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PROSPECTIVE, MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL EVALUATING THE USE OF PRIMATRIX DERMAL REPAIR SCAFFOLD FOR THE MANAGEMENT OF DIABETIC FOOT ULCERS

Short Title: Efficacy of PriMatrix in the Management of Diabetic Foot Ulcers

Protocol Number: T- PMXDFU-01

Protocol Version: 5.0

Protocol Version Date: 06 Nov 2018

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Confidentiality Statement

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STATEMENT OF COMPLIANCE

By signing this document, I, the investigator, certify that this trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 11, 21 CFR Part 50, and 21 CFR Part 56)

Additionally, I and any clinical trial site staff who are responsible for the conduct, management, or oversight of this trial will complete Human Subjects Protection/ICH GCP Training.

The protocol, informed consent form(s), any recruitment materials, and/or all subject materials associated with this trial will be submitted to an Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is screened.

Finally, I understand that any amendments to the protocol or consent forms will require review and approval by the sponsor and IRB before the changes are implemented to the study.

Investigator Name

Investigator Signature Date

DEFINITIONS AND ABBREVIATIONS

TERM	DEFINITION
(ICH) GCP	(International Conference on Harmonisation) Good Clinical Practice
510(k)	The regulatory pathway companies use to obtain marketing clearance for Class II devices.
ABI	Ankle-Brachial Index
Active Treatment Group	The cohort which will be treated with the PriMatrix product in addition to standard of care materials and procedures. (See Section 5.17)
AE	Adverse Event, See Section 5.15 for Definitions
Anticipated	A determination of expectedness of a SAE that is related to the study product or procedures. (See Section 5.15.4)
BMI	Body Mass Index
CE Marked	A certification that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area.
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel test; a statistical test used in the analysis of data from this trial.
Complete Wound Closure	100% re-epithelialization of the ulcer surface without detectable exudate, confirmed on 2 consecutive study visits 1 week apart (i.e., Treatment Visit where 100% re-epithelialization of the ulcer surface without detectable exudate was initially documented and the Closure Confirmation Visit). (See Section 5.18)
Control Treatment Group [i.e., Standard of Care (SOC)]	The cohort that the active treatment group will be compared against. The terms Standard of Care (SOC) and Control Treatment are synonymous for this protocol. (See Section 5.11)
DFU	Diabetic Foot Ulcer
DM	Diabetes Mellitus
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
Female of child-bearing potential	A subject who is neither post-menopausal nor sterile, either naturally or through surgical methods.

TERM	DEFINITION
Full-Thickness	Refers to the depth of an ulcer in which both the epidermis and dermis are lost.
HbA_1c	Glycosylated Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
Integra	Integra LifeSciences Corporation, this study's sponsor
IRB	Institutional Review Board
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward; a method of analysis where certain values are missing in the data set.
MedDRA	Medical Dictionary for Regulatory Activities
MRU	Medical Resource Utilization
Partial-Thickness	Refers to the depth of an ulcer involving only a portion of the dermal layer of the skin and the entire epidermal layer of the skin.
Plethysmography	In this protocol, a synonym for toe pressure.
PP	Per-Protocol
PriMatrix	PriMatrix Dermal Repair Scaffold; The investigational product being studied in this trial. This term is synonymous with Active Treatment in this protocol.
QC	Quality Control
SAE	Serious Adverse Event, See Section 5.15.1 for definition
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
Sharp Debridement	The removal of all devitalized tissue involving the use of a knife, curette or blade. (See Section 5.9.1 for full debridement requirements)
SNF	Skilled Nursing Facility
SOC	Standard of Care; The terms Standard of Care and Control Treatment are synonymous for this protocol. (See Section 5.11)
SOP	Standard Operating Procedures

TERM	DEFINITION
SV	Screening Visit
$TcPO_2$	Transcutaneous Oxygen Pressure
TV	Treatment Visit
UADE	Unanticipated Adverse Device Effect
Unanticipated	A determination of expectedness of a SAE that is related to the study product or procedures. (See Section 5.15.4)
US(A)	United States (of America)
Wound	Also known as “ulcer”. In this protocol, the two terms are synonymous.

PROTOCOL SYNOPSIS

PROTOCOL TITLE	Prospective, multi-center, randomized, controlled trial evaluating the use of PriMatrix Dermal Repair Scaffold for the management of diabetic foot ulcers
PROTOCOL NO.	T-PMXDFU-01
PROTOCOL VERSION	05
PROTOCOL DATE	06 Nov 2018
SHORT TITLE	Efficacy of PriMatrix in the management of diabetic foot ulcers
DEVICES	PriMatrix, derived from fetal bovine dermis, is a dermal repair scaffold for the management of challenging ulcers. PriMatrix is rich in Type III collagen, a collagen that is active in developing and healing tissues. PriMatrix is a freeze-dried product that is stored at ambient conditions with a shelf life of five years.
INDICATIONS FOR USE	PriMatrix® is intended for the management of wounds that include: • Partial and full thickness wounds • Pressure, diabetic, and venous ulcers • Second-degree burns • Surgical wounds—donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence • Trauma wounds —abrasions, lacerations and skin tears • Tunneled/undermined wounds • Draining wounds PriMatrix is FDA 510(k) cleared (K061407, K083440, K100261, K131286, and K153690) for marketing in the United States and is also marketed in the European Union (CE Marked), Mexico, Canada, and many other countries.
STUDY SPONSOR	Integra LifeSciences Corporation 311 Enterprise Drive Plainsboro, NJ 08536, USA
SPONSOR CONTACT	Jessica Knowlton Manager, Clinical Research, Clinical Operations E-mail: Jessica.Knowlton@integralife.com Study Email: TPMXDFU1studymailbox@integralife.com
OBJECTIVE	The objective of this study is to evaluate the efficacy of PriMatrix in the management of diabetic foot ulcers (DFUs) in subjects with diabetes mellitus (DM) and without significantly compromised arterial circulation, in comparison to Standard of Care (SOC, i.e., Control) treatment. In addition to the efficacy data, safety associated with the management of DFUs will be evaluated, as well as medical resource utilization.
STUDY DESIGN	This is a multicenter, randomized, parallel-group clinical trial designed to establish the superior efficacy of the Active Treatment (PriMatrix) over that of SOC in achieving complete wound closure of DFUs in diabetic subjects with adequate arterial circulation. The study will have three phases: A Screening Phase, a Treatment Phase and a Follow-up Phase. All subjects will be seen weekly in the Screening and Treatment Phases. Subjects that have achieved complete wound closure during the treatment phase will be entered into the follow-up phase and will return to the site 4-weeks following the confirmation visit. Study enrollment

	will be paused once 50 subjects (25 in each treatment arm) have been enrolled in order to perform an early data review and an interim analysis is planned after 128 subjects have completed study participation. **<u>Screening Phase – 2 weeks ± 3 days (Max 17 days)</u>** Prior to any study-related procedures, subjects will sign the IRB/IEC approved informed consent form (ICF). Medical history will be obtained and clinical assessments performed to determine subject eligibility. Certain eligibility criteria will be reaffirmed on Screening Visit 2 and Randomization. Photographs and planimetric area evaluation will be performed to document ulcer area before and after debridement. The study ulcer will receive SOC daily for two weeks. **<u>Treatment Phase – up to 13 weeks ± 3 days (Max 94 days)</u>** **Randomization/Treatment Visit 1 (TV1)** Following the two-week screening phase, the subject will return to the clinic and physical assessments will be made to confirm the subject's final eligibility. The ulcer will be photographed, sharply-debrided (if necessary), and photographed again. Planimetric evaluation will be performed to determine the area of ulcer post debridement. Subjects who meet all eligibility criteria will be randomized 1:1 to receive either Active Treatment or Control Treatment. **Treatment Visits 2 through 13** After randomization, subjects will be evaluated weekly (7 ± 3 days). Assessments will include photographs of the study ulcers, investigator assessment of wound closure, and planimetric evaluations of ulcer area. Safety parameters will be documented, and Medical Resource Utilization data will be collected by reviewing subject source documentation and medical records and subject interviews. Subjects will receive Active or Control treatment for up to 13 weeks or until the study ulcer achieves confirmed complete wound closure. **<u>Follow-up Phase – 4-weeks ± 3 days (Max 31 days)</u>** Subjects with complete wound closure in the treatment phase will have a final study visit 4-weeks after the closure confirmation visit to evaluate if the ulcer has remained closed.
ENROLLMENT	Up to 30 centers in the US will randomize up to 256 subjects.
STUDY DURATION	A subject may participate in the study for up to 136 days in total, inclusive of the allowed time range for visits. Up to 30 centers will participate in this study and it is anticipated that each site will enroll approximately 0.5 subject/month. Based on this estimation, 256 subjects will be randomized and complete the study in 30 months.
STUDY CONDUCT	This study will be conducted with adherence to current standards; these include good clinical practice (GCP) requirements and the applicable regulatory requirements.

SUBJECT ELIGIBILITY CRITERIA	**Inclusion Criteria** Subjects are required to meet all of the following criteria for enrollment into the study and subsequent randomization: 1. The subject has signed and dated an informed consent form. 2. In the opinion of the investigator, subject is able and willing to comply with study procedures, including study visits, study dressing regimens and compliance with study required off-loading device. 3. The subject is ≥ 18 years of age. 4. The subject, if female of child-bearing potential, must not be pregnant. To document pregnancy status, subject statement is acceptable. 5. The subject has Type I or Type II diabetes mellitus with investigator-confirmed glycosylated hemoglobin (HbA_1c) of ≤ 12% within 3 months prior to screening visit 1. 6. The subject has at least one diabetic foot ulcer that meets ALL of the following criteria: • Ulcer which has been in existence for a minimum of two weeks, prior to signing the Informed Consent Form for trial participation. • Ulcer is a partial or full thickness diabetic foot ulcer without capsule/tendon/bone exposure. • Ulcer does not have tunneling, undermining, or sinus tracts that necessitates surgical OR debridement and/or penetrates to capsule/tendon/bone. • Ulcer is located on the foot or ankle (with no portion above the top of the malleolus). • Ulcer size (area) is $\geq$ 1 cm^2 and $\leq$ 12 cm^2 post-debridement. 7. There is a minimum 1 cm margin between the qualifying study ulcer and any other ulcer on that same foot, post-debridement. • If the subject has more than one ulcer that meets the eligibility criteria, the ulcer designated as the study ulcer will be at the discretion of the investigator. 8. The subject has adequate vascular perfusion of the affected limb as defined by at least one of the following: • Ankle-Brachial Index (ABI) ≥ 0.65 or ≤1.2, performed within 3 months of screening, • Toe pressure (plethysmography) > 50 mmHg at time of screening, • $TcPO_2$ > 40 mmHg at time of screening 9. The subject or responsible caregiver is willing and able to maintain required applicable dressing changes as well as study required off-loading/protective device for the duration of the study. **Exclusion Criteria** Subjects will not be enrolled in the study if any of the following criteria are met: 1. The subject was previously randomized and treated under this clinical study protocol.

	2. The subject has suspected or confirmed gangrene or ulcer infection of the study ulcer or receiving systemic antibiotics for the treatment of such. 3. The subject has suspected or confirmed osteomyelitis of the foot with the study ulcer. 4. The subject has a history of hypersensitivity to bovine collagen, as determined by prior medical history. 5. The subject has participated in another clinical trial involving a device or a systemically administered investigational study drug/treatment within 28 days of randomization. 6. The subject has received, within 28 of signing Informed Consent Form, or is scheduled to receive during study participation, a medication or treatment which is known to interfere with or affect the rate and quality of ulcer healing (e.g., systemic steroids, immunosuppressive therapy, autoimmune disease therapy, dialysis, radiation therapy to the foot, vascular surgery, angioplasty, or thrombolysis). 7. The subject has a history of bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or has had chemotherapy within the 12 months prior to signing Informed Consent Form for trial participation. 8. In the opinion of the investigator, the subject has a history of, or is currently diagnosed with, any illness or condition, other than diabetes, that could interfere with ulcer healing (e.g., end-stage renal disease, severe malnutrition, liver disease, aplastic anemia, connective tissue disorder, acquired immune deficiency syndrome, HIV positive, or sickle cell anemia). 9. In the opinion of the investigator, the subject has unstable Charcot foot or Charcot with bony prominence that could inhibit ulcer healing. 10. The subject has ulcers secondary to a disease other than diabetes (e.g., vasculitis, neoplasms, or hematological disorders). 11. In the opinion of the investigator, the subject has excessive lymphedema that could interfere with off-loading and/or ulcer healing. 12. The study ulcer has received ulcer dressings that included growth factors, engineered tissues, or skin substitutes within 28 days of randomization or is scheduled to receive treatment during the study (e.g., Regranex, Dermagraft, Apligraf, EpiFix, GraftJacket, OASIS, Omnigraft, or Integra BMWD). 13. At the end of the screening phase and based on planimetric assessment, the area of the study ulcer after sharp debridement has decreased by more than 30% over the two-week screening period.
ENDPOINTS	**<u>Primary Endpoint</u>** The primary endpoint of this study is the incidence of complete wound closure, as assessed by the investigator at or before Week 12 of the treatment phase.
	<u>Secondary Endpoints</u> 1. Proportion of subjects with complete closure of the study ulcer at or before Week 12 as assessed by computerized planimetry. 2. Time to complete wound closure, as assessed by the investigator. 3. Time to complete wound closure, as assessed by computerized planimetry. 4. Rate of wound closure, as assessed by computerized planimetry.

	Safety Endpoints Incidence of all adverse events (AEs) related to the study treatment, study ulcer or study procedures and all serious adverse events (SAEs). **Exploratory Endpoints** Medical resource utilization associated with treatment of DFU and related complications, including: • Interference of activities of daily living • Interference of paid work (full-time or part-time)/school • Physician office visits • Emergency room visits • Hospitalizations • Home health nursing visits • Skilled nursing facilities (SNF) • Procedures • Medication regimens to treat complications (analgesics, antibiotics, etc.) • Diagnostic tests, imaging, etc. • Treatment of AEs • Use of durable medical equipment (off-loading/protective device, crutches, wheelchair, etc.) • Dressing regimen and materials • wound closure/healed status at the 4-week Follow-up visit
DATA COLLECTION	The following data will be collected: • Medical Resource Utilization information • Demographics • Medical history • Medications and non-study treatments • AEs • Physical examination • Vascular perfusion tests, vital signs • Ulcer assessments & treatments • Supplies Usage • Duration, size, exudate, location, infection, percent re-epithelialization (Documented or measured using clinical judgment, photography, and/or computerized planimetry)
STATISTICAL METHODS	This is a prospective, multicenter, parallel-group, randomized, controlled trial designed to establish the superior efficacy of the Active Treatment (PriMatrix Dermal Repair Scaffold) over SOC in achieving complete wound closure of DFUs in a population with adequate arterial circulation. Subjects will be randomized 1:1, stratified by site and ulcer area, to receive either the Active Treatment or SOC. **Sample Size** 102 subjects in each treatment group, for a total of 204 subjects for the study, yields the 80% power required to demonstrate superiority of the Active Treatment to SOC in the proportion of subjects whose ulcer has closed by Week 12, assuming:

	1. 46% of DFUs managed with the Active Treatment achieve complete wound closure by 12 weeks. 2. 26% of DFUs managed with SOC achieve complete wound closure by 12 weeks. To accommodate the potential early discontinuations, the trial proposes to randomize 256 subjects (128 per treatment). Overall 2-sided Type I Error rate (alpha) of 0.05. A single interim analysis, when 50% of subjects complete the trial, will be performed using group-sequential methods and Pocock alpha spending function, the hypotheses will be tested at a two-sided alpha of 0.031. A two-sided alpha of 0.028 will be used to test the hypothesis at the final analysis. **Data Evaluation** **Analysis Population** The Intent-to-Treat (ITT) population, defined as all randomized subjects, will be the primary population for the analysis of primary and secondary efficacy endpoints. The Per Protocol (PP) population, defined as all subjects who were not associated with a major protocol violation, will be used in supportive analyses of the primary and secondary endpoints. In all efficacy analyses, covariate analyses will be conducted to assess the impact of various prognostic factors on closure and also to demonstrate the robustness of the primary analysis. Prognostic factors (i.e., covariates) will be included if they are found to be contributing factors (i.e., the individual covariate p-value is less than 0.05). Potential prognostic factors to be considered include: • Ulcer area • Age of Ulcer at Baseline • Gender • HbA_1c • Ulcer location • Diabetes type • Race • Nicotine Use • Baseline BMI
	Primary Efficacy Analysis The primary analysis will test the difference between the proportion of subjects who achieve complete wound closure by 13 weeks in the Active Treatment and SOC using the *Cochran–Mantel–Haenszel (CMH)* test. For the primary efficacy analysis, missing values will be imputed using last observation carried forward (LOCF).

	Secondary Efficacy Analyses Proportion of ulcers with complete wound closure during the treatment phase as assessed by computerized planimetry will be compared using Logistic Regression with the stratification factors in the model. Time to complete wound closure will be analyzed using log rank test or Cox proportional regression model. Kaplan-Meier methods will be used to present median time to complete wound closure. Analysis of Covariance will be used to compare the rate of wound closure for the two treatment groups. **Safety Analyses** AEs related to the device, study ulcer and/or study procedures and all SAEs will be recorded. All safety parameters will be summarized descriptively by treatment assignment. No inferential statistics are planned. **Exploratory Analyses** Exploratory analyses will be performed to examine patterns of medical resource utilization by treatment group and to estimate the diabetic foot ulcer related treatment costs by treatment. Additionally, wound closure status at the 4-week Follow-up visit will be evaluated. **Early Data Review** An early data review will be performed when 50 patients reach the primary endpoint. The purpose of this review is to ensure the study execution is as originally planned, and therefore, no alpha spending is involved. **Interim Analysis** A single interim analysis will be performed when 50% of subjects complete the study. Employing a group-sequential design with a Pocock alpha spending function, the following decisions will be made at the interim analysis with respect to the efficacy outcome: • Stop the study due to demonstrating statistically significant superiority of the Active Treatment to SOC if the two-sided p-value testing the stated hypotheses is ≤ 0.031 and the difference is in favor of the Active Treatment. • Stop the study due to demonstrating futility of the Active Treatment to SOC if the two-sided p-value testing the stated hypotheses is ≤ 0.031 and the difference is in favor of SOC.

	• Continue the study if the two-sided p-value testing the stated hypotheses is > 0.031. With this design and assuming the 46% of DFUs managed with the Active Treatment achieve complete wound closure by 13 weeks and 26% achieve complete wound closure when managed with SOC, the probability of stopping early due to showing superiority with the Active Treatment is 0.479. If the decision at the interim analysis is to continue the study, the hypotheses at the end of the study will be tested at a two-sided alpha level of 0.028 to maintain an overall two-sided alpha of 0.05. Further, conditional power will be calculated at the interim analysis for predicting the final study success. In case more data information is needed, appropriate sample size re-estimation will be considered in order to meet the final study objective.

1. Introduction

1.1. Background

Diabetic foot ulcers (DFUs) are a major health complication that affects up to 15% of individuals with diabetes mellitus (DM) over their lifetime. The treatment of DFUs is an extremely challenging task, as these ulcers may be recalcitrant to SOC modalities and may become infected. It is estimated that approximately 15% of all DFUs will result in a lower extremity amputation and develop concomitant medical complications that are associated with increased mortality rates.[1–4]

DFUs not only have a detrimental effect on a person's quality of life,[5,6] but also pose a significant burden on the health care system. It is estimated, in the USA alone, that the annual cost associated with the management of DFUs is as high as $13 billion, which is in addition to the costs associated with DM itself.[7]

1.2. Clinical Use of PriMatrix to Treat Diabetic Foot ulcers

Advanced ulcer therapies have become an important strategy in the treatment of hard-to-heal chronic DFUs. Since FDA clearance in 2006, more than 45,000 units of PriMatrix Dermal Repair Scaffold (Integra LifeSciences Corporation, Plainsboro, NJ) have been shipped and to be used in the management of ulcers. Both prospective and retrospective studies conducted in practices and centers around the country have demonstrated the clinical benefit of using PriMatrix to manage DFUs.

In a recent single-arm study led by the Mayo Clinic in Rochester MN, 64% of ulcers managed with PriMatrix achieved closure in a 12-weektime period.[8] In a head-to-head comparison against Apligraf (Organogenesis, Canton, MA), an alternate cellular and tissue based product, PriMatrix managed ulcers achieved closure in half the time as Apligraf treated ulcers.[9] Furthermore, by matching product size to ulcer size and requiring fewer applications, significant cost savings could be attributed to the use of PriMatrix over Apligraf. Additionally, the success of PriMatrix in managing complicated DFUs has been reported to reduce the incidence of amputation thus avoiding associated costs and improving patient quality-of-life.[10–12]

1.3. PriMatrix Description

PriMatrix, derived from fetal bovine dermis, is a unique dermal repair scaffold for the management of challenging ulcers. PriMatrix is rich in Type III collagen, a collagen active in developing and healing tissues.[13]

The scientific foundation for PriMatrix is well-documented and has been discussed at length in multiple review articles that highlight the differentiating characteristics of PriMatrix.[13–15] This scaffold has been identified for its superior biocompatibility, ability to trap and bind the recipient's own cells and growth factors within the matrix, and to rebuild dermis capable of supporting re-epithelialization.[11,16]

PriMatrix is freeze-dried and may be stored at ambient conditions with a shelf life of five years.

1.4. PriMatrix Indication

PriMatrix is FDA 510(k) cleared (K061407, K083440, K100261, K131286, and K153690) for marketing in the United States and is also marketed in the European Union (CE Marked), Mexico, Canada, and many other countries.

PriMatrix® is intended for the management of wounds that include:

- Partial and full thickness wounds
- Pressure, diabetic, and venous ulcers
- Second-degree burns
- Trauma wounds — abrasions, lacerations and skin tears
- Surgical wounds — donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence
- Tunneled/undermined wounds
- Draining wounds

2. Study Objective

The objective of this study is to evaluate the efficacy of PriMatrix Dermal Repair Scaffold in the closure of DFUs in subjects with DM and without significantly compromised arterial circulation in comparison to Control treatment. In addition to the efficacy data, safety associated with the management of DFUs will be evaluated, as well as medical resource utilization data.

3. Study Design

This is a multicenter, randomized, open-label, parallel-group clinical trial designed to establish the superior efficacy of PriMatrix over that of Control treatment in the management of DFUs in subjects with DM and adequate arterial circulation. Study enrollment will be paused once 50 subjects (25 in each treatment arm) have been enrolled in order to do an early data review. There will also be an interim analysis after 128 subjects have completed their study requirements.

3.1. Treatment Groups (Further defined in Section 5)

- Active Treatment – PriMatrix Dermal Repair Scaffold + Standard of Care
- Control Treatment – Standard of Care

3.2. Study Phases

3.2.1. Screening Phase

After the informed consent process is complete, medical history will be collected and clinical assessments will be performed to determine subject eligibility for the study. If the required eligibility criteria are met, the subject will begin the two-week screening phase. During this phase, the subject will receive the control treatment as defined in Section 5. During the two-week screening phase, the investigator will determine if the subject continues to meet all eligibility criteria, and if confirmed, the subject will be randomized and enter the treatment phase. For detailed information, see Figure 1 and Table 3 below.

3.2.2. Treatment Phase

Subjects will be randomized to receive the Active or Control Treatment in a 1:1 scenario (details can be found in Section 8.4). Efficacy evaluations during this phase include weekly investigator assessments of wound closure and planimetric evaluations of ulcer area. Safety evaluations will include AE assessments at each visit. Additionally, collection of medical resource utilization (MRU) data will occur. The randomized study treatment will be administered for up to 12 weeks or until the study ulcer has closed, as assessed by the investigator.

At the end of the treatment phase, subjects, all of whom will be considered treatment phase completers, will be assigned to one of two outcomes:

- Subjects with confirmed closed ulcers will be considered treatment successes.

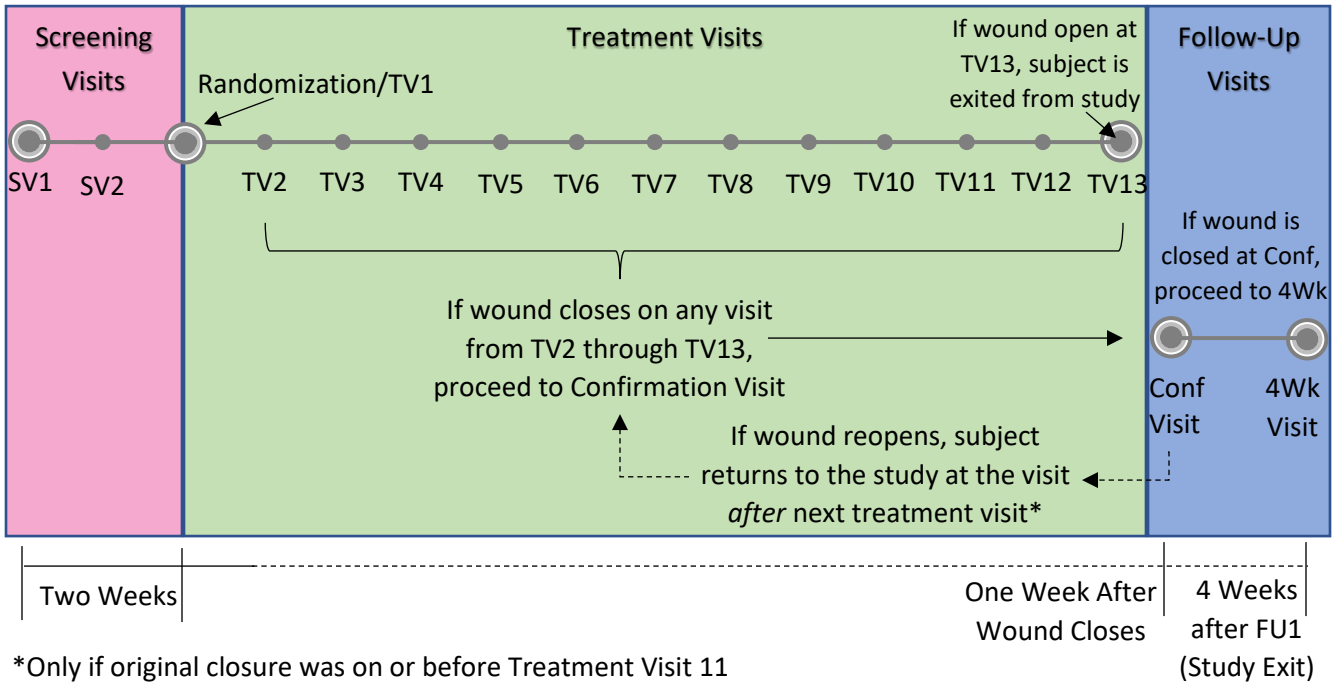
- Subjects with open ulcers at the end of the treatment phase will be considered treatment failures.

Unscheduled Visits (i.e., those not specifically scheduled per protocol) are at the discretion of the investigator. If the unscheduled visit is for treatment of the target ulcer, data for that visit will be collected and reported on the Unscheduled Visit eCRF page. For detailed information, see Figure 1 and Table 3 below.

3.2.3. Follow-up Phase

Subjects whose ulcer is confirmed closed at the Confirmation Visit (i.e., 1 week after closure is observed) will return to the clinic 4-weeks later for a follow-up visit (28 ± 3 days) to evaluate if the ulcer has remained closed. For detailed information, see Figure 1 and Table 3 below.

Figure 1: Study Design



*Only if original closure was on or before Treatment Visit 11

3.3. Study Duration

A subject can participate in the study for up to 136 days in total with the allowed time range for visits during the treatment phase.

4. Study Population: Eligibility Criteria

4.1. Inclusion Criteria

Subjects are required to meet all of the following criteria for enrollment into the study and subsequent randomization:

1. The subject has signed and dated an informed consent form.
2. In the opinion of the investigator, subject is able and willing to comply with study procedures, including study visits, study dressing regimens and compliance with study required off-loading device.
3. The subject is ≥ 18 years of age.
4. The subject, if female of child-bearing potential, must not be pregnant. To document pregnancy status, subject statement is acceptable.
5. The subject has Type I or Type II diabetes mellitus with investigator-confirmed glycosylated hemoglobin (HbA_1c) of ≤ 12% within 3 months prior to screening visit.
6. The subject has at least one diabetic foot ulcer that meets ALL of the following criteria:
   - Ulcer which has been in existence for a minimum of two weeks, prior to signing the Informed Consent Form for trial participation.
   - Ulcer is a partial or full thickness diabetic foot ulcer without capsule/tendon/bone exposure.
   - Ulcer does not have tunneling, undermining, or sinus tracts that necessitates surgical OR debridement and/or penetrates to capsule/tendon/bone.
   - Ulcer is located on the foot or ankle (with no portion above the top of the malleolus).
   - Ulcer size (area) is $\geq$ 1 cm^2 and $\leq$ 12 cm^2 post-debridement.
7. There is a minimum 1 cm margin between the qualifying study ulcer and any other ulcer on that same foot, post-debridement.
   - If the subject has more than one ulcer that meets the eligibility criteria, the ulcer designated as the study ulcer will be at the discretion of the investigator.
8. The subject has adequate vascular perfusion of the affected limb as defined by at least one of the following:
   - Ankle-Brachial Index (ABI) ≥ 0.65 or ≤1.2, performed within 3 months of screening,
   - Toe pressure (plethysmography) > 50 mmHg at time of screening,
   - $TcPO_2$ > 40 mmHg at time of screening
9. The subject or responsible caregiver is willing and able to maintain required applicable dressing changes as well as study required off-loading/protective device for the duration of the study.

4.2. Exclusion Criteria

Subjects will not be enrolled in the study if any of the following criteria are met:

1. The subject was previously randomized and treated under this clinical study protocol.
2. The subject has suspected or confirmed gangrene or ulcer infection of the study ulcer or receiving systemic antibiotics for the treatment of such.
3. The subject has suspected or confirmed osteomyelitis of the foot with the study ulcer.
4. The subject has a history of hypersensitivity to bovine collagen, as determined by prior medical history.

5. The subject has participated in another clinical trial involving a device or a systemically administered investigational study drug/treatment within 28 days of randomization.
6. The subject has received, within 28 of signing Informed Consent Form, or is scheduled to receive during study participation, a medication or treatment which is known to interfere with or affect the rate and quality of ulcer healing (e.g., systemic steroids, immunosuppressive therapy, autoimmune disease therapy, dialysis, radiation therapy to the foot, vascular surgery, angioplasty, or thrombolysis).
7. The subject has a history of bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or has had chemotherapy within the 12 months prior to signing Informed Consent Form for trial participation.
8. In the opinion of the investigator, the subject has a history of, or is currently diagnosed with, any illness or condition, other than diabetes, that could interfere with ulcer healing (e.g., end-stage renal disease, severe malnutrition, liver disease, aplastic anemia, connective tissue disorder, acquired immune deficiency syndrome, HIV positive, or sickle cell anemia).
9. In the opinion of the investigator, the subject has unstable Charcot foot or Charcot with bony prominence that could inhibit ulcer healing.
10. The subject has ulcers secondary to a disease other than diabetes (e.g., vasculitis, neoplasms, or hematological disorders).
11. In the opinion of the investigator, the subject has excessive lymphedema that could interfere with off-loading and/or ulcer healing.
12. The study ulcer has received ulcer dressings that included growth factors, engineered tissues, or skin substitutes within 28 days of randomization or is scheduled to receive treatment during the study (e.g., Regranex, Dermagraft, Apligraf, EpiFix, GraftJacket, OASIS, Omnigraft, or Integra BMWD).
13. At the end of the screening phase and based on planimetric assessment, the area of the study ulcer after sharp debridement has decreased by more than 30% over the two-week screening period.

5. Description of Protocol Assessments & Procedures

5.1. Informed Consent and HIPAA Authorization

Written informed consent will be obtained from each subject before any study-related procedures may commence. Informed consent will be obtained by the investigator or designee at each study site. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has been provided a signed and dated ICF as well as the required site HIPAA authorization (if separate from the ICF).

5.2. Inclusion/Exclusion Criteria

Site staff and the investigator will document the date of ICF signature and review all of the inclusion and exclusion criteria with respect to the potential subject in question. Review of

criteria may require sites to review the potential subject's medical records or ask questions of the potential subject. All questions relevant to the visit must be answered at that visit for the subject to be able to proceed with that and future visits.

5.3. Medical Resource Utilization (MRU)

Standardized assessments to document MRU (e.g., physician services, treatment/procedures, medications, etc.) required to manage the subject's current DFU will be performed by a review of the subject's source document/medical record and by the investigator or designee completing an interview with the subject.

The MRU assessment should be performed prior to any other study procedures or assessments in order to minimize bias.

The following information will be collected related to the DFU and its care:

- Physician office visits
- Emergency room visits
- Hospitalizations
- Home health nursing visits
- Skilled nursing facilities
- Procedures
- Diagnostic tests, imaging, etc.
- Treatment of AEs
- Interference with activities of daily living
- Interference with paid work (full-time or part-time)/school
- Use of durable medical equipment (e.g., off-loading/protective device, crutches, wheelchair, etc.)
- Dressing regimen and materials

5.4. Baseline Demographics

For the purposes of this study, demographic information will include:

- Date of birth
- Gender
- Race
- Ethnicity
- Use of nicotine products
- Use of alcohol

5.5. Medical History

The site will assess and document the DM type (Type 1 or Type 2) and date/year of diagnosis. Subject's HbA_1c level and date of test must be recorded (***Note: The test results must be valid within 3 months of SV1 and must be in existence on SV1***).

In addition to diabetic status, additional medical history that, in the opinion of the investigator, is ***relevant to the safety of the subject or that could impact diabetic foot ulcer healing*** is to be recorded (i.e., obesity, neuropathy, etc.).

Relevant medical histories will be recorded using the body system categories outlined below:

- Cardiovascular
- Lymphatic
- Respiratory
- Hematologic
- Gastrointestinal
- Immunologic
- Renal
- Dermatologic
- Hepatic
- Psychiatric
- Neurological (Including Neuropathy)
- Genitourinary
- Endocrine
- Other

For each relevant medical history, the following will be documented:

- Condition (i.e., name of disease/disorder)
- Medical History Category (e.g., general medical history, surgical procedure, other)
- Date/ Year of Onset
- Status (i.e., resolved or ongoing)

5.6. Physical Examination

The physical examination will include routine examinations for the following:

- Abnormalities of the extremities
- Neurologic abnormalities (Including Neuropathy)
- Heart/cardiovascular abnormalities
- Musculoskeletal abnormalities
- Dermatologic abnormalities
- Other abnormality (i.e., any other body system for which an abnormality is noted and which, in the opinion of the investigator, is relevant to the safety of the subject or could impact ulcer healing should be considered clinically significant.)
- Height (inches) & Weight (pounds)

Each abnormality will be recorded, and the investigator will record an assessment of its clinical significance. ***Any abnormality noted at SV1 should be listed on the medical history eCRF, if relevant***. If an abnormality presents later in the trial, it should be listed as an AE if it meets the criteria in Section 5.15.

5.6.1. Physical Examination

Only one of the following assessments is required to verify adequate perfusion of the affected limb; however, more than one test may be performed to determine eligibility. The assessment chosen is at the discretion of the investigator; however, the acceptability of parameters of each test must be followed as stated below.

5.6.1.1. Ankle-Brachial Index (ABI)

ABI, if conducted, will be determined on the affected side (i.e., the side of the body on which the study ulcer resides) according to standard procedure/protocol at the study site.

If ABI is ≥ 0.65 or ≤ 1.2, then vascular perfusion is considered adequate. An ABI measurement that has been collected within 3 months of screening is acceptable.

5.6.1.2. Systolic Pressure of the Great Toe

The systolic pressure of the great toe of the affected foot (i.e., the foot on which the study ulcer resides) will be obtained while the subject is sitting. If toe pressure is > 50mmHg, then vascular perfusion is considered adequate. This must be done at SV1; previous measurements are not accepted.

5.6.1.3. Transcutaneous Oxygen Pressure

Transcutaneous Oxygen Pressure ($TcPO_2$) will be determined according to standard procedure/protocol at the study site. If $TcPO_2$ is > 40mmHg, then vascular perfusion is considered adequate. This must be done at SV1; previous measurements are not accepted.

5.6.2. Number and Location of Study Ulcer(s)

The number and location of any and all DFUs will be documented during the physical exam.

5.7. Ulcer Assessments

5.7.1. Extent and Location of Ulceration

On SV1, the date that the ulcer was first observed will be documented.

Documentation of tunneling, undermining, or sinus tracts that necessitates surgical debridement in the OR and/or penetrates to capsule/tendon/bone is required. Additionally, a determination of whether the ulcer is partial or full thickness and if there is exposure of capsule, tendon, or bone will be documented.

The location of the study ulcer will be documented according to foot (left or right), surface (plantar or dorsal), and area (forefoot, midfoot, hindfoot [with the hindfoot area to include the calcaneus], ankle [with no portion above the top of the malleolus]).

If the subject has more than one qualifying DFU, the ulcer designated as the study ulcer will be at the discretion of the investigator.

5.7.2. Ulcer Exudate Assessments

The investigator will determine the amount and type, if any, of study ulcer exudate. In determining the amount of study ulcer exudate, the investigator must take into account the amount of exudate absorbed into the study ulcer dressing. The following categories will be used to quantify the amount of ulcer exudate:

- Not applicable: No exudate
- Minimal amount
- Light (scant) or small amount
- Moderate amount
- Heavy/large/copious amounts

The following categories will be used to describe the type of exudate:

- Serous: clear or light yellow watery plasma
- Serosanguineous: pink to light-red watery plasma
- Sanguineous: red with fresh bleeding
- Purulent: thick and opaque exudate, of creamy yellow, green, white, or tan color

5.7.3. Ulcer Infection Assessment

The presence/absence of infection at the study ulcer site will be documented at each visit.

IMPORTANT: If the study ulcer is considered infected during the screening phase, or at Randomization visit (TV1), the subject is considered a screen fail and is excluded from participation in the trial at that time. The infection must be treated, and symptoms resolved before the subject may be re-screened (one time only, according to Section 6.1.2). Additionally, and per exclusion criterion 2, the subject must not be taking antibiotics for a DFU infection.

If the study ulcer becomes infected after the subject is randomized, it must be recorded as an AE. The study ulcer infection may be treated, per investigator judgement, and the subject may remain in the study unless a prohibited medication or treatment is used (see Section 5.14.1).

PriMatrix is contraindicated for infected ulcers. In the event of a study ulcer infection in the PriMatrix treatment group, PriMatrix may be re-applied after the study ulcer infection has been treated and no longer demonstrates signs/symptoms of the infection.

All infections will be followed until resolved or the subject is withdrawn or discontinued. If an infection progresses to tissue necrosis requiring deep debridement which exposes bone, tendon or capsule, the subject must be withdrawn.

In no case, does the presentation of infection alter the study schedule of events nor allow the subject additional days of treatment.

5.8. Study Ulcer Photography

Photographs of the study ulcer are required at each visit except Unscheduled Visits. The investigator will take a digital photograph using the study-supplied imaging system. ***At minimum, pre-debridement photographs of the study ulcer are to be taken at every visit.***

Additionally:

- ***At SV1 and Randomization/TV 1 (Day 0), post-debridement images are required.***
- ***Further, and if the subject is randomized to the Active Treatment cohort, photographs of the PriMatrix product after application are required.***

Ulcer photographs are being obtained for ulcer measurements, documentation, and archival purposes and may also be used in educational and/or marketing materials.

Note: Specific imaging instructions are explained in a separate manual.

5.9. Sharp Debridement

Only sharp debridement is permitted in this study and includes debridement of all non-living or contaminated tissue from the wound bed. All callus should be removed, and any undermined or tunneled areas explored to ensure exposure of the full wound bed. Broad area cauterization should be avoided. Anesthetics are permitted during debridement.

IMPORTANT: Sharp debridement of the study ulcer is required at SV1 and Randomization/TV 1 (Day 0).

Sharp debridement includes removal of:

- the surrounding callus
- All non-viable tissue, as evidenced by punctate bleeding across the wound bed

At visits other than SV1 and Randomization and if needed, sharp debridement should be performed to:

- Remove callus or devitalized tissue
- Remove infected tissue

Whenever debridement is performed, details of debridement will be captured on the eCRF (i.e., reason(s) for performing debridement, type of debridement performed, and method used for debridement).

5.9.1. Debridement Certification

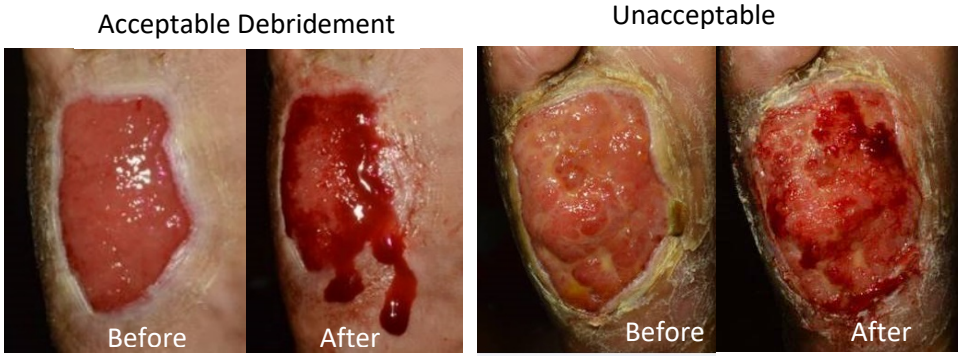
Each investigator and sub-investigator who will be debriding subjects for the trial is required to complete debridement certification prior to debriding subjects.

Certification will consist of the investigator providing a photograph of a non-study patient* they have debrided. This photograph will be evaluated by the Lead investigator or sponsor approved personnel. If debridement is acceptable, the investigator/sub-investigator will receive documentation of approval from the sponsor. If debridement is not acceptable, feedback will be provided to the investigator/sub-investigator and the process will be repeated. This will continue until the debridement technique is satisfactory. Satisfactory verification of training must occur prior to enrollment of first subject.

* *An exception may be made in the case of an ethics board that does not allow for transmission of images for non-study subjects. In this case, the first study subject debrided by the investigator will serve as the certification subject. If the debridement on this subject is not certified, the subject is screen failed. As above, the process repeats until a sufficiently debrided image is produced.*

The images in figure 2 have been supplied to provide examples of acceptable and unacceptable debridement.

Figure 2: Images of Acceptable Debridement



5.10. Ulcer Measurements

5.10.1. Computerized Planimetry

Ulcer measurements are required at each visit. The study DFU area will be determined by computerized planimetric analysis of digital photographs using software created by an external vendor.

The software allows the user to capture digital ulcer images and generate area measurements. Data collected by the software will be uploaded to a central server. All ulcer assessment data will be organized as a patient record on a central server and available for review and reporting. To ensure consistency between sites, training for procedures will be provided by a representative from the external vendor or by a trained sponsor representative. A manual containing information regarding how to use the software will be provided to the sites.

In addition, measurements will be performed by the investigator or qualified site staff at each visit.

5.10.2. Ulcer Area Reduction

Percent change in study ulcer area from the post-debridement SV1 to post debridement randomization will be calculated by the imaging vendor using computerized planimetry of images taken of the ulcers.

At the Randomization/TV 1 (Day 0), ulcer area reduction will be used to qualify the subject for randomization and study enrollment. ***The reduction in study ulcer area may not exceed 30% after sharp debridement in order for the subject to be randomized.***

5.11. Standard of Care (Control) Treatment

During the Screening Phase of the study, all subjects will have SOC products applied by the investigative site at the weekly visits. They will be then instructed on how to change their dressings on a daily basis. After randomization, only subjects who are randomized to the SOC cohort will continue daily dressing changes. Those subjects in the Active Treatment cohort will only have their dressings changed weekly at follow-up visits until the investigator determines that their wound has closed. If the wound closes on or before treatment visit 13, offloading (if previously utilized for that subject) will continue *without* dressings during the follow-up period.

Application of the dressings & boot by the Investigator:

1. Gently remove any dressing previously applied to the wound and clean the area with a gentle cleanser.
2. If appropriate, debridement and hemostasis will be performed. (Note: in this study only sharp debridement will be used)
3. During Screening and for SOC-randomized subjects: Instruct the subject on the proper way to change dressing
    - Inspect the wound and perform study assessments as directed elsewhere
4. Apply normal saline gel to the thickness of a coin.
5. Cover the gel with a foam dressing.
6. Secure the foam dressing with conforming roller gauze.
7. Cover the roller gauze with Coban.
8. For subjects who have ulcers that require offloading, apply the boot.

Daily Changing of the Dressings by the Subject:

1. Remove boot, if applicable
2. Gently remove dressings
3. Clean the wound with tap water and pat the area dry

4. Inspect the wound
    a. Subject will contact the site by phone if they believe there is anything wrong with the wound.
5. Apply normal saline gel to the thickness of a coin.
6. Cover the gel with a foam dressing.
7. Secure the dressings with conforming roller gauze.
8. Cover the roller gauze with Coban.
9. For subjects who have ulcers that require offloading, re-apply the boot.

Note: Subjects who use the offloading boot will be instructed that it is to be worn **at all times** except when bathing or sleeping.

5.12. Compliance with Offloading & Dressing Changes

At SV1, and as indicated in Section 5.11 above, subjects will be instructed on the proper use of the off-loading/protective device and in the proper procedures for dressing changes and care as required by the treatment assignment. At SV2 through TV13 and unscheduled visits, the subject will be queried about their compliance with dressing changes and offloading, as prescribed. If subject non-compliance is noted, documentation of the incident will be recorded. If continued non-compliance is detected, the subject may be withdrawn from the study at the discretion of the investigator and/or sponsor.

5.13. Appropriate Off-loading/Protective Device

The off-loading/protective device to be used in this study will be provided by the sponsor through a specific distributor. This off-loading/protective device will be used by all subjects with study ulcers located on the plantar or lateral surfaces of the foot (i.e., any location experiencing weight-bearing or shear forces) throughout the Screening, Treatment and Follow-up phases.

All subjects enrolled in this study are required to use the sponsor-provided off-loading/protective device for the duration of their participation (see Inclusion Criteria 9).

Off-loading devices MUST be continually used throughout the entire duration that the subject is enrolled in the study.

Note: If a subject is wheelchair bound, meaning that their primary form of locomotion is in the wheelchair, the offloading boot will not be required. If at any point in time, the subject ceases to be wheelchair bound, they will begin using the offloading boot if necessary.

Subjects with ulcers located on non-weight bearing surfaces (i.e., the dorsum of the foot) may use the provided off-loading boot as a protective device or may use another form of protective foot wear. The off-loading/protective device used will be noted in the eCRF.

Complete compliance information on the use of the off-loading/protective device by the subject will be collected by the study staff at each visit via subject interviews. Off-loading information collected will include type of off-loading/protective device used, number of hours per day that the device was not used since the last study visit and what proportion of that time involved weight-bearing, and any problems or issues with the off-loading/protective device. Subjects will be instructed to wear the off-loading/protective device at all times, except during sleeping, bathing, or showering.

5.14. Concomitant Medications and Non-Study Treatments

Only therapies/medications that may impact healing, are related to AEs (e.g., antibiotics/antimicrobials, surgical excision/amputation) or linked to DM (i.e., insulin and oral hypoglycemics) will be collected. These medications/therapies administered or taken by the subject beginning 28 days prior to signing the ICF and throughout the study will be recorded in the source documents and, for randomized subjects, on the appropriate eCRF. For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosage, not total daily dose).
- Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.
- Route of dosing
- Indication for use
- The start date
- Whether the medication is ongoing or was discontinued
- The stop date (if medication/therapy is not ongoing)
- Adverse event number (if applicable)

5.14.1. Prohibited Medications and Therapies

The following treatments/medications/procedures are prohibited during the subject participation in this study, beginning with the first Screening Visit (SV1) and should they be medically required, the subject must be discontinued from the study.

To the study ulcer:

- Application of growth factors, engineered tissues or skin substitutes, other than the Active Treatment (PriMatrix), including but not limited to: Regranex® (Smith & Nephew), Dermagraft® (Organogenesis), Apligraf® (Organogenesis), EpiFix (MiMedx), AMNIOEXCEL (Integra), GraftJacket® (KCI, an Acelity Company), OASIS (Smith & Nephew), MatriStem® (ACell), Omnigraft® (Integra

LifeSciences), or Integra BMWD® (Integra LifeSciences) Enzymatic debriding agents
- Topical Oxygen Therapy
- Negative Pressure Wound therapy

To the subject:

- Systemic investigational treatment/medications
- Dialysis
- Immunosuppressive agents
- Systemic steroids/oral corticosteroids (>25mg/d for >3 days) (**Note**: inhaled steroids are acceptable)
- Autoimmune disease therapies
- Radiation therapy to the foot
- Cytostatic drugs
- Vascular surgery of the affected limb
- Thrombolysis and/or angioplasty

Only dressing materials provided by the sponsor may be used on the target ulcer. Ulcer dressings that have not been provided by the study sponsor for use in the trial may be used on ulcers that are NOT designated as the study ulcer.

5.15. Adverse Events

5.15.1. Definitions

An adverse event (AE) is defined as any untoward medical occurrence occurring in a clinical trial. An AE does not necessarily have a causal relationship with the device. A device-related AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study device, whether or not related to the device.

For the purposes of this study, only AEs that are possibly, probably, or definitely related to the study ulcer, study treatment, and/or study procedures are to be recorded. All events starting or worsening beginning at SV2 through Treatment Visit Week 13 and unscheduled visits will be collected. Follow-up treatment and evaluation should continue until the AE has resolved or until 2 weeks after the final visit, whichever occurs first.

AEs not related or unlikely related to the study treatment, study ulcer and/or study procedures are not to be recorded for this study.

A Serious Adverse Event (SAE) is defined as any AE that:

- Results in death

- Is life threatening (the subject is at immediate risk of dying from the adverse experience)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For the purposes of this study, only SAEs that are possibly, probably, or definitely related to the study ulcer, study treatment, and/or study procedures are to be recorded. All events starting or worsening after the first randomized treatment through Treatment Visit Week 12 will be collected. Follow-up treatment and evaluation should continue until the SAE has resolved or until 2 weeks after the final visit, whichever occurs first.

SAEs not related or unlikely related to the study treatment, study ulcer and/or study procedures are not to be recorded for this study.

5.15.2. AE Severity Assessments

The guidelines outlined in Table 1 will be used for severity assessments.

Note: The term “severe” is a measure of intensity and a severe AE is not necessarily serious.

Table 1 Adverse Event Severity – Description of Severity Grades

Severity Grade	Description
Mild	Symptoms barely perceptible by the patient, do not affect his/her performance or activity, do not normally require the administration of drugs for relief of the symptoms but they may, however, be administered depending on the patient's needs.
Moderate	Symptoms sufficiently serious to cause patient discomfort, having impact on the performance of daily activities; the patient may be able to continue in the study, but it may be necessary to treat the symptoms.
Severe	Symptoms cause serious discomfort and they may be serious to a degree that the patient may not be able to continue in the study; treatment may be administered for the symptoms and/or the patient hospitalized.

5.15.3. Adverse Event Relatedness Assessments

All AEs will be assessed for their relatedness to the study device or the procedures. An AE is considered device-related if there is a reasonable possibility that the device caused or contributed to the event. Information that "reasonably suggests" a causal relationship includes any information such as professional, scientific or medical facts and observations or opinions that would reasonably suggest that a device has caused or may have caused or contributed to the event. If the chance that a device may have caused or contributed to an event is very remote or very unlikely, the event should be considered not related to the device.

AE causality will be assessed using the guidelines outlined in Table 2.

Table 2: Adverse Event Causality Categories

Relationship	Comment
Definitely	This category applies to those AEs which the investigator feels are **incontrovertibly related to the study treatment**, study ulcer or study procedures. An AE may be assigned an attribution of definite if or when (must have all three): a) It follows a reasonable temporal sequence from application of the device. b) It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. c) It follows a known response pattern to treatment with the device.

Probable	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a **high degree of certainty to be related to the device**. An AE may be considered probable if or when (must have three): a) It follows a reasonable temporal sequence from application of the device. b) It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. c) Disappears or is decreased upon removal of the device. d) It follows a known response pattern to treatment with the device.
Possibly	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged **unlikely but cannot be ruled out with certainty to the device**. An AE may be considered possible if or when (must have two): a) It follows a reasonable temporal sequence from application of the device. b) It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. c) Disappears or is decreased upon removal of the device. d) It follows a known response pattern to treatment with the device.
Unlikely	In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged **likely to be unrelated to the device**. An AE may be considered unlikely if or when (must have two): a) It does not follow a reasonable temporal sequence from application of the device. b) It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. c) Disappears or is decreased upon removal of the device. d) It does not follow a known or expected response pattern to treatment with the device.
Unrelated	This category applies to those AEs that, after careful consideration, are **clearly and incontrovertibly due to extraneous causes** (disease, environment, etc.) and determined with certainty to have no relationship to the study device.

5.15.4. Adverse Event Expectedness

If an AE is determined to be serious and related, either possibly, probably, or definitely related, to the study device or procedure, a determination of expectedness will be made. Expectedness is specifically related to the functioning of the product or the conduct of the procedure and is NOT related to whether the study team perceived that the AE might have happened in the subject. That is, the question is "Have we seen this SAE in relation to the product/procedure?" and is ***not*** "Did we think this SAE would happen in this subject?".

A SAE is expected, that is "**Anticipated**" if the SAE is (1) related to the product or procedure ***and*** (2) the nature, severity, or frequency of the SAE has been seen previously either in personal experience or documented in literature. Note: The vast *majority* of related SAEs are Anticipated.

Conversely, a SAE is not expected, that is "**Unanticipated**" if the SAE is (1) related to the product or procedure ***and*** (2) the nature, severity, or frequency of the SAE has ***NOT*** been seen previously either in personal experience or documented in literature. Note: The vast *minority* of related SAEs are unanticipated.

Therefore, an unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IFU, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

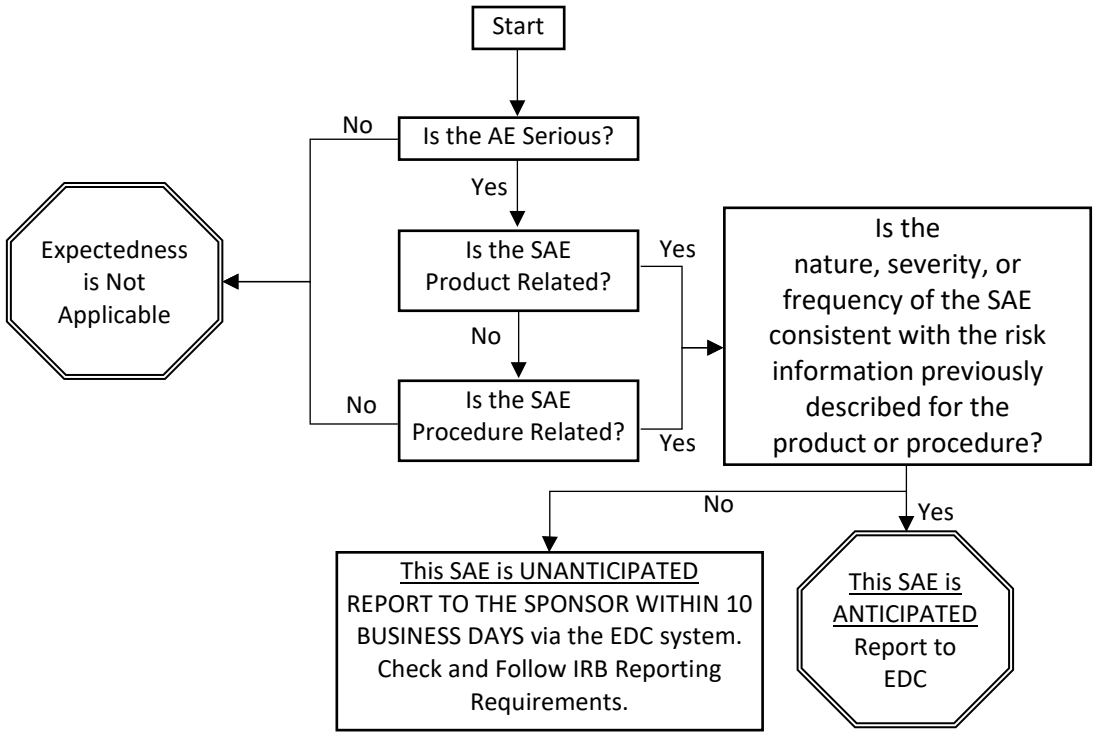
The decision tree in figure 3 should be used when determining expectedness.

For the purposes of this study, the following AEs commonly occur in individuals with DM and DFUs and are thereby defined as Anticipated if they were to occur:

- Ulcer enlargement, tunneling and/or undermining
- Malodor
- Erythema
- Edema
- Maceration
- Excessive drainage
- Development of a new ulcer,
- Ulcer infection or abscess,
- Osteomyelitis
- Trauma/falls and
- Amputation

Questions about any AEs or SAEs should be directed to the sponsor for clarification; however, the ultimate decision for grading severity and expectedness resides with the study investigators.

Figure 3: SAE Expectedness Determination Decision Tree



5.15.5. Adverse Event Reporting Procedures

All AEs related to study treatment, study ulcer and/or study procedures spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be evaluated.

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking standard questions such as:

- "Have you had any (other) medical problems since your last visit / assessment?"
- "Have you taken any new medicines since your last visit /assessment?"

The following AEs will be recorded on the appropriate eCRF:

- All AEs related to study treatment, study ulcer and/or study procedures occurring after the 1st randomization treatment.

- All SAEs occurring after signing of ICF through the last study visit

When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Special instructions for SAEs

Study centers are instructed to report SAEs to Integra within 5 business days of becoming aware of the SAE.

SAEs must be reported by the investigator to Integra by completing the eCRF SAE Form. Only SAEs that are considered causally related to the study device or procedures need to be reported. Reporting will utilize the standard AE eCRF. Note: Follow-up information on the SAE may be requested by the sponsor.

5.15.6. Adverse Event Follow-up

All AEs will be followed until resolution or stabilization to the best of the site's ability. Any subjects reporting SAEs that have not resolved by their last treatment visit will be followed via phone or clinic visit through resolution or 14 days post final visit, whichever comes first.

5.16. Method for Assigning Eligible Subjects to Treatment (i.e., Randomization)

Once it has been determined that a subject meets all eligibility criteria, subjects will be assigned to one of the following treatment groups, based on a randomization schedule provided by the sponsor.

Randomization is accomplished through the Clindex EDC system. After entering your name and password, you will go into the RDE System and click on Subject List or Visit Manager. After selecting the subject to be randomized, click on the Randomization eCRF in the Randomization Visit. You will be asked to answer the following:

- Did the subject meet all eligibility criteria?
  - Select Yes if eligible
  - Select No if not eligible
- Is the percent ulcer reduction ≤ 30%* since the initial screening visit?
  - Select Yes if the ulcer decreased in size less than or equal to 30% ***or*** if the ulcer got bigger
  - Select No if the area of the ulcer decreased in size more than 30% during the screening period
  - Enter the size of the decrease or increase
- Is the area of the study ulcer between 1cm^2 and 12cm^2*?
  - Select Yes if between 1 and 12cm^2

- Select No if not between 1 and 12cm^2
- Enter the size of the ulcer area.

Important: Rounding up or down is not allowed to achieve eligibility. For instance, if the ulcer decreased 30.1% between SV1 and Randomization, the subject is still ineligible for randomization. Similarly, if the area of the wound is 0.99cm^2 at either SV1 or Randomization, the subject is ineligible.

After all of the questions have been answered, you will click on the Save button. Click "Yes" on each of the following pop-up screens. A third screen will pop up with the randomization group: Active or Control. The active treatment is the PriMatrix product (see Section 5.17 below). The control treatment is SOC that has been used during the past two screening visits.

5.17. Active Treatment

5.17.1. PriMatrix Dermal Repair Scaffold Disposition, Storage and Accountability

PriMatrix will be supplied sterile, in single use, double peel packages. For the purposes of this study, it will only be supplied in 4 x 4cm, meshed sheets with 1 sheet per box. Once received, PriMatrix should be stored at ambient conditions and has a shelf life of five years. Upon receipt, each piece will be logged on the Device Accountability Log, which will be updated each time PriMatrix is used.

The investigator will also use the device accountability log to maintain current and accurate inventory records covering the dispensing and the disposal of the study devices. At the conclusion of the study, the investigator must agree to return or destroy all study device materials as instructed by the sponsor.

5.17.2. PriMatrix Application Training

All investigators and Sub-investigators who will be applying PriMatrix for the trial will be trained on the use of the study device, PriMatrix, for the management of DFUs, along with other study-related procedures.

5.17.3. PriMatrix Application

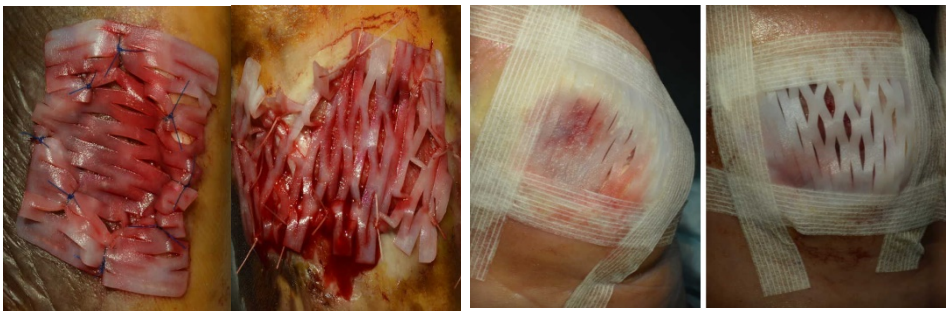
Active treatment for this trial is PriMatrix Dermal Repair Scaffold plus secondary dressings to maintain a moist wound environment and an appropriate off-loading/protective device. After randomization, subjects assigned to the active treatment group will not perform any dressing changes but rather have their dressings changed weekly at the site.

PriMatrix and secondary dressing kits will be provided to the site. Dressing kits will be used on every subject at each dressing change. PriMatrix is ONLY to be applied to a freshly debrided ulcer with punctate bleeding and will always be handled using aseptic technique. PriMatrix will be rehydrated using a sterile saline solution at room temperature and allowed to soak for at least 2 minutes. The product should be kept in the solution until ready for application.

Once ready to apply, the product will be cut to fit the ulcer bed and applied immediately following ulcer bed preparation and hemostasis. **Note: PriMatrix should turn red as it absorbs the blood from the debrided wound bed (Figure 4)**. If the PriMatrix is white, debridement is likely insufficient. As well, it is critical that the PriMatrix be in direct contact with the ulcer bed. Any air bubbles should be carefully removed by gentle rolling with a moistened cotton tip application. PriMatrix should be secured in place with adhesive strips, staples, sutures or bolster.

Figure 4: PriMatrix Application

Adequate Absorption | Inadequate Absorption



Secondary dressings, supplied by the sponsor will include the following and should be applied as follows:

1. Non-adherent contact layer
2. Bolster of saline moistened gauze (if necessary to maintain intimate contact between PriMatrix and ulcer bed)
3. 0.9% sodium chloride gel applied over contacting non-adherent layer, if necessary to maintain a moist wound environment
4. Non-adhesive foam
5. Elastic gauze
6. Self-adherent wrap

Care should be taken to ensure that the 0.9% sodium chloride gel is applied only to the ulcer bed and not to the intact skin on the ulcer perimeter.

5.17.4. PriMatrix Re-Application

PriMatrix may be reapplied a second time, if appropriate, based upon the investigator's judgement, given the clinical assessment of the ulcer. PriMatrix may be replaced if any of the following are satisfied:

- At any point, the PriMatrix is non-adherent or sloughing,

- At any point, PriMatrix is lost due to infection. The infection will be treated and resolve before PriMatrix is replaced.
- If at 4-weeks after initial application, the rate of closure is 30% or less.

IMPORTANT: If the investigator feels a third application of PriMatrix is necessary during the trial, the Integra Clinical Research Manager or site's CRA must be consulted prior to reapplication. Note that review of these requests may take up to 1 day, so the subject may need to return the next day for re-application.

The reason for PriMatrix loss/reapplication will be recorded in the source document and eCRF. All PriMatrix applications must be documented on the Device Accountability Form.

When replacing PriMatrix, follow application procedures described in Section 5.17.3 of this protocol.

5.18. Investigator Assessments of Ulcer Closure

Complete wound closure is defined as 100% re-epithelialization of the ulcer surface without detectable exudate, confirmed on 2 consecutive study visits 1 week apart (i.e., Treatment Visit where 100% re-epithelialization of the ulcer surface without detectable exudate was initially documented and the Closure Confirmation Visit). For efficacy analyses, the first date of assessment of 100% re-epithelialization of the ulcer surface without detectable exudate will be used as the date of closure.

If, at Treatment Week 12, the ulcer remains open, the investigator will document why, in his opinion, the ulcer did not close.

5.19. Investigator Assessment of Ulcer Recidivism

If, following confirmed ulcer closure, the ulcer is *open* at the 4-week Follow-up visit, the investigator will document why, in his/her opinion, the ulcer re-opened. NOTE: *The subject will not re-enter the study at this visit.* According to section 6.2.3, subjects can re-enter the study at the *Confirmation Visit* if the wound reopens. This opportunity is not available at the 4-week Follow-up visit.

6. Study Activities by Phase and Visit

The schedule for the protocol-specific assessments and procedures in each phase are detailed below and are summarized in Table 3: Schedule of Events. Detailed descriptions of these assessments and procedures have been previously defined in Section 5.

The results from all of the assessments and procedures discussed in the sections below will be recorded in source documents and on the appropriate eCRF.

6.1. Screening Phase

6.1.1. Screening Visit 1 (SV1)

At SV1, the following data will be collected, or activities performed:

1. Informed Consent and HIPAA Authorization
    - Note: Once the ICF and HIPAA authorization are signed, the screening assessments/activities identified must be completed within a **30-day window** from the date of ICF signature. Further, all screening assessments/procedures must be completed on the same day, and that date will constitute the first day of the screening phase.
2. Review of Inclusion and Exclusion criteria for eligibility
3. Demographics
4. Medical history, medications, and non-study treatments
5. Physical exam (including vital signs, height and weight)
6. Vascular perfusion
7. Perform ulcer assessments
8. Photograph the study ulcer pre-debridement
9. Perform ulcer measurements pre-debridement
10. Perform sharp debridement of the study ulcer
11. Photograph of the study ulcer post-debridement
12. Perform ulcer measurements post-debridement
13. Apply SOC treatment to the ulcer (see Section 5.11 for specific application processes)

14. Discuss treatment compliance with the subject
15. If appropriate, apply the off-loading/protective device and discuss compliance with its use
16. Document applicable Concomitant Medications noted by the subject or seen within the subject's medical records (see Section 5.14 for information on which medications require documentation).

**Remember to schedule the next visit for SV2, 7±3 days from SV1.*

6.1.2. Screening Visit 2 (SV2)

Screening Visit 2 assessments and procedures are summarized in Table 3. At SV2 the following data will be collected, and procedures performed:

1. Review Inclusion and Exclusion criteria for continued eligibility
2. Medical Resource Utilization assessment will be performed (see Section 5.3 for specific information on how to perform this assessment).
3. Ask subject about compliance with the treatment during the previous week
4. Perform ulcer assessments
5. Photograph the study ulcer pre-debridement
6. Perform ulcer measurements pre-debridement
7. Perform sharp debridement of the study ulcer, if necessary per investigator discretion.
8. Photograph of the study ulcer post-debridement, if debridement occurred.
9. Perform ulcer measurements post-debridement, if debridement occurred.
10. Apply SOC treatment to the ulcer (see Section 5.11 for specific application processes)
11. Discuss treatment compliance with the subject
12. If appropriate, apply the off-loading/protective device and discuss compliance with its use
13. Document applicable Concomitant Medications noted by the subject or seen within the subject's medical records (see Section 5.14 for information on which medications require documentation).
14. Document any applicable AEs as noted by the subject or as documented in their medical record (see Section 5.15 for information on which AEs require documentation).

** Remember to schedule the next visit for Randomization/TV 1 (Day 0), 14±3 days from SV1.*

IMPORTANT: If a subject initially fails to meet inclusion/exclusion criteria, e.g., because the ulcer is too large or is infected, and is later reconsidered for participation, the subject will be re-

consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of one time and may be entered into the study a second time if they are found to meet ALL inclusion and NO exclusion criteria.

6.2. Treatment Phase

The treatment phase of the study begins when the subject completes the two-week screening phase, meets all eligibility criteria, and is randomized.

During this phase, subjects will return to the clinic every 7±3 days for up to 13 weeks or until confirmed ulcer closure. When determining the visit dates, the reference should always be to the Randomization/TV 1 (Day 0) date and not the subject's previous visit. Every attempt should be made to maintain subjects on their original treatment schedule.

The schedule of assessments for the treatment phase of the study is provided in Table 3. Detailed descriptions of these assessments and procedures have been previously defined in Section 5.

6.2.1. Randomization/TV 1 (Day 0)

1. Review Inclusion and Exclusion criteria for eligibility
    - *Important: The final exclusion criteria will only be determined after debridement and measurement as detailed below in this Section.*
2. Medical Resource Utilization assessment will be performed (see Section 5.3 for specific information on how to perform this assessment).
3. As subject about compliance with the treatment during the previous week
4. Perform ulcer assessments
5. Photograph the study ulcer pre-debridement
6. Perform ulcer measurements pre-debridement
7. Assess the ulcer for wound closure status
    - If the wound is closed, the subject is exited at this point; complete the study exit form.
8. Perform sharp debridement of the study ulcer
9. Photograph of the study ulcer post-debridement
10. Perform ulcer measurements post-debridement
11. Document ulcer size reduction
12. Complete the randomization process in the EDC system.
13. Apply either SOC or the Active treatment to the ulcer, depending on the cohort that is assigned during the randomization process (see Section 5.16 for specific application processes)

14. Discuss treatment compliance with the subject
15. If appropriate, apply the off-loading/protective device and discuss compliance with its use
16. Document applicable Concomitant Medications noted by the subject or seen within the subject's medical records (see Section 5.14 for information on which medications require documentation).
17. Document any applicable AEs as noted by the subject or as documented in their medical record (see Section 5.15 for information on which AEs require documentation).

** Remember to schedule the next visit for Treatment Visit Week 2, 7±3 days from Randomization/TV 1.*

6.2.2. Subsequent Treatment Phase Visits (TVs 2 through 13)

The subject will return every 7±3 days for treatment visits for 13 weeks or until the ulcer is confirmed closed, whichever occurs first. The following data will be collected, and procedures performed:

1. Medical Resource Utilization assessment will be performed (see Section 5.3 for specific information on how to perform this assessment).
2. As subject about compliance with the treatment during the previous week
3. Perform ulcer assessments
4. Photograph the study ulcer pre-debridement
5. Perform ulcer measurements pre-debridement
6. Assess the ulcer for wound closure status
    - If criteria for complete wound closure are met at a visit, the subject will return to the clinic 7±3 days for a Confirmation Visit. If the first assessment of complete wound closure occurs at the Week 12 Visit, a Confirmation visit will be required at 7±3 days to confirm complete wound closure.
    - If criteria for complete wound closure are not met and the subject has not yet completed 13 weeks of treatment the subject will be instructed to return to the clinic in 7±3 days for the next visit in the treatment phase.
    - If criteria for complete wound closure are not met, but the subject is at Treatment Visit 13, the subject will not have items 7 through 12 below completed; the subject has completed their study requirements and is to be exited.
7. Perform sharp debridement of the study ulcer, if necessary per investigator discretion.
8. Photograph of the study ulcer post-debridement, if debridement occurred.
9. Perform ulcer measurements post-debridement, if debridement occurred.

10. Apply either SOC or the Active treatment to the ulcer, depending on the cohort that is assigned during the randomization process (see Section 5.11 or 5.17 for specific application processes of SOC or Active treatment, respectively.)
11. Discuss treatment compliance with the subject
12. If appropriate, apply the off-loading/protective device and discuss compliance with its use
13. Document applicable Concomitant Medications noted by the subject or seen within the subject's medical records (see Section 5.14 for information on which medications require documentation).
14. Document any applicable AEs as noted by the subject or as documented in their medical record (see Section 5.15 for information on which AEs require documentation).
15. investigator assessment for Complete Wound Closure (Section 5.18).

** Remember to schedule the next Treatment Visit (TV) if the wound is still open and the current visit is not TV 13. If the subject's ulcer is not closed at TV 13, the subject is exited; complete the study exit form. If the wound is closed on or before TV13, schedule the Closure Confirmation Visit (Section 6.2.3).*

6.2.3. Closure Confirmation Visit (7±3 days after ulcer determined to be closed)

Closure Confirmation assessments and procedures are identified in Table 3.

1. Medical Resource Utilization assessment will be performed (see Section 5.4 for specific information on how to perform this assessment).
2. Perform ulcer assessments
3. Photograph the study ulcer
4. Assess the ulcer for wound closure status
5. Document any applicable AEs as noted by the subject or as documented in their medical record (see Section 5.15 for information on which AEs require documentation).

Special Instructions: If the subject returns for the closure confirmation visit AND the ulcer has reopened AND Treatment Visits 12 or 13 has not yet been reached, the subject re-enters the study at the visit after the previously scheduled next visit (e.g., if the ulcer closed at TV9, but at the Confirmation Visit the ulcer is reopen, the subject re-enters at TV11). The subject will then return every 7±3 days for up to 13 weeks or until the ulcer closure is confirmed, whichever occurs first. This process repeats until all treatment visits are used up. If the subject's wound is closed on TV 12 or 13, but is open at the Confirmation Visit they do not re-enter the study and are exited.

** Remember to schedule the next Treatment Visit or the 4-Week Follow-Up visit as appropriate.*

6.2.4. 4-Week Follow-Up Visit (28±3 days after Confirmation Visit)

The 4-week follow-up visit assessments and procedures are identified in Table 3.

1. Perform ulcer assessments
2. Photograph the study ulcer
3. Assess the ulcer for wound closure status

6.2.5. Unscheduled Visits

IMPORTANT: Unscheduled visits are to ***ONLY*** be used when a subject has an unexpected clinic visit that falls outside the next visit window. If the date of the unexpected visit falls within the window of the next regular visit, the procedures for that visit will be followed.

In the event an unscheduled visit occurs, the following will be occur:

1. Perform ulcer assessments
2. Perform sharp debridement of the study ulcer, if necessary per investigator discretion.
3. Apply either SOC or the Active treatment to the ulcer, depending on the cohort that is assigned during the randomization process (see Section 5.11 or 5.17 for specific application processes of SOC or Active treatment, respectively.).
4. Discuss treatment compliance with the subject
5. If appropriate, apply the off-loading/protective device and discuss compliance with its use
6. Document applicable Concomitant Medications noted by the subject or seen within the subject's medical records (see Section 5.14 for information on which medications require documentation).
7. Document any applicable AEs as noted by the subject or as documented in their medical record (see Section 5.15 for information on which AEs require documentation).

Important: If the Unscheduled Visit occurs between the closure visit and either the Confirmation Visit or the 4-Week follow-up visit, activities 2 through 5 will not be performed. If the wound is open at the follow-up visit, and the subject has not reached their Confirmation Visit, the subject will be re-entered per the Special Instructions in 6.2.3. SOC dressings may be applied until the next Treatment Visit. If the subject is open between the Confirmation Visit and the 4-Week follow up visit, the subject is exited.

Table 3: Schedule of Events

Procedure	Screening Phase		Treatment Phase													Follow-Up Phase		Unscheduled Visit[1,2]
	SV 1 -14±3d	SV 2 -7±3d	Randomiza-tion/ TV[3] 1 (Day 0)	TV 2 7±3d	TV 3 14±3d	TV 4 21±3d	TV 5 28±3d	TV 6 35±3d	TV 7 42±3d	TV 8 49±3d	TV 9 56±3d	TV 10 63±3d	TV 11 70±3d	TV 12 77±3d	TV 13 84±3d	Conf Visit 7±3d After Closure	4-Week 28±3d After Confirm.	
Inf. Consent/HIPAA	X																	
Inclusion/Exclusion	X	X	X															
MRU Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographics	X																	
Medical History	X																	
Physical Exam	X																	
Vascular Perfusion	X																	
Ulcer Assessments[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ulcer Photography	X[5]	X[6]	X[4,7]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[8]	X[8]	
Ulcer Debridement	X	X[9]	X	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]				X[9]
Ulcer Measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Control Treatment	X	X	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]				X[10]
Treatment Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Offloading[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ulcer Size Reduction			X															
Randomization			X															
Active Treatment			X[12]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]				X[13]
Closure Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X[14]	X	X	

[1] Only to be used for a visit that falls out of range of one of the other visit windows. If the proposed Unscheduled Visit falls within the next visit window, use that visit instead of documenting an unscheduled visit.
[2] See important information in section 6.2.5 for guidance on Unscheduled Visits after wound closure.
[3] "TV" = Treatment Visit
[4] Study Ulcer Assessments include: 1) location 2) duration 3) size 4) exudate 5) infection 6) measurement of ulcer area
[5] Collect pre- and post-debridement images
[6] Collect pre-debridement image; if performing debridement, collect post-debridement image
[7] Post-application image required if randomized to PriMatrix
[8] Image of the closed wound area to be taken
[9] Debride, if necessary
[10] If randomized to the Standard of Care cohort
[11] Not required for dorsal wounds; required for plantar ulcers or lateral ulcers that would benefit from offloading
[12] If randomized to the Active Treatment and if necessary; see Section 5.17 for guidelines on applying PriMatrix.
[13] Optional application of PriMatrix. See Section 5.17 for guidelines on applying or re-applying PriMatrix
[14] If wound is not healed at Treatment Week 13, Investigator will document why, in his opinion, the wound did not heal.

7. Study Discontinuation and Withdrawal

All subjects have the right to withdraw at any point during treatment without prejudice. If for any subject, study treatment or observations were discontinued, the reason(s) will be recorded and the sponsor will be notified promptly. Reasons that a subject may discontinue participation in a clinical study include:

- Subject withdrew consent
- Subject chooses to withdraw due to an adverse experience
- Lost to follow-up (LTFU)

Before a subject is identified as LTFU, the site will make all reasonable efforts to contact the subject. **These attempts will be documented and will include, at a minimum two phone calls and/or email communications and one follow-up letter sent via certified mail**.

The investigator may discontinue a subject at any time if it is considered medically necessary. Rationale for discontinuation of a subject for medical reasons include, but are not limited to, the following:

- Repeat infections with no response to allowable treatments
- Subject repeated non-compliance with randomized treatment
- It is in the best interest of the subject to not participate in the study.
- Medical reason or situation in which the subject is no longer under the care of the investigator and unable to return for required study visits (e.g., hospitalization).

Every attempt should be made to collect follow-up information. The reason for treatment discontinuation or withdrawal from the study will be recorded in the source documents and on the appropriate eCRF.

The subject may be discontinued by the sponsor if the study is discontinued or for lack of compliance/protocol deviations.

All subjects choosing to withdraw from the study will be asked to undergo the appropriate study visit procedures for the visit at which they are withdrawing. All subjects being discontinued by either the investigator or the sponsor will undergo the appropriate study visit procedures for the visit at which the decision is made to withdraw them from the study.

Subjects who are discontinued or withdrawn and who have not achieved 100% ulcer closure during the treatment phase of the study will not be replaced and will be categorized as treatment failures.

8. Statistical Analysis

This Section presents general information about statistical methodologies and concepts for this study. Further technical details (e.g., data poolability across sites) will be provided in the Statistical Analysis Plan (SAP).

8.1. Treatment Groups

The following treatment groups will be assessed:

Group	Description
Control (SOC)	Moist ulcer dressings consisting of 0.9% sodium chloride gel plus secondary dressings and an appropriate off-loading/protective device. (See Section 5.11 for full information)
Active Treatment	PriMatrix Dermal Repair Scaffold plus secondary dressings to maintain a moist wound healing environment and an appropriate off-loading/protective device. (See Section 5.17 for full information)

8.2. Description of Study Endpoints

8.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint for the study is the incidence of confirmed complete wound closure of the study ulcer, as assessed by the investigator, during the 12-week treatment phase.

8.2.2. Secondary Efficacy Endpoints

The secondary endpoints are:

1. Proportion of subjects with complete wound closure of the study ulcer during the 12-week treatment phase as assessed by computerized planimetry, during the treatment phase
2. Time to complete wound closure, as assessed by the investigator.
3. Time to complete wound closure, as assessed by computerized planimetry.
4. Rate of ulcer closure as assessed by computerized planimetry.

8.2.3. Exploratory Endpoints

9. Medical resource utilization associated with treatment of DFU and related complications, including:
    - Interference of activities of daily living
    - Interference of paid work (full-time or part-time)/school
    - Physician office visits
    - Emergency room visits
    - Hospitalizations
    - Home health nursing visits
    - Skilled Nursing Facilities
    - Procedures
    - Medication regimens to treat complications (analgesics, antibiotics, etc.)

- Diagnostic tests, imaging, etc.
- Treatment of AEs
- Use of durable medical equipment (off-loading/protective device, crutches, wheelchair, etc.)
- Dressing regimen and materials

10. Wound closure status at the 4-week follow-up visit

8.2.4. Safety Endpoints

Safety will be assessed through reports of AEs and SAEs.

8.3. Sample Size Determination and Rationale

This is a randomized study with two treatment groups. Assuming:

- 46% of DFUs receiving PriMatrix close by 12 weeks (84 days).
- 26% of DFUs receiving with SOC close by 12 weeks (84 days).

Overall 2-sided Type I Error rate (alpha) of 0.05. Under the above assumptions, 102 subjects per treatment group will be required to meet the Type I error rate of 0.05 and 80% power; for a total of 204 subjects for the study. As the treatment duration is short, the discontinuation rate is predicted to be around 15%. To accommodate the potential discontinuations, 256 subjects will be randomized (128 per treatment group) to this trial. The subjects will be randomized to the treatment groups in a 1:1 ratio.

A single interim analysis when 50% of subjects complete the trial, using group-sequential methods and Pocock alpha spending function, where the hypotheses will be tested at a two-sided alpha of 0.031 at the interim analysis and at a two-sided alpha of 0.028 at the final analysis.

8.4. Randomization

The randomization will be stratified by center and will use mixed blocks of 2 and 4 with a 1:1 ratio of Active Treatment to Control Treatment to ensure even distribution of Active and Control subjects at each site. Trial ulcer size (area) at the time of randomization (2 strata: 1 cm^2 to ≤3 cm^2 vs. >3 cm^2 to 12 cm^2) will also be used as a stratification factor to ensure balance between each treatment group in this stratum.

8.5. Blinding

Due to the nature of this trial and the product, the subjects, investigators and personnel involved in this trial cannot be blinded. The assessment of ulcer closure, determination of ulcer area and ulcer closure parameters will be determined by both the investigator and by computerized planimetric analysis of digital photographs of the DFU using an imaging system and associated software.

8.6. Interim Analysis for Sample Size Adjustment

A single interim analysis will be completed when 50% of subjects complete the study. Employing a group-sequential design with a Pocock alpha spending function the following decisions will be made at the interim analysis with respect to the efficacy outcome:

1. Stop the study due to demonstrating statistically significant superiority of the Active Treatment to SOC if the two-sided p-value testing the stated hypotheses is ≤ 0.031 and the difference is in favor of the Active Treatment.
2. Stop the study due to demonstrating futility of the Active Treatment to SOC if the two-sided p-value testing the stated hypotheses is ≤ 0.031 and the difference is in favor of SOC.
3. Continue the study if the two-sided p-value testing the stated hypotheses is > 0.031.

With this design and assuming 46% of DFUs managed with the Active Treatment achieve complete wound closure by Week 12 (or by TV13) and 26% achieve complete wound closure when managed with the Control Treatment, the probability of stopping early due to showing superiority with the Active Treatment is 0.479. If the decision at the interim analysis is to continue the study, the hypotheses at the end of the study will be tested at a two-sided alpha level of 0.028 to maintain an overall two-sided alpha of 0.05.

Further, conditional power will be calculated at the interim analysis for predicting the final study success. In case more data is needed, sample size re-estimation will be considered in order to meet the final study objective.

In addition, an early data review will be performed when 50 patients reach the primary endpoint. The purpose of this review is to ensure the study execution is as originally planned, and therefore, no alpha spending is involved.

8.7. General Statistical Considerations

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.2 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

8.8. Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations will be summarized by treatment group, for all centers combined and each center separately. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

8.9. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group using appropriate descriptive statistics.

8.10. Analysis Populations

8.10.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all randomized subjects. The Intent-to-Treat population will be the primary population for the analysis of the primary and secondary endpoints.

8.10.2. Per Protocol Population

The Per Protocol (PP) population is defined as all randomized subjects who were not associated with a major protocol violation. This population will be identified before the database lock. The PP analysis of primary and secondary endpoints will be considered supportive.

For the per protocol analysis, no data points will be imputed, all missing values will remain as missing.

8.10.3. Safety Population

The Safety population is defined as any subject receiving the allocated treatment after randomization. This population will be used for the analysis of safety parameters.

8.11. Statistical Methods

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial.

8.12. Efficacy Analyses

8.12.1. Primary Analysis

Primary Endpoint: The primary analysis will be conducted on the ITT population. The proportion of subjects with confirmed closed study ulcers during the treatment phase of the study, as assessed by the investigator, will be compared using the *Cochran–Mantel–Haenszel (CMH)*. For the primary efficacy analysis, missing values will be imputed using last observation carried forward.

For the primary analysis, the first date of assessment of 100% re-epithelialization of the ulcer surface without detectable exudate will be used.

The Breslow-Day test will be used to assess the homogeneity of the primary endpoint across study sites. If the Breslow- Day test concludes lack of homogeneity

(at a two-sided alpha level of 0.10), additional exploratory analyses will be performed to characterize the differences in results among sites.

Secondary Endpoints: To maintain the trial-wise Type I error rate at 0.05, a closed test procedure will be used for the secondary endpoints. For efficacy analyses, the first date of assessment of 100% re-epithelialization of the ulcer surface without detectable exudate or visible non-epidermal tissue will be used.

The order of the endpoints will be as follows:

1. Proportion of subjects with confirmed complete wound closure of the study ulcer during the 12-week treatment phase as assessed by computerized planimetry, during the treatment phase
2. Time to complete wound closure, as assessed by the investigator.
3. Time to complete wound closure, as assessed by computerized planimetry.
4. Rate of ulcer closure as assessed by computerized planimetry.

Prognostic Factors Assessments: For the Intent-to-Treat population, a covariate analyses will be conducted to assess the impact of various prognostic factors on ulcer closure and also to demonstrate the robustness of the primary analysis. Prognostic factors (i.e., covariates) will be included if they are found to be contributing factors (i.e., the individual covariate p-value is less than 0.05). Potential prognostic factors to be considered include:

- Baseline ulcer size
- DM type
- Age of ulcer at baseline
- Race
- Gender
- Nicotine Use
- Recorded HbA1c
- Baseline BMI
- Ulcer location

Additional planned analyses include the use of Analysis of Covariance (ANCOVA) models which incorporate consideration of stratification factors (i.e., site and baseline ulcer area) in order to compare reduction in study ulcer size between the two treatment groups and Kaplan-Meier analysis to assess and describe the differences in the time to ulcer closure in the two treatment groups.

8.12.2. Exploratory Analyses

An exploratory analysis will be performed to assess costs associated with the management of DFUs for the active and control groups using medical resource utilization data and standardized direct and in-direct unit costs. Additionally, ulcer closure status at the 4-week follow up visit will be evaluated.

8.12.3. Treatment Failures

Subjects who are withdrawn or discontinue during the treatment phase and/or who do not achieve complete wound closure during the treatment phase will not be replaced and will be considered treatment failures.

For missing data that are used in continuous data analyses, the last available observation (LOCF) will be used. In the analyses using the planimetry data, the last available planimetric value will be used for discontinued subjects.

8.12.4. Safety Analyses

The Safety population will be used for the analysis of safety endpoints.

Safety will be assessed through reports of AEs and SAEs. AEs related to the device, study ulcer and/or study procedures and all SAEs will be recorded.

All safety parameters will be summarized descriptively by treatment. No inferential statistics are planned.

8.12.5. Adverse Events

AEs will be coded using the MedDRA Medical Dictionary. Treatment Emergent AEs (TEAEs) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment.

In addition, separate summaries of SAEs, and AEs resulting in discontinuation of study treatment will be presented.

8.12.6. Supportive Analysis

To assess the robustness of the primary analysis results, supportive analysis will be conducted using the PP population. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population used. The PP population will be used for the supportive analysis while ITT population will be used for the primary analysis. Subjects in these populations with no post randomization data for the primary endpoint will be considered NOT CLOSED, i.e., treatment failures, in this analysis.

9. Direct Access to Source Data/Documentation

The monitors, auditors, personnel authorized by the sponsor, and regulatory and health authority inspectors or their agents will be given direct access to source data and documentation (e.g., medical charts/records, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical

records may be governed by institution policy and each site will be required to ensure access to medical records as allowed by institutional requirements.

10. Quality Control and Quality Assurance

10.1. Monitoring Requirements

In an effort to fulfill the obligations outlined in ICH guidelines which requires the sponsor to maintain current personal knowledge of the progress of a study, the sponsor has developed a Monitoring Plan in order to establish and document practical methods for the clinical team in monitoring and maintaining adequate study oversight. The sponsor's designated monitor will visit the center(s) during the study as well as maintain frequent telephone and written communication. The investigator will permit the sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable, and that protocol adherence is satisfactory.

The investigator will permit representatives of the sponsor and/or designated CRO to inspect all eCRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but is not limited to, study, laboratory and diagnostic reports, ulcer images and tracings, diary pages, quality of life questionnaire, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the case report forms, in accordance with federal regulations. A Monitoring Log will be maintained at each study site which the monitor will sign, date and state the type of visit.

The investigator should be aware that the study site and subject records may be inspected by the sponsor or other representatives or other regional regulatory authorities.

For any data transfer through e-mail, the data file(s) will be password protected; the password will be exchanged in the separate e-mail or by phone.

For the Interim Analysis, a cut-off date for data collection and monitoring will be determined and sites will be requested to provide current information up to the cut-off date.

The final statistical analysis of data will be performed after all clinical monitoring has been completed, all data queries have been resolved, and all data have been verified (QC) prior to formal database lock. The sponsor will authorize the final database lock for all sites.

10.2. Acceptability of Case Report Forms

Electronic Case Report Forms will be used for the collection of data via electronic data capture (EDC). An eCRF must be completed for each subject who has signed an ICF. For subjects who are screen failures, this would be limited to the screen failure eCRF page. All source documents and eCRFs will be completed as soon as possible after the subject's visit. Corrections to data on the eCRFs will be documented in the electronic audit trail which is 21 CFR Part 11 compliant. The investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. eCRFs will be reviewed by the sponsor/designee who will make a decision as to their acceptability.

10.3. Reporting Protocol Deviations

The investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the investigator deviates from the protocol requirements, the sponsor will make the determination as to whether the subject will continue in the study. The sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the eCRF.

10.4. Study Device Accountability

The investigator or designee will verify the contents of each shipment against the shipping documents. Verification of study device receipt will be documented on the device accountability log which will be provided to the site.

The investigator will also use the device accountability log to maintain current and accurate inventory records covering the dispensing and the disposal of the study devices.

At the conclusion of the study the investigator must agree to return or destroy all study device materials as instructed by the sponsor.

11. Ethics and Regulatory Requirements

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Good Clinical Practice (GCP), ICH E6 and HIPAA regulations in 45 CFR Part 164. No protocol changes will be implemented without the prior review and approval of the sponsor and IRB, except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the change will be reported to the IRB as soon as possible, according to IRB regulations. Additionally, all study products used in this study are manufactured, handled and stored in accordance with applicable Good Manufacturing Practices (GMP) and the products provided for this study will be used only in accordance with this protocol.

11.1. Institutional Review Board/Independent Ethics Committee

The Principal investigator will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, ICF, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal investigator and sponsor or sponsor designee. The investigator will not participate in the decision. If the investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the sponsor. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC and must agree to share all such documents and reports with the sponsor.

11.2. investigator's Responsibilities

The investigator is responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any study centers participating in this study that cannot comply with these standards will be documented.

11.3. Subject Informed Consent Requirements

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the investigator and/or designee. Written informed consent will be obtained from each subject before any procedures or assessments that would not otherwise be required for the care of the subject are done and after the objectives, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written ICF is to be in compliance with Code of Federal Regulations (CFR) 21 Part 50.27 and Good Clinical Practice (GCP) guidelines. The sponsor will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the investigator to the IRB/IEC for review and approval prior to the start of the study. Each study site must provide the sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject's medical record, if allowed by institutional policy.

12. Data Handling and Record Keeping

12.1. Recording and Collection of Data

The Site is responsible for keeping source documents for all data collected via EDC. All source documents and eCRFs must be completed as soon as possible after the subject's visit. Corrections to data on the eCRFs will be documented in the electronic audit trail which is 21 CFR Part 11 compliant. The investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the investigator will need to again sign the investigator signature page electronically. Designated source documents will be signed and dated by the appropriate study personnel. The investigator must agree to complete and maintain source documents and eCRFs for each subject participating in the study.

12.2. Clinical Data Management

The sponsor will be responsible for the processing and quality control of the data. Data management will be carried out as described in the sponsor's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the sponsor's SOPs as well as provisions of the study-specific Data Management Plan.

12.3. Archiving

All study documentation at the investigator site and sponsor site will be archived in accordance with ICH GCP E6 and the sponsor's quality standards and SOPs.

Study records must be retained by the investigator for 2 years following the conclusion/ termination of the study and the publication (if applicable). Study records should not be destroyed without prior written agreement between the sponsor and the study investigator. At the completion of the study, details of the archival process must be provided to the sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, AE data, test results, and any other diagnostic procedures required to evaluate the progress of the study).
- Signed protocols and protocol amendments
- Product (e.g., Device, SOC supplies and Off-loading/protective device) accountability records
- Study personnel signature log

- Monitoring logs
- Correspondence to and from the sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and HIPAA consent forms
- Subject screening and randomization log
- SAE reports
- Institutional Review Board approval and re-approval letters
- Ulcer images
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the investigator so that the conduct of the study can be fully documented and monitored.

13. Publication Plan

Manuscripts and abstracts will be prepared by both the investigator(s) and the sponsor. The results of the study may be published in scientific literature and may also be used in submissions to regulatory authorities. It is the intent of the sponsor, and the Lead investigator to publish or present the study results together with the other sites, unless specific permission is obtained in advance from the sponsor to publish separate results. Co-authorship with any of the sponsor's personnel will be discussed and mutually accepted upon submission of a manuscript or publication.

All information concerning the sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator and not previously published) is considered confidential by the sponsor and shall remain the sole property of the sponsor. The investigator agrees not to use it for other purposes without written consent.

It is understood by the investigator that the sponsor will use the information developed in this clinical trial in connection with the development of PriMatrix Dermal Repair Scaffold. Therefore, this information may be disclosed as required to other investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the investigator understands that he/she has an obligation to provide the sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: Because this is a multi-center trial, site and investigator shall not independently publish, publicly disclose, present or discuss any results of or information pertaining to site's and investigator's activities conducted under this study protocol until such a multi-center publication is released under sponsor's direction, unless otherwise agreed upon in the study agreement.

14. Protocol Versions

Table 4: Previous Versions and Overview of Changes to the Previous Version

Version	Changes
Version 1.0	Original
Version 2.0	• Include preliminary analysis after enrollment of 50 subjects
Version 3.0	• Update sponsor contact information • Addition of protocol version table • Addition of 4-week follow-up phase • Include specific time frame for vascularization measurements • Removal of specific brands or examples from offloading/protective device and dressings • Specified that the investigator or designee is to act as an interviewer for the MRU worksheet • Clarification on osteomyelitis on the foot with the study ulcer • Clarification on undermining and tunneling • Update 30 day use of products or therapies to 28 days • Change necrotic tissue to devitalized tissue
Version 4.0	• Refer to Summary of Changes document
Version 5.0	• Refer to Summary of Changes document

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