety of skin substitutes exist, varying in their composition (animal or human origin) as well as their mechanism of action.[1]

Hyaluronic acid is a major component of the extracellular matrix.[2] During the wound healing process, hyaluronic acid impacts several stages of healing by modulating inflammation, cellular proliferation and migration.[3] Consequently, skin substitutes composed of hyaluronic acid may accelerate the wound healing process by providing the patient with the substrate to generate neodermis.[4] In patients who ultimately need a split-thickness skin graft (STSG) to heal their wound, the use of a hyaluronic acid based skin substitute may lead to decreased time-to-grafting, improving patient outcomes and quality of life. The current study will evaluate the clinical use of an esterified hyaluronic acid based wound matrix device on time-to-STSG and ultimate wound outcome.

2.2. Clinical Product

Hyalomatrix® Wound Device (henceforth described as “device”) is a non-woven pad composed of esterified hyaluronic acid, covered with a semipermeable silicone layer to protect the wound and control water vapor loss. The device should be used with an appropriate secondary dressing.

The device is currently marketed in the United States and is approved for use in numerous conditions: chronic vascular ulcers, diabetic ulcers, draining wounds, partial- and full-thickness wounds, pressure ulcers, second-degree burns, surgical wounds, trauma wounds, tunneled/undetermined wounds, and venous ulcers. The device achieves its effect by depositing hyaluronic acid, which is a major component of the extracellular matrix, into the wound bed to support the healing process. The device acts as a scaffold for cellular colonization and capillary growth. Further information on the product can be found in Appendix 11.1.

2.3. Risk/Benefit Profile

2.3.1. Potential Study Risks

If the participants have an unknown sensitivity to hyaluronan, hyaluronan derivatives or silicone, they may experience a reaction to the device. This risk will be mitigated by screening potential participants regarding any sensitivity to the dressing material. Additionally, patients will be under the care of a physician, who will be able to appropriately address any potential reaction from the dressing.

2.3.2. Potential Study Benefits

Through use of the wound device, patients may experience decreased time to receiving an STSG and achieve faster overall resolution of their wound.

2.3.3. Assessment of Potential Risk/Benefit Profile

Since this is a post-market study and the device is used within its intended use by or under supervision of the Investigator who is a burn specialist, participation in this study presents minimal risk to the patient, while offering the potential for benefits to the patients enrolled in the study. Therefore, the risk-benefit profile for the study is favorable.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Evaluate the capability of the device to prepare post-escharectomy wounds in burn patients to receive an STSG.	Number of days from initial application of the device to approval of wound to receive an STSG.	Marker of wound healing progress
Secondary		

1. Evaluate clinical outcomes of burn patients 2. Health outcomes	(1a) Change in wound volume from the time prior to application of the device to the time before the application of STSG and after STSG (1b) Length-of-stay at inpatient unit (1c) Patient pain rating (1d) Proportion of STSG take for the wound at 28 days, per clinician judgement (1e) Proportion of patients who develop an infection of the target wound at any time, per confirmation with culture (2a) Length-of-stay as inpatient (2b) Type of care setting where patient is discharged	Common clinical endpoints to measure outcomes in wound management. Common analysis to determine cost-effectiveness of device usage.

4. STUDY DESIGN

4.1. Overall Design

This study is a multi-site, open-label case series collecting data on the clinical use of an esterified hyaluronic acid wound matrix in preparing post-escharectomy wounds in burn patients for STSGs. The study will be split into two phases. Phase I will include use of the device on the wound, with the intent of measuring how quickly the wound becomes prepared for an STSG. Phase II will occur after the STSG is placed; in this phase, the device will not be applied. Rather, the key assessment will be how well the wound is receiving the STSG. The Schedule of Activities in Section 1.2 describes the timing and sequencing of the events and phases.

In addition to the use of the wound device, physicians will provide the standard of care per their facility. However, in order to avoid confounding any conclusions attributable to the wound matrix, negative pressure wound therapy (NPWT) of the target wound will not occur during the study. Patients having NPWT on the target wound when they are screened may be included in the study (provided they meet all the inclusion criteria and none of the exclusion criteria), except when NPWT is not or cannot be discontinued after application of the device. The potential use of NPWT on the target wound, after application of the device, on a patient is listed below as an exclusion criterion. During the course of the study, if a physician determines that a patient could benefit from NPWT on the target wound, the physician can implement this therapy, and the patient will be discontinued from the study.

4.2. End of Study Definition

A patient's participation in the study may end at several critical points:

- The patient completes Phase II.

- The patient's physician determines a STSG is no longer necessary.
- The patient is unwilling or clinically inappropriate, per determination by the Investigator, to receive a second application of the device or STSG. The silicone backing should be removed at 21 days but the decision to reapply the device or schedule the STSG may happen up to three days thereafter.
- The patient is not ready to receive a STSG after two applications of the device. The silicone backing should be removed 21 days after the second application of the device but the decision to schedule the STSG may happen up to three days thereafter.
- The patient develops an infection of the target wound at any time.
- The patient needs NPWT of the target wound after application of the device.

The end of the study will coincide with the issuance of a clinical study report that has been approved by Medline's Clinical Affairs Director.

5. STUDY POPULATION

5.1. Inclusion Criteria

A patient will be eligible to participate in the study if he or she satisfies *ALL* of the inclusion criteria below:

- Patients who are 18-85 years old
- Patient with a wound originating from a thermal or electrical burn
- Total burn area is less than 20% of TBSA
- Target burn wound is greater than 0.5% of TBSA
- Patient has undergone escharectomy procedure or will undergo escharectomy on the target wound before application of the device, and resulting wound will likely need an STSG, but wound site is not immediately ready for grafting.
- For patients with diabetes, an A1C hemoglobin level below 11 percent (taken within 90 days).

5.2. Exclusion Criteria

A participant is ineligible for the study if he or she meets *ANY* of the criteria below:

- Current active diagnosis of substance abuse, per the Investigator
- Patient currently taking non-inhaled corticosteroids
- Patient needs or is likely to need NPWT of the target wound after application of the device
- Patient is pregnant, planning to become pregnant during study period, or breastfeeding
- Unstable medical condition as determined by the site investigator or sub-investigator
- Patients with known sensitivities to hyaluronan, hyaluronan derivatives, silicone, or any other ingredients of the device

5.3. Strategies for Recruitment and Retention

Each site investigator regularly treats burn patients at the burn centers they serve. The site investigators and their staff will recruit potentially eligible patients from their practice. As the use of the wound device in this study will be a core piece of the patient's treatment plan, it is expected that retention will not be an issue during Phase I (pre-STSG).

6. STUDY PROCEDURES AND ASSESSMENTS

6.1. Phase I – Pre-STSG

6.1.1. Day 0 – Screening Visit and Informed Consent

6.1.1.1. Informed Consent

Prior to conducting study activities, written consent will be obtained from all participating subjects and documented on an informed consent form (ICF) that has received approval 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 International Conference on Harmonization (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). A copy of the signed consent form will be given to each participating subject.

6.1.1.2. Eligibility Screening

Potential participants will be screened for eligibility via a combination of the screening form, provided separately by Medline Industries, Inc., and by a review of the potential participant's burn wound and medical chart by one of the site investigators or their staff. In the event a participant has multiple burn wounds, the site investigator will select the target wound that meets the inclusion criteria; in the event more than one wound meets all inclusion criteria, the site investigator will choose the wound (target wound) he or she believes to be most clinically appropriate for treatment with the device. If a potential participant with diabetes does not have an A1C level recorded in his or her chart within the past 90 days, a qualified member of the study staff or a site investigator's institution will perform a blood draw to be used for A1C calculation. If a potential participant has NPWT on the target wound during screening, that participant may still be included in the study provided that participant meets all the inclusion criteria, none of the exclusion criteria, and if NPWT will be discontinued right before application of the device.

6.1.2. Day 1 – Initial Visit

6.1.2.1. Demographics, Comorbidities, Wound history and Medication

To allow for a deeper understanding of the effect of the device on patients' wounds, demographic information, patient co-morbidities, historical treatment modalities of the target wound, and current medication list will be collected at the time of initial visit. Intake of analgesics will be captured throughout the study. Information pertaining to the escharectomy procedure will also be recorded. This will allow for post-hoc analyses that may inform the design of the larger clinical study. Information will be recorded on the Case Report Forms (CRFs) provided separately by Medline Industries, Inc.

6.1.2.2. Wound Photograph and Area Measurement

During the initial visit, a member of the study staff will take a photograph of the wound using a specialized wound camera with image analysis software (inSight® by eKare Inc.), postescharectomy and immediately prior to application of the device. The image analysis software will calculate wound volume and area automatically, and will collect wound depth. In the event the camera or software malfunction, wound area and volume will be assessed manually with a ruler or other measuring device used for measuring wound area and volume.

6.1.2.3. Pain Assessment

Patients will be asked to rate their current level of pain, both overall and at the wound, using a verbal Likert-type scale. Patients will respond with a whole number between 0-10, with 0 corresponding to "no pain" and 10 corresponding to "the worst pain imaginable."

6.1.2.4. Analgesic Usage

Since usage of analgesic(s) will likely affect a patient's self-assessment of pain, analgesic usage will be recorded throughout the study in order to provide a full picture of pain management. This information will be recorded on CRFs provided separately by Medline Industries, Inc.

6.1.2.5. Infection Evaluation

At this visit, as well as all visits and during the continuum of the patient's participation in the study, the wound site will be evaluated for the development of an infection. In the event of a suspected infection, clinical staff will collect a wound culture. Should a patient develop an infection, this will be noted as an expected adverse event (AE) and the participant's participation in the study will be terminated.

6.1.2.6. Placement of the device

After taking wound photograph (post-escharectomy), conducting wound area and volume measurement and assessment, the site investigator or qualified study staff will place the

device on the wound, along with an appropriate secondary dressing. Wound photograph will also be taken immediately after application of the device.

6.1.3. Interim Visits – Day 7, 14, 21, 28, 35, 42

At the interim visits during Phase I, patients will have their wound assessed, and will then be photographed using the same method as described in section 6.1.2.2. Remaining Interim visit activities will then be performed as stated in 6.1.2.3 through 6.1.2.5. The site investigator will assess if the wound is ready to receive an STSG at these visits. If the wound is ready for an STSG, the date of STSG approval and planned date of STSG procedure will be noted on the CRF provided by Medline Industries, Inc.. Should the site investigator deem that healing has progressed such that an STSG is no longer necessary, the patient's participation in the study will be discontinued. If after 21 days of device usage the patient is not ready to receive an STSG, a second application of the device may be applied and Phase I will be extended for an additional 21 days (for a maximum of 42 total days of device usage). If the patient is unwilling or clinically inappropriate, per determination by the PI, to receive a second application of wound matrix or STSG after 21 days, the patient's participation in the study will end. Alternatively, if the site investigator believes the wound will be ready to receive an STSG within three additional days of healing, but does not require another device application, the silicone backing of the device will be removed at Day 21 and the STSG will be scheduled by the Investigator or treating physician. Similarly, after 21 days of second application of the device, if the site investigator believes the wound will be ready to receive an STSG within three additional days of healing, the silicone backing of the device will be removed 21 days after the second application of the device and the STSG will be scheduled by the investigator or treating physician.STSG will be scheduled by the investigator or treating physician. Information pertaining to length-of-stay and discharge will also be collected. The timing of the visit days is approximate, as scheduling challenges may cause the exact visit days to not occur exactly every seven days. However, visits should occur within +/- two days of the original sevenday interval.

6.2. Phase II – Post-STSG

6.2.1. Interim Visits – Post-STSG Days 7, 14, 21, 28,

Following the completion of the STSG procedure, the patient will attend up to four interim visits to monitor wound healing progress and percent take of the STSG. Also, at Day 7 visit, information relating to the graft procedure will be recorded on the Surgical Procedures CRF provided separately by Medline Industries, Inc. At each visit, a photograph of the wound will be taken and the site investigator will also determine the percentage of STSG take at each visit, which will be based on the clinical judgement. The patient will also rate current pain level (overall and at the target wound) in an identical fashion to Section 6.1.2.3. A patient's participation in Phase II of the study will continue for 28 days post-STSG or until the site investigator determines weekly care is no longer needed. To document wound healing completion, a photograph of the healed wound will be taken. In order to track the participant's overall outcomes, any returns to the operation

room to treat the target wound, any additional inpatient stays, and the type of facility the patient goes to at discharge will be captured on the CRFs. The timing of the visit days is approximate, as scheduling challenges may cause the exact visit days to not occur exactly every seven days. However, visits should occur within +/- two days of the original seven-day interval.

7. ADVERSE EVENTS

7.1. Definition of Adverse Event

Since this is a post-market study and the device is used within its intended use, participation in the study presents minimal risk to the patient. Additionally, this patient population may have numerous comorbidities and health issues unrelated to the wound. Therefore, a narrower definition of a nonserious adverse event (AE) will be used. In this study, an AE is any untoward medical occurrence related to the wound or treatment of the wound, including infection, significant increases in pain, and unexpected reactions at the site of wound device placement.

7.2. Definition of Serious Adverse Event

The FDA definition of a serious adverse event (SAE) will be used in this study: An AE or suspected adverse reaction is considered "serious" if, in the view of either the site investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or,
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All SAEs will be reported to the sponsor, regardless of potential relationship to the wound or treatment of the wound.

7.3. Severity of Adverse Event

The severity of all adverse events will be graded on a scale of one through five according to 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 ageappropriate 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

7.4. Relatedness of Adverse Event and Serious Adverse Event

- **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.

7.5. Expectedness

The site investigator will be responsible for determining whether an AE or SAE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the device.
Expected AEs include a reaction at the wound site following application of the wound device or infection.

7.6. Adverse Event Reporting

AEs will be recorded on the AE form provided separately by Medline Industries, Inc. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. Changes in severity will necessitate a new AE form to document the new level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

Non-serious AEs should be reported to the study sponsor routinely at a cadence negotiated by the site and CRA. Any AE that meets the requirements for IRB reporting should be done so according to the timeline for this per the IRB.

7.7. Serious Adverse Event Reporting

The site investigator shall complete an SAE Form provided separately by Medline Industries, Inc. and submit to the study sponsor as soon as possible, but in no event later than 48 hours after the PI first learns of the event. The PI will be responsible for reporting the event to the IRB if applicable per the IRB's reporting requirements. The study sponsor is responsible for conducting an evaluation of the SAE and shall report the results of such evaluation to the FDA, if applicable, and to all reviewing IRBs, if applicable, within 10 working days after the sponsor first receives notice of the event. Thereafter, the sponsor shall submit such additional reports concerning the event as FDA requests.

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

Name: Kara Cassady
Phone: 847-643-3809
E-mail: kcassady@medline.com

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Determination

This study is a case series meant to evaluate the clinical usage of the device and is not intended to inform any hypothesis testing. Therefore, a sample size of 20 patients was chosen, which is consistent with a case-series.

8.2. Populations for Analyses

An evaluable population will be used for all analyses, with the definition of evaluable depending on the Phase of the study. For Phase I, all patients with an initial visit and a final interim visit resulting in resolution of Phase I will be included. In Phase II, patients with data from any interim visits who also complete Phase II to resolution will be included in analyses for Phase II.

8.3. Statistical Analysis

Descriptive statistics, including measures of central tendency (mean or median), measures of variation (standard deviations, coefficients of variation) and 95% confidence intervals and interquartile ranges, as appropriate, for the data distribution will be calculated for all endpoints. Demographic and baseline characteristics will be assessed as above and additional statistical analyses may be conducted in an exploratory fashion, as appropriate, for the data distribution.

- Time (in days) from initial application of wound matrix to approval of wound to receive an STSG.
- Change in wound volume from the time prior to application of the wound matrix to the time before the application of STSG and after STSG
- Length-of-stay as an inpatient

- Patient pain ratings
- Proportion of STSG take, per clinician judgement, for the wound at 28 days
- Proportion of patients who develop an infection of the target wound at any time, per confirmation with culture
- Type of care setting where patient is discharged

Healthcare economics outcomes will be explored by combining length-of-stay data (both phases) and the type of care setting where the participant is discharged, with standard costs, reimbursement codes and other relevant health economics economic factors.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Clinical Monitoring

The Clinical Research Associate (CRA) will confirm that the rights and well-being of subjects are protected, and that the reported trial data are accurate, complete, and verifiable from source documents. Moreover, the CRA will confirm the conduct of the trial by the site investigators and sites are in compliance with the protocol, GCP, and regulatory requirements as well as any applicable institution or IRB and federal or local processes. Monitoring will occur at minimum every two months, or more or less depending on enrollment, during the study duration or more frequently if:

- The volume or quantity of data is large or there is a backlog of review due to unexpected issues
- This would also include any large volume of CRFs to be reviewed
- The site compliance with the protocol or compliance with expected ICH/GCP and regulatory requirements is lacking or there are continuing unresolved compliance issues
- There are unexpected AE/SAE or subject safety concerns noted
- There are any unexpected inconsistencies with study product management
- There is a request for more frequent monitoring by the site
- Any mutually agreeable situation as determined by the sites and Medline

The frequency of routine monitoring may be increased to a longer interval after three monitoring cycles if on-site situations support this change. CRA will discuss this with Medline Director or Clinical Managers and will inform the site investigator prior to implementation.

Monitoring activities will include subject eligibility, source data review, CRF completion verification, product accountability, site continued suitability, investigator study oversight, compliance, and all general monitoring activities as outlined in FDAs Code of Federal Regulations and ICH/GCP guidelines that guide that activity.

Medline Industries Inc. may, on occasion, contract with external Clinical Research Organizations to provide CRA services and those CRAs are authorized to act on behalf of Medline Industries, Inc.

It is expected that the site will be compliant with any institutional Standard Operating Procedures during the execution of the protocol and evidence of that compliance should be readily documented and verifiable by the CRA.

The CRA will generate an internal Medline Industries Inc. visit report that will be filed with the Medline Industries, Inc. trial master file and will provide the site investigators a detailed follow-up letter after each monitoring visit that will outline the completed monitoring activities as well as any identified areas of concern and the expected/applicable corrections needed. Medline Industries Inc., reserves the right to perform audit of the study activities – either routine or for-cause – as needed, and may also perform clinical monitoring audit as well.

9.2. Regulatory and Ethical Considerations

9.2.1. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the site investigators, their staffs, and the Sponsor. Therefore, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. All study data and study records will be managed and stored in accordance with the site's HIPAA compliant policies on data storage and security. All electronic transmission of data will adhere to HIPAA Security Rules.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB and regulatory agencies may inspect all documents and records required to be maintained by the site investigators, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

A master list linking subject numbers to patient name and medical record number will be maintained in a secure database or secure paper file(s) by the site investigators. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for at least a period of two years, or longer if dictated by the reviewing IRB, Institutional policies, Sponsor requirements, or ICH/GCP and FDA requirements. The site investigator will agree to notify Sponsor of any intent to move or destroy these documents.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be maintained at the research sites on the CRFs. Copies of the CRFs, which will not contain any identifiable information, will be provided to the Sponsor for the purposes of data analysis. The study data entry and study management systems used by clinical sites and by Medline Industries, Inc. research staff will be secured and stored in an access controlled locked drawer (any paper forms) and password protected (electronic records). At the end of the study,

all study databases that are not already de-identified will be de-identified and archived at Medline Industries, Inc.

9.2.2. Safety Oversight

Given that this is a post-market study on a device used in accordance with its labeling, there is minimal safety risk to participants. The site investigators specialize in treating burn wounds and are qualified to provide adequate safety oversight for the study. In the event there any AEs or SAEs, the site investigator will review them any make any necessary safety determinations as needed.

9.2.3. Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The site investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents of any kind (electronic, paper, etc.) should be completed in accordance with Good Documentation Practices (GDP) to ensure accurate interpretation of data. CRFs will be created for each subject. The CRA will verify the data entered into the CRF with the site source regardless of the type of source. The site will be responsible for developing a written process that ensures the CRA is able view the source data.

Data from the CRFs will be entered into an electronic spreadsheet via dual-entry to assure no errors. Analyses will be conducted in the Statistical Analysis System, SAS® 9.4 of the SAS System for Windows. Copyright © 2013 SAS Institute Inc. This system allows for internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Medline Industries, Inc. will be responsible for overseeing final data analysis and confirmation of results.

9.2.4. Study Records Retention

Study documents should be retained until at least two years have elapsed since the formal discontinuation of the study intervention or as required by any applicable FDA guidelines or for a longer period if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the site investigator when these documents no longer need to be retained. The site investigator is required to notify Medline if the location of the stored documents is changed after it is defined at the time of the Close Out Visit at study end.

9.2.5. Study Discontinuation

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the site investigator, Sponsor, and IRB. If the study is prematurely terminated or suspended, the site investigator will promptly inform the IRB and Sponsor and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants as determined by AE review
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor and/or IRB.

9.2.6. Study Closeout

Upon completion of the study, Medline and/or its designees will notify the sites of closeout related procedures and will coordinate with the site the return of equipment and/or any unused product. Medline CRA will communicate closely with the site investigators at that time point and will review all close out steps and materials. All study data, related study documents, and unused study product, will be returned to the Sponsor. The site will also notify the IRB that the study has completed.

9.2.7. Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication or any aspect of this trial will be disclosed and managed.

9.3. Protocol Deviations

It is the responsibility of the site investigators and study staff to use continuous vigilance to identify and report deviations on a routine basis. All deviations must be addressed in study source documents, and reported to Medline Industries, Inc. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.4. Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations

CRA	Clinical Research Associate
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Documentation Practice
HIPAA	Health Insurance and Portability Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IRB	Institutional Review Board
NPWT	Negative Pressure Wound Therapy
SAE	Serious Adverse Event
STSG	Split-thickness skin graft
TBSA	Total body surface area

10. REFERENCES

1. Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, Natesan S, Chan RK,Christy RJ, Chung KK. Burn wound healing and treatment: review and advancements. Crit Care. 2015 Jun 12;19:243. doi: 10.1186/s13054-015-0961-2.
2. Fraser JR, Laurent TC, Laurent UB. Hyaluronan: its nature, distribution,functions and turnover. J Intern Med. 1997 Jul;242(1):27-33.
3. Voigt J, Driver VR. Hyaluronic Acid Derivatives and Their Healing Effect on Burns, Epithelial Surgical Wounds, and Chronic Wounds: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Wound Repair Regen. 2012 May-Jun;20(3):317-31.
4. Gravante G, Sorge R, Merone A, et al. Hyalomatrix PA in Burn Care Practice: Results From a National Retrospective Survey, 2005–2006. Ann Plast Surg. 2010;64(1):69–79.

11. APPENDIX

11.1. Hyalomatrix® Wound Device Instructions for Use

Corius® Tissue Regeneration

Hyalomatrix®
Hyaluronic Acid Wound Device

INSTRUCTIONS FOR USE

PRODUCT DESCRIPTION:

Hyalomatrix® is a bilayered, sterile, flexible and conformable hyaluronic acid wound device for advanced wound care. It is comprised of a non-woven pad made entirely of HYAFF®, a benzyl ester of hyaluronic acid, and a semi-permeable silicone membrane, which controls water vapor loss, provides a flexible covering for the wound surface, and adds increased tear strength to the device. The biodegradable matrix acts as a scaffold for cellular invasion and capillary growth.

As Hyalomatrix is applied on the wound bed, the HYAFF wound contact layer provides a 3D scaffold able to be colonized by fibroblasts and onto which extracellular matrix components are regularly laid down,facilitating an ordered reconstruction of the dermal tissue.

INDICATIONS FOR USE:

Hyalomatrix is indicated for the management of wounds including:

- Partial and full-thickness wounds
- Second-degree burns
- Pressure ulcers
- Venous ulcers
- Diabetic ulcers
- Chronic vascular ulcers
- Tunneled/undetermined wounds
- Surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence)
- Trauma wounds (abrasions, lacerations, skin tears)
- Draining wounds

CONTRAINDICATIONS

Individuals with hypersensitivity to hyaluronan and/or its derivatives and silicone.

WARNINGS AND PRECAUTIONS:

- Hyalomatrix does not possess intrinsic bacteriostatic or bactericidal properties; therefore, it should not be normally used on infected wounds. When wound infection is suspected, the treating physician should consider, as a standard pre-surgical practice and prior to product application, a topical antiseptic or antibiotic treatment associated with a systemic antibiotic course.
- When wound infection is suspected, daily inspection of the wound should be considered. Should the infection be confirmed, Hyalomatrix must be removed.
- Hyalomatrix is for single use only. Portions of unutilized product must be discarded. Sterility is guaranteed as long as the package is closed and undamaged.
- In case of damaged primary packaging, do not use the product and report to local distributor.

STORAGE

Store at room temperature.

INSTRUCTIONS FOR USE

APPLICATION INSTRUCTIONS:

1. Always handle Hyalomatrix using aseptic techniques.
2. Open the outer pouch and let the inner tray fall onto the sterile field.
3. Open the tray, gently remove the product.
4. Prepare wound bed using standard methods to ensure wound is free of debris and necrotic tissue. If necessary, surgically debride the wound to ensure the wound edges contain viable tissue.
5. Following wound bed preparation, immediately apply the device, keeping the fibrous HYAFF-based layer in contact with the wound bed. Hyalomatrix conforms well to wound edges and it can be cut to suit to the shape of the wound.
6. Hyalomatrix should be firmly secured using surgical clips, or other mechanical means.
7. Do not overlap adjacent Hyalomatrix units.
8. Once in place, cover Hyalomatrix with an appropriate non-adherent, secondary dressing. The optimum secondary dressing is determined by wound location, size, depth, and user preference. Secure with an appropriate absorbent secondary dressing.

POST-APPLICATION (DAY 1-14):

- Inspection of the wound bed is recommended every 3-4 days. During this time frame, patients normally experience a significant reduction in local pain. Frequently, Hyalomatrix forms a yellow-green colored gel that is sometimes characterized by a bad odor. This is the result of the normal degradation process of HYAFF and is not necessarily indicative of a local infection.
- Change secondary dressing as needed – the frequency of secondary dressing change will be dependent upon volume of exudates produced and type of dressing used.
- After the first week, weekly inspections of the wound bed may be sufficient to monitor the repair process.
- When the resorption/integration process of the HYAFF based material has progressed, a well-vascularized granulation tissue becomes clearly visible.
  Note: if excess exudates collect under the sheet, small openings can be cut in the sheet to allow fluid to drain.

REMOVAL (DAY 14-21):

- Removal of the silicone layer of Hyalomatrix is recommended when the tissue underneath is healed, or ready for grafting. Typically, this process occurs between 14 to 21 days after application.
- Remove by starting at one corner and pull gently. The silicone layer will easily peel off from the underlying healed tissue.
- It is not necessary to remove the remnants of HYAFF fibers which have not yet resorbed. Nevertheless, should one choose to remove such remnants, the wound should be rinsed with sterile saline prior to gentle removal of the remaining fibers using sterile forceps.
- In case of incomplete healing by day 21, a second application of Hyalomatrix or a tissue graft may be required.

AVAILABLE SIZES

Hyalomatrix is available in various presentations:

Re Order Number	Size	Pouch Count	Box Count
MSS4011	2.5 x 2.5 cm (1.0 x 1.0 in)	1 per pouch	10 per box
MSS4022	5 x 5 cm (2.0 x 2.0 in)	1 per pouch	10 per box
MSS4044	10 x 10 cm (3.9 x 3.9 in)	1 per pouch	1 per box
MSS4048	10 x 20 cm (3.9 x 7.9 in)	1 per pouch	1 per box
MSS4088	18 x 20 cm (7.0 x 7.9 in)	1 per pouch	1 per box

CAUTION:

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

REF MSS4011 REF MSS4022 REF MSS4044 REF MSS4048 REF MSS4088

www.medlinecorius.com