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ETS-MG-DFU-02

Version 2.0	Date: May 12, 2023

A Randomized Controlled Clinical Trial Evaluating The Efficacy Of A Borate-Based Bioactive Glass Advanced Wound Matrix And Standard Of Care Versus Standard Of Care Alone

Protocol Number: ETS-MG-DFU-02
Version: 2.0
Date: May 12, 2023

INVESTIGATOR'S SIGNATURE PAGE

INVESTIGATOR'S SIGNATURE

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with the applicable US Food and Drug Administration (FDA) regulations and Investigational Review Board (IRB) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Investigator's Signature Date

Print Name

Site Number

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TABLE 1: CONTACT INFORMATION

Role	Contact Information
Sponsor	ETS Wound Care, LLC 13210 Dillon Outer Road Rolla, MO 65401
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TABLE 2: VERSION HISTORY

Version Number	Release Date	Change(s)	Reason for Change
1.0	08AUG2023		Initial Release
2.0	04MAY2023	Revised language to Exclusion Criteria #10 to a 30% heal rate from SV1-TV1. Addition of Randomization Review Panel between SV2 and TV1 Updated number of sites and other minor administrative changes were also added.	Change to Inclusion/Exclusion Criteria Change to Randomization Process Administrative Change

LIST OF ABBREVIATIONS

TERM	DEFINITION
ABI/ABPI	Ankle/Brachial Index/Ankle Brachial Pressure Index
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
DFU	Diabetic foot ulcer
EOS	End of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Healing Confirmation Visit
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency virus
IRB	Institutional Review Board
ITT	Intent-to-treat
PAR	Percentage area reduction
RCT	Randomized controlled trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
SOP	Standard operating procedure
SPP	Skin perfusion pressure
SV	Screening visit
TCOM	Transcutaneous oxygen measurement
TV	Treatment Visit
US	United States of America
WOUND-Q	Wound quality scale

PROTOCOL SYNOPSIS: ETS-MG-DFU-02

Objective	The purpose of this clinical evaluation is to collect patient outcome data on a commercially available 510K FDA cleared synthetic, absorbable skin substitute matrix. The commercially available product is MIRRAGEN™ Advanced Wound Matrix and consists of a borate-based bioactive glass fiber and particulate. In this trial, two groups of diabetic foot ulcers (DFUs), will receive standard of care (SOC) treatment for their condition. Half of the patients will have their SOC treatment with a 510K FDA cleared Collagen alginate dressing FIBRACOL™ and the other half will have a 510K FDA cleared MIRRAGEN™ Advanced Wound Matrix as the primary treatment. The primary endpoint is the percentage of patients that go on to complete closure of the target ulcer between the two groups: SOC with FIBRACOL™ or SOC with MIRRAGEN™. Secondary endpoints include the proportion of subjects achieving complete wound closure of the target ulcer by end of 12 weeks.
Intervention Groups	Group 1: SOC primary dressing with MIRRAGEN™ Group 2: SOC primary dressing with FIBRACOL™
Study Design	Multi-center, open label, randomized controlled trial
Sample Size	For this RCT, N = up to 240 subjects
Centers	Up to 15 centers within the United States, Open/competitive enrollment.
Endpoints	**Primary endpoint:** - The proportion of subjects that obtain complete closure over the 12-week treatment period **Secondary endpoints:** - The time to achieve complete wound closure of the target ulcer by the end of 12 weeks - Percentage wound area reduction from TV1 to TV13 measured weekly with digital photographic planimetry and physical examination - The number and type of Treatment Emergent Adverse and Serious Adverse Events - Change in peripheral neuropathy of the target foot assessed using the standard 10-point Semmes-Weinstein monofilament exam [Time Frame: TV1, TV3, TV7, TV9, and EOS1] - Change in pain in the target ulcer assessed using the NPRS scale. [Time Frame: TV1, TV3, TV7, TV9, and EOS1]

	- Change in quality of life using WOUND-Q assessment [Time Frame: SV1, TV3, TV7, EOS1] **Exploratory Endpoint:** • Difference in cellulitis and/or infection at 12 weeks • Use of near-infrared tissue oxygenation imaging assessment of wounds at select sites to evaluate changes in vascularization/oxygenation of wounds with treatment (Kent Imaging SnapshotNIR: Time Frame: SV1, TV1 pre-randomization, TV2, TV4, TV7, and EOS1.
Safety	There is no formal safety objective for this study as MIRRAGEN™ and FIBRACOL™ are commercially available, 510K FDA cleared dressings for diabetic foot wounds. Therefore, in accordance with FDA regulations, adverse reactions to the dressings will be recorded and provided to the study Sponsor for required FDA reporting and will be concurrently reported to all Investigators and IRBs. Adverse events associated with application of standard of care dressing will be collected during the course of the study. Collection and reporting of any adverse reaction data, in accordance with FDA regulations and adverse events associated with dressing application will ensure study subject safety.
Surveillance Schedule	Following initial enrollment, subjects will undergo a screening phase, consisting of 14 days, to determine eligibility. Eligible subjects will then undergo up to a 12-week treatment phase involving weekly evaluations and after 12 weeks, will exit the study. Additionally subjects in either group whose ulcers have not reduced by 50% at week 7 of treatment will be considered a treatment failure and will be exited from the study and permitted to seek alternative treatment.
Study Duration	It is estimated that about 15 months will be required to complete the study with data collection and reporting.

Inclusion Criteria	Potential subjects are required to meet all the following criteria for enrollment into the study and subsequent randomization. 1. Subjects must be at least 18 years of age or older. 2. Subjects must have a diagnosis of type 1 or 2 Diabetes mellitus. 3. At randomization subjects must have a target diabetic foot ulcer with a minimum surface area of 1.0 cm^2 and a maximum surface area of 20.0 cm^2 measured post debridement with a photographic planimetry app. 4. The target ulcer must have been present for a minimum of 4 weeks and a maximum of 52 weeks of standard of care prior to the initial screening visit. 5. The target ulcer must be located on the foot with at least 50% of the ulcer below the malleolus. 6. The target ulcer must be full thickness on the foot or ankle that does not probe to bone. 7. Adequate circulation to the affected foot as documented by any of the following methods performed within 3 months of the first screening visit: a. TCOM ≥30 mmHg b. ABI between 0.7 and 1.3 c. PVR: Biphasic d. TBI >0.6 e. As an alternative arterial Doppler ultrasound can be performed evaluating for biphasic dorsalis pedis and posterior tibial vessels at the level of the ankle 8. If the subject has two or more ulcers, they must be separated by at least 2 cm. The largest ulcer satisfying the inclusion and exclusion criteria will be designated as the target ulcer. 9. Target ulcers located on the plantar aspect of the foot must be offloaded for at least 14 days prior to randomization. 10. The subject must consent to using the prescribed off-loading method for the duration of the study. 11. The subject must agree to attend the weekly study visits required by the protocol. 12. The subject must be willing and able to participate in the informed consent process.

Exclusion Criteria	**Exclusion Criteria:** Potential subjects meeting any of the following criteria will be excluded from enrollment and subsequent randomization**.** 1. A subject known to have a life expectancy of < 6 months is excluded. 2. If the target ulcer is infected or if there is cellulitis in the surrounding skin, the subject is excluded. 3. Presence of osteomyelitis or exposed bone, probes to bone or joint capsule on investigator's exam or radiographic evidence. 4. A potential subject cannot have an infection in the target ulcer or in a remote location that requires systemic antibiotic therapy. 5. A subject receiving immunosuppressants (including systemic corticosteroids at doses greater than 10 mg of Prednisone per day or equivalent) or cytotoxic chemotherapy is excluded. 6. The topical application of steroids to the ulcer surface within one month of initial screening is not permitted. 7. A subject with a previous partial amputation on the affected foot is excluded if the resulting deformity impedes proper offloading of the target ulcer. 8. If a subject has a glycated hemoglobin (HbA1c) greater than or equal to 12% taken at or within 3 months of the initial screening visit he/she is excluded. 9. If a subject has a serum creatinine ≥ 3.0mg/dL within 6 months of randomization he/she is excluded. 10. The subject is excluded if the surface area measurement of the target ulcer has reduced in size by more than 30% in the 2 weeks prior to the initial screening during the 2-week screening phase: the 2 weeks from the initial screening visit (SV1) to the TV1/randomization visit during which time the subject received SOC. 11. A subject with an acute Charcot foot, or an inactive Charcot foot, that impedes proper offloading of the target ulcer is excluded. 12. Women who are pregnant or considering becoming pregnant within the next 6 months are excluded. 13. A potential subject with end stage renal disease requiring dialysis is excluded. 14. A subject who participated in a clinical trial involving treatment with an investigational product within the previous 30 days is excluded. 15. A subject who, in the opinion of the Investigator, has a medical or psychological condition that may interfere with study assessments is excluded.

	16. A subject treated with hyperbaric oxygen therapy or a Cellular and/or Tissue Product (CTP) in the 30 days prior to the initial screening visit is excluded.

1 INTRODUCTION

1.1 Costs of Non-healing Diabetic Foot Ulcers

The economic burden of DFUs costs the United States over $50 billion each year.[1] The cost to treat one patient with DFUs ranges from $11,700 to $16,883.[2] Although approximately 70% of DFUs are shown to heal with good SOC, at least 30% become chronic wounds.[3] These non-healing wounds are at greater risk for infection and lower extremity amputation.[4] Consequently, good standard of care therapy is important for patients with chronic DFUs to improve patient outcomes, lower treatment costs and reduce the risk of complications.

1.2 MIRRAGEN™ Advanced Wound Matrix

MIRRAGEN™ Advanced Wound Matrix is intended for the use in the management of wounds. Wound types include: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds and draining wounds.

Boron-containing compounds have an extensive history of use in medicine due to several mechanisms of action, including inhibition of phodsphodiesterase-4 (PDE4), which reduces production of pro-inflammatory cytokines[4]; broad-spectrum antifungal activity (inhibitor of amino-acyl (leucyl) *t*RNA synthetase)[5]; treatment of various cancers (e.g., non-Hodgkin's lymphoma and multiple myeloma)[6,7]; antimicrobial activity against Gram-negative bacteria (AN3365)[8]; and antiprotozoal activity against Trypanosoma brucei.[9]

Although borate itself was shown to accelerate wound healing in wounds nearly 30 years ago[10,] it has taken some time to understand the mechanisms involved. Boron facilitates the activity of several key enzymes in fibroblasts, including elastase, trypsin-like enzymes, collagenase, and alkaline phosphatase.[11] Further research showed that it also regulates mRNA expression of a wide range of extracellular-matrix proteins, including collagen type 1 (COL1), osteopontin (OPN), bone sialoprotein (BSP), and osteocalcin (OCN), as well as alkaline phosphatase and bone morphogenetic proteins (BMPs).[12,13]

In vitro studies of bioactive boron-based glass fiber matrices have been conducted for several years, primarily in bone and cartilage although two in-vitro studies suggest that boron-doped bioactive glass fibers are capable of eliciting VEGF responses from cells[14,15] although no studies to date have confirmed such responses in chronic wounds. In general, it has been found that the degradation rate of bioactive glass can be altered by changing its composition; for example, by partially replacing the SiO_2 in silicate 45S5 or 13–93 glass with B_2O_3 (yielding a borosilicate bioactive glass), or fully replacing the SiO_2 with B_2O3 (producing a borate bioactive glass)[16,17].

Recent clinical studies have pointed to the efficacy of boron-based bioactive glass fiber matrix in wound management[18-21]. This RCT is a larger, follow-up study to the recently

published 40-patient pilot study in DFU which demonstrated a statistically significant 2.8 fold increase in healing rates compared to SOC alone (p=0,004) and doubled the rate of wound are reduction at all time points (p-0.027)[22].

2 Rationale for Study

MIRRAGEN™ is a bioactive borate-based glass fiber matrix (BBGFM) that can dissolve in wound fluids over a period of several days. A recent 40-patient RCT and additional case studies involving the treatment of chronic diabetic foot ulcers (DFUs) with BBGFM suggest that when used as dressing as part of the standard of care (SOC), improved healing trajectories result. Based on this early promising data, a larger RCT is necessary to further validate these results. For consistency one type of wound will be studied in this trial and we have chosen DFU's as they are some of the most common wounds seen in the wound clinics.

3 Study Endpoints

The purpose of this clinical evaluation is to collect patient outcome data on 2 commercially available standard of care dressings in partial/full-thickness diabetic foot ulcer subjects. Patient outcomes will be compared at 6 and 12 weeks.

The **primary endpoint** is the proportion of subjects that obtain complete closure over the 12-week treatment period.

Secondary endpoints include a comparison between groups of the following clinical measures:

1. The time to achieve complete wound closure of the target ulcer by the end of 12 weeks.
2. Percentage wound area reduction from TV1 to TV13 measured weekly with digital photographic planimetry and physical examination.
3. The number and type of Treatment Emergent Adverse Events.
4. Change in peripheral neuropathy of the target foot assessed using the standard 10-point Semmes-Weinstein monofilament exam [Time Frame: TV1, TV3, TV7, TV9, and EOS1].
5. Change in pain in the target ulcer assessed using the NPRS scale. [Time Frame: TV1, TV3, TV7, TV9, and EOS1].
6. Change in quality of life using WOUND-Q assessment.

Exploratory/Tertiary Endpoints

7. Difference in cellulitis and/or infection at 12 weeks.
8. Use of near-infrared tissue oxygenation imaging assessment of wounds at select sites to evaluate changes in vascularization/oxygenation of wounds with treatment (Kent Imaging SnapshotNIR; Time Frame: SV1, TV1 pre-randomization, TV2, TV4, TV7, and EOS1).

4 Study Design

This study is a prospective, multi-center, open label, RCT designed to collect patient outcome data on two commercially available SOC dressings for the treatment of DFUs. Wound healing assessment will be conducted by a clinician, other than the Investigator at each site. Confirmation of wound healing will be overseen by an independent adjudication committee made up of wound care experts.

There are two standard of care arms in the study:

Arm 1: The SOC therapy in this study is offloading of the DFU (CAM boots or total contact casting [TCC] if the subject's foot is too large for a CAM), appropriate sharp or surgical debridement, infection management (systemic antibiotics only in conjunction with debridement) and wound care covering with Bioactive glass dressing, MIRRAGEN™, followed by a padded 3-layer dressing comprised of 4x4 gauze pads, soft roll and compressive wrap (Dynaflex™ or equivalent).

Arm 2: The SOC therapy in this study is offloading of the DFU (CAM boots or total contact casting [TCC] if the subject's foot is too large for a CAM), appropriate sharp or surgical debridement, infection management (systemic antibiotics only in conjunction with debridement) and wound care covering with calcium alginate FIBRACOL™ dressing followed by a padded 3-layer dressing comprised of 4x4 gauze pads, soft roll and compressive wrap (Dynaflex™ or equivalent).

The study involves two phases: Screening and Treatment.

FIGURE 2: OVERVIEW OF STUDY PHASES

4.1 Phase 1: Screening

The Screening Phase (14 days required) is designed to determine whether subjects are eligible to proceed to the Treatment Phase of the study and consists of a series of screening assessments designed to determine eligibility.

At the first Screening Phase Visit (SV1), written informed consent (ICF) from the subject will be obtained by the Investigator or suitably qualified designee before any protected health information is obtained and prior to the performance of any protocol-specific procedures.

After obtaining ICF, the Investigator will select the study index ulcer. Each subject will have only one DFU selected as the index ulcer. If the subject has more than one DFU at the SV 1 visit, the Investigator will select the largest DFU that meets the eligibility criteria of the protocol as the index ulcer.

Subjects whose index ulcer has been treated with SOC for two weeks during screening are eligible to enter the Treatment Phase immediately once all of the inclusion and exclusion criteria are met. Further, a panel of three board-certified plastic surgeons will review each wound, as well as inclusion/exclusion criteria, in a blinded fashion to ensure that randomizations are appropriate. The review will occur between SV2 and the day of randomization. The plastic surgeon will provide correspondence to the trial manager that the subject is appropriate for randomization, prior to the site being able to randomize the patient.

4.2 Phase 2: Treatment

The Treatment Phase (up to 13 weeks) begins with a series of assessments designed to confirm the subject's continued eligibility. Investigators will debride the ulcer, in accordance with SOC if required. Subjects whose ulcers continue to meet eligibility criteria will then be randomized to one of two groups: (1) SOC with MIRRAGEN™ primary dressing or (2) SOC with FIBRACOL™ primary dressing. Additionally for the most compassionate care subjects in either group whose ulcers have demonstrated wound area reduction by less than 50% at week 7 of treatment will be considered a treatment failure and will be permitted to obtain additional outside treatment and thus will be exited from the study.

4.3 Subject Treatment Assessments

4.3.1 DFU Assessments

During the Treatment Phase, subjects will be evaluated on a weekly basis. Weekly patient outcome evaluations include the Investigator's assessment of ulcer healing and measurements of ulcer size using digital imaging to measure wound area and provide photos of wounds, including photos of healed wounds for adjudication.

Note: All procedures required during baseline are included in TV1 prior to the Randomization visit.

Other evaluations during the Treatment Phase are detailed in the procedures section.

Subjects will be seen weekly (± 3 days) until the ulcer is healed or they meet protocol criteria to exit the study.

4.3.2 Wound Healing Assessment

Initial and confirmation evaluations of wound healing will be subject to oversight to reduce bias. An adjudication panel, consisting of at least two wound care experts with significant experience in treating diabetic foot ulcers will be employed.

The adjudication will be made using photographs of the DFU and will comprise:

1. An initial wound healing assessment by an Investigator.
2. The subject proceeds to the wound healing confirmation visit, two weeks later.
3. Subject photographs will be cataloged and presented to the adjudicators during an adjudication meeting held at interim points throughout the study (up to two interim adjudication meetings) and at the end of the study (up to three total adjudication meetings).
4. Final healing confirmation will be determined by the adjudicator during an adjudication meeting.

4.4 Study Subjects

This prospective RCT will enroll up to 240 subjects in up to 12 centers located in the USA.

4.4.1 Inclusion Criteria

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

1. Subjects must be at least 18 years of age or older.
2. Subjects must have a diagnosis of type 1 or 2 Diabetes mellitus.
3. At randomization subjects must have a target diabetic foot ulcer with a minimum surface area of 1.0 cm^2 and a maximum surface area of 20.0 cm^2 measured post debridement with a photographic planimetry app.
4. The target ulcer must have been present for a minimum of 4 weeks and a maximum of 52 weeks of standard of care prior to the initial screening visit.
5. The target ulcer must be located on the foot with at least 50% of the ulcer below the malleolus.
6. The target ulcer must be full thickness on the foot or ankle that does not probe to bone.
7. Adequate circulation to the affected foot as documented by any of the following methods performed within 3 months of the first screening visit:
    a. TCOM ≥30 mmHg
    b. ABI between 0.7 and 1.3
    c. PVR: Biphasic
    d. TBI >0.6
    e. As an alternative arterial Doppler ultrasound can be performed evaluating for biphasic dorsalis pedis and posterior tibial vessels at the level of the ankle.
8. If the subject has two or more ulcers, they must be separated by at least 2 cm. The largest ulcer satisfying the inclusion and exclusion criteria will be designated as the target ulcer.
9. Target ulcers located on the plantar aspect of the foot must be offloaded for at least 14 days prior to randomization.
10. The subject must consent to using the prescribed off-loading method for the duration of the study.
11. The subject must agree to attend the weekly study visits required by the protocol.
12. The subject must be willing and able to participate in the informed consent process.

Patients must have read and signed the IRB approved ICF before screening procedures are undertaken.

4.4.2 Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from enrollment and subsequent randomization:

1. A subject known to have a life expectancy of < 6 months is excluded.
2. If the target ulcer is infected or if there is cellulitis in the surrounding skin, the subject is excluded.
3. Presence of osteomyelitis or exposed bone, probes to bone or joint capsule on investigator's exam or radiographic evidence.
4. A potential subject cannot have an infection in the target ulcer or in a remote location that requires systemic antibiotic therapy.
5. A subject receiving immunosuppressants (including systemic corticosteroids at doses greater than 10 mg of Prednisone per day or equivalent) or cytotoxic chemotherapy is excluded.
6. The topical application of steroids to the ulcer surface within one month of initial screening is not permitted.
7. A subject with a previous partial amputation on the affected foot is excluded if the resulting deformity impedes proper offloading of the target ulcer.
8. If a subject has a glycated hemoglobin (HbA1c) greater than or equal to 12% taken at or within 3 months of the initial screening visit he/she is excluded.
9. If a subject has a serum creatinine ≥ 3.0mg/dL within 6 months of randomization he/she is excluded.
10. The subject is excluded if the surface area measurement of the target ulcer has reduced in size by more than 30% in the 2 weeks prior to the initial screening during the 2-week screening phase: the 2 weeks from the initial screening visit (SV1) to the TV1/randomization visit during which time the subject received SOC.
11. A Subject with an acute Charcot foot, or an inactive Charcot foot, that impedes proper offloading of the target ulcer is excluded.
12. Women who are pregnant or considering becoming pregnant within the next 6 months are excluded.
13. A potential subject with end stage renal disease requiring dialysis is excluded.
14. A subject who participated in a clinical trial involving treatment with an investigational product within the previous 30 days is excluded.
15. A subject who, in the opinion of the Investigator, has a medical or psychological condition that may interfere with study assessments is excluded.
16. A Subject treated with hyperbaric oxygen therapy or a Cellular and/or Tissue Product (CTP) in the 30 days prior to the initial screening visit is excluded.

4.5 Study Schedule

The study is divided into two phases: Screening and Treatment Phases. The schedules for the protocol-specified assessments and procedures in each phase are detailed in the following sections. Note that there is an end of study visit (EOS1) scheduled on Week 13 or

earlier if the wound heals or does not demonstrate at least 50% wound area reduction at 6 weeks after randomization (Week 7) and a follow-up visit (HCV1) to confirm that a wound is healed two weeks after first being assessed as healed.

4.5.1 Visit Windows

Subject visit dates must be scheduled within the visit windows detailed in the Schedule of Study Visits table. One week equals 7 days (± 3 days). During the Screening Phase, each visit is scheduled, with reference to the allowed visit window. During the Treatment Phase, each visit is also scheduled with reference to the allowed visit window.

TABLE 1: SCHEDULE OF VISITS. LIGHT GREY (SCREENING); LIGHT YELLOW (TREATMENT); LIGHT BLUE (END OF TREATMENT VISIT); LIGHT PURPLE (ADDITIONAL WOUND HEALING CONFIRMATION VISIT FOR THOSE WOUNDS THAT HEAL)

Visit	SV1	SV2	Wk 1 TV1		Wk 2 TV2	Wk 3 TV3	Wk 4 TV4	Wk 5 TV5	Wk 6 TV6	Wk 7 TV7	Wk 8 TV8	Wk 9 TV9	W 10 TV10	W 11 TV11	W 12 TV12	W 13* EOS 1	HCV1
			Pre Rand	Post Rand													
Weeks from Randomization Date	-2	-1	0		1	2	3	4	5	6	7	8	9	10	11	13	2 weeks after initial healing
Window Period	±3 days	±3 days	±3 days**		±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3days
Assessment of eligibility	X	X	X														
Informed consent	X																
Ulcer history	X																
Demographics	X																
Medical History or changes	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prohibited Therapies assessment	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Medication assessment	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ABI/SPP/TCOM/ TBI or arterial Doppler study	X																
Randomization				X													
WOUND-Q instrument assessment	X					X				X						X	
Ulcer assessments	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Infection assessment of index ulcer	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam or changes	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Assess for Adverse Effects and Adverse Events					X	X	X	X	X	X	X	X	X	X	X	X	X[A]

Visit	SV1	SV2	Wk 1 TV1		Wk 2 TV2	Wk 3 TV3	Wk 4 TV4	Wk 5 TV5	Wk 6 TV6	Wk 7 TV7	Wk 8 TV8	Wk 9 TV9	W 10 TV10	W 11 TV11	W 12 TV12	W 13* EOS 1	HCV1
			Pre Rand	Post Rand													
Urine or blood pregnancy test control (females of childbearing potential)	X								X								
Assurance of effective birth control (females of childbearing potential)	X								X								
Pain assessment	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Monofilament Test with vibratory (10 point)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine	X																
Blood Sugar	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c Lab	X															X	
Take X-ray to rule out osteomyelitis or bone infection	X																
SnapshotNIR	X		X		X		X			X						X	
Index ulcer photographs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Index ulcer measurements	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[A]
Assess index ulcer healing > 50%										X							
Index ulcer cleaning	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[A]
Index ulcer debridement	X[B]	X[B]	X[B]		X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[B]	X[A]
Index ulcer closure assessment			X		X	X	X	X	X	X	X	X	X	X	X	X	X[C]
Assessment of offloading	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Apply MIRRAGEN™ or FIBRACOL™				X	X	X	X	X	X	X	X	X	X	X	X		
Apply outer dressing	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[D]	X[D]

[A]: Only assess for reopening of wound; [B]: If required per guidelines; [C]: Confirmation of wound closure; [D] Only if subject is not healed

*Will be earlier if wound heals before this date or subject is withdrawn from the study.

**Visit windows applicable given that TV1 is at least 14 days from SV1. Subject MUST complete a minimum of a 14-day screening period.

4.5.2 Screening Phase

The subject will sign and date the ICF and HIPAA authorization (according to site practices) prior to the collection of any protected health information, as well as any study-related procedures. A screening number will be assigned to each subject in successive order of entering the study after signing the ICF at each center, beginning with 001 at each site.

The screening phase may be broken into two visits. SV1 can occur up to 14 days prior to Randomization. SV2 should occur seven days prior to randomization.

SV1: Procedures to be performed include:

- Informed consent will be obtained prior to the collection of any protected health information as well as any study related procedures and the subject will sign a written ICF
- Assess current wound therapies for anything prohibited within 30 days of Randomization
- Demographics
- Medical history
- Physical examination
- Assess concomitant medications and any prohibited therapies
- Vital signs
- Pain assessment (see section 8.9)
- Labs: HbA1c (if no documented results within 90 Days of Randomization are available), assess blood glucose, and serum creatinine (if no documented results within 6 months of Randomization are available)
- Pregnancy test (blood or urine) if female subject is of childbearing potential. If female is not of childbearing potential the reason for inclusion must be included in the study record
- Assurance of effective birth control if female subject is of childbearing potential
- Ulcer history
- Index Ulcer assessment
- Assess signs and symptoms for clinical infection of the index ulcer (see section 8.10.3)
- Index ulcer foot neuropathy Semmes Weinstein 10-point test with vibratory; See section 8.14
- Clean the index ulcer
- Debridement of the index ulcer, if applicable (see Appendix E)
- Digital imaging of the index ulcer
- Record Index ulcer measurements
- Obtain X-ray to rule out osteomyelitis or bone infection of the affected foot
- ABI, SPP, TCOM, TBI, PVR measurement or Arterial Doppler Study will be obtained (see Appendices B-D)
- Initiate offloading of the index ulcer
- WOUND-Q

- Assessment of subject's eligibility to continue in the study
- Apply appropriate SOC to index ulcer and outer dressing
- SnapshotNIR (at select sites)

SV2: Procedures to be performed include:

- Medical history changes from previous visit
- Physical examination changes from previous visit
- Assess concomitant medications, changes from previous visit and prohibited therapies
- Vital signs
- Pain assessment (see section 8.9)
- Assess blood glucose
- Index ulcer assessment
- Assess signs and symptoms for clinical infection of the index ulcer (see section 8.10.3)
- Index ulcer foot neuropathy Semmes Weinstein10 point test with vibratory; See section 8.14
- Clean the index ulcer
- Debridement of the index ulcer if applicable (see Appendix E)
- Digital imaging of the index ulcer
- Record Index ulcer measurements
- Assessment of offloading
- Assessment of subject's eligibility to continue in the study
- Apply appropriate SOC to index ulcer and outer dressing

A panel of three board-certified plastic surgeons will review each wound, as well as inclusion/exclusion criteria, in a blinded fashion to ensure that randomizations are appropriate. The review will occur between SV2 and the day of randomization. The plastic surgeon will provide correspondence to the trial manager that the subject is appropriate for randomization, prior to the site being able to randomize the patient.

4.5.3 Treatment Phase

When determining the visit dates, the reference should always be seven days (±3 days). Every attempt should be made to maintain subjects on their original treatment schedule.

4.5.3.1 TV1: Prior to Randomization

The following assessments and activities are performed at this visit:

- Medical history changes from previous visit
- Physical examination changes from previous visit
- Assess concomitant medications, changes from previous visit and prohibited therapies
- Vital Signs

- Pain assessment (see section 8.9)
- Assess Blood glucose
- Index ulcer Assessments
- Assess signs and symptoms for clinical infection of the index ulcer (see section 8.10.3)
- Index ulcer foot neuropathy Semmes Weinstein 10-point test with vibratory; See section 8.14
- Clean the index ulcer
- Debridement of the index ulcer if applicable (see Appendix E)
- Digital imaging of the index ulcer
- Record Index ulcer measurements
- Assessment of offloading
- Index ulcer closure assessment will be determined by a site Investigator
    - If the index ulcer is 100% re-epithelialized, the subject will be considered a screen failure.
- Assessment of subject's eligibility to continue in the study
- SnapshotNIR (at selected sites)
- If the subject is eligible, randomization will be performed
- If the subject is not eligible, discharge the subject from the study as a screen failure

4.5.3.2 TV1: Randomization

The following assessments and activities are performed at this visit:

- Randomize the subject
- Apply appropriate treatment to index ulcer:
    - Apply SOC therapy with MIRRAGEN™ group 1
    - Apply SOC therapy with FIBRACOL™ group 2
- Apply outer layer dressing
- Ensure offloading of the wound is satisfactory
- Schedule the next study visit for one week later (±3 days)

4.5.3.3 Treatment Phase Visits: Weeks 2-12 (with additional tests week 2, 3, 4, 6 and 7 listed below)

The following assessments and activities are performed at these visits:

- Medical history changes from previous visit
- Physical examination changes from previous visit
- Assess concomitant medications, changes from previous visit and prohibited therapies
- Vital Signs

- Pain assessment (see section 8.9)
- Assess Blood glucose
- Assessment of offloading
- Index ulcer foot neuropathy Semmes Weinstein 10-point test with vibratory; See section 8.14
- Check for any changes in the subject's health and assess them for any adverse effects and adverse events
- Index ulcer closure assessment will be determined by a site Investigator
    - If the index ulcer is 100% re-epithelialized, the subject will be scheduled for an HCV two weeks later. Please perform all applicable assessments and study procedures.
- Index ulcer Assessments
- Check for signs of clinical infection. If a clinical diagnosis of infection has been made, then the subject can be treated with oral antibiotics, but topical antibiotics or antimicrobial dressings CANNOT be used on the study ulcer
- Clean the index ulcer
- Debridement of the index ulcer if applicable (see Appendix E)
- Digital imaging of the index ulcer
- Record Index ulcer measurements
- Apply appropriate treatment to index ulcer:
    - Apply SOC therapy with MIRRAGEN™ group 1
    - Apply SOC therapy with FIBRACOL™ group 2
- Ensure offloading of the index ulcer is satisfactory
- Apply outer layer dressing
- The next visit will be scheduled for one week (+/- 3 days)

4.5.3.3.1 TV2: Treatment Visit 2

In addition to the procedures required at every treatment visit, perform the following additional procedures:

- SnapshotNIR (at select sites)

4.5.3.3.1 TV3: Treatment Visit 3

In addition to the procedures required at every treatment visit, perform the following additional procedures:

- WOUND-Q

4.5.3.3.1 TV4: Treatment Visit 4

In addition to the procedures required at every treatment visit, perform the following additional procedures:

- SnapshotNIR (at select sites)

4.5.3.3.2 TV6: Treatment Visit 6

In addition to the procedures required at every treatment visit, perform the following additional procedures:

- Pregnancy test (blood or urine) if female subject is of childbearing potential
- Assurance of effective birth control if female subject is of childbearing potential

4.5.3.3.3 TV7

In addition to the procedures required at every treatment visit, perform the following additional procedures:

- Evaluate wound for greater than 50% wound area reduction, and if less than 50% healed proceed to End Of Study (EOS1) visit
- SnapshotNIR (at selected sites)
- WOUND-Q

4.5.4 End of Study (EOS1) Visit

The following assessments and activities are performed at this visit:

- Medical history changes from previous visit
- Physical examination changes from previous visit
- Assess concomitant medications, changes from previous visit and prohibited therapies
- Vital Signs
- Pain assessment (see section 8.9)
- Assess Blood glucose
- HbA1c
- Assessment of offloading
    - Index ulcer foot neuropathy Semmes Weinstein 10-point test with vibratory; See section 8.14
- WOUND-Q
- Check for any changes in the subject's health and assess them for any adverse effects and adverse events
- Index ulcer closure assessment will be determined by a site Investigator
    - If the index ulcer is 100% re-epithelialized, the subject will be scheduled for a Healing Confirmation Visit (HCV) two weeks later. Please perform all applicable assessments and study procedures.
- Index Ulcer Assessments
- Check for signs of clinical infection. If a clinical diagnosis of infection has been made, then the subject can be treated with oral antibiotics, but topical antibiotics or antimicrobial dressings CANNOT be used on the study ulcer

- Clean the index ulcer
- Debridement of the index ulcer if applicable (see Appendix E)
- Digital imaging of the index ulcer
- Record Index ulcer measurements
- Ensure offloading of the index ulcer is satisfactory and make an appointment for the subject with their desired clinician for follow-up care OR if subject is healed apply outer layer dressing and schedule Healing Confirmation Visit two weeks later (+/- 3 days)
- SnapshotNIR (at select sites)
- Apply outer layer dressing

4.5.5 HCV: Healing Confirmation Visit

Perform the following procedures and assessments at this visit:

- Medial History Changes from previous visit
- Physical examination changes from previous visit
- Assess concomitant medications, changes from previous visit and prohibited therapies
- Vital signs
- Pain assessment (see section 8.9)
- Assess Blood glucose
- Assessment of offloading
- Index ulcer foot neuropathy Semmes Weinstein 10-point test with vibratory; See section 8.14
- Check for any changes in the subject's health and assess them for any adverse effects and adverse events
- If wound has re-opened, clean index ulcer
- If wound has re-opened, apply outer layer dressing
- Debridement of the index ulcer if applicable (see Appendix E)
- Digital imaging of the index ulcer
- If wound has re-opened, index ulcer measurements
- Confirm that the wound remained completely epithelized
- If wound has re-opened, document any other index ulcer assessments. If this is the EOS visit, discharge the subject from the study and make an appointment for the subject with their desired clinician for follow-up care; otherwise continue subject in study with allocated treatment schedule

4.5.6 Unscheduled Visits

Unscheduled visits may be required in addition to the visits detailed above. Additional visits are at the discretion of the Investigator. An example of an unscheduled visit is when a change in dressings is required between scheduled visits. The details of these unscheduled visits with

subjects will be recorded in the medical records/source documents and on the Unscheduled Visit CRF.

4.5.7 Missed Visits

If a subject misses a visit, the site is to make every effort to have the subject return as soon as possible to make up the visit. Once the subject is seen, he/she is to return to his/her original weekly visit schedule. For example, if a subject was seen regularly on Mondays but missed a scheduled Monday visit and came in on Wednesday, he/she should return the next Monday to maintain his/her weekly Monday visit schedule.

5 Subject Completion, Success/Failure, Withdrawal and Screen Failure

5.1 Subject Completion

- A subject whose index ulcer has closed will be considered as having completed the study
- A subject who completes the Treatment Phase up to TV7 with the wound healed less than 50% will be considered as having completed the study
- A subject who completes the Treatment Phase but still has an unhealed index ulcer will be considered as having completed the study
- A subject who does not complete the Treatment Phase and still has an unhealed index ulcer will be considered as not completing the study

5.2 Success and Failure

- A subject whose ulcer heals by 13 weeks and has been confirmed as healed two weeks later will be considered a treatment success
- A subject whose ulcer has failed to heal by 50% or greater at TV7 or six weeks after randomization will be considered a treatment failure
- A subject whose ulcer has failed to heal by 13 weeks will be considered a treatment failure
- A subject who is withdrawn from the trial and/or experiences an amputation is also considered a treatment failure

5.3 Premature Withdrawal from the Study

A subject who is randomized into the Treatment Period of the study but who does not complete the study has prematurely discontinued.

All subjects have the right to withdraw at any point during treatment without prejudice. It will be documented whether or not each subject completes the study. If for any subject, study treatment or observations were discontinued, the reason(s) will be recorded.

The Investigator can discontinue a subject at any time if it is considered medically necessary. In addition, the subject will be withdrawn from the study, if any of the following events occur:

- A subject is significantly non-compliant with the requirements of the protocol
- A subject becomes pregnant or does not confirm use of birth control. (Note: the pregnancy will be followed up to term for safety. Relevant safety information collected after the study has been completed will be reported as supplemental information.)
- A subject has revascularization surgery on the lower extremity on which the index ulcer is located
- The subject's index ulcer deteriorates and is infected to the point where there is exposed bone
- An infection episode lasting more than two weeks with no response to allowable treatments

Premature withdrawal from the study may occur if:

- A subject is treated with a prohibited medication. This decision will be made by the Investigator as to whether premature withdrawal is warranted.

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 CRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. Three follow-up attempts are required. These attempts must be documented and should include two phone calls and one certified letter.

In the event that a subject is prematurely discontinued from the study at any time due to an adverse effect or adverse event, the procedures in Section 10 of this protocol must be followed.

5.4 Screen Failures

A subject who has signed a consent form, has been assigned a screening number, but is not randomized is classified as a screen failure. Subject number, demography and reason for screen failure will be collected. Subjects who fail their first screening attempt may be re-screened again (i.e., up to two screenings total) and may be enrolled if they are found to meet all inclusion and none of the exclusion criteria at SV2. Rescreening follows a subject, not a specific wound, so subjects cannot be screened > 2 times for different wounds. Anytime a subject screen fails and later rescreens (outside of the original 2 weeks screening window), they must be re-consented for the study.

6 Standard of Care Study Treatment Primary Dressing

6.1 Method for Assigning Eligible Subjects to Treatment

Eligible subjects will be assigned to one of the treatment groups based on a randomization schedule. Details of the randomization are provided in the statistical analysis section.

6.2 MIRRAGEN™ Product Information (provided from IFU)

Product Description

The MIRRAGEN™ Advanced Wound Matrix is a wound dressing solely composed of biocompatible and resorbable borate-based bioactive glass fibers and particles. It is a flexible and moldable advanced wound dressing that can be easily customized to fit the wound bed. The fiber structure of the MIRRAGEN™ Advanced Wound Matrix allows it to absorb fluid from the wound and facilitate natural wound healing. The bioabsorbable material used in the MIRRAGEN™ Advanced Wound Matrix is a borate glass specially designed for medical applications. The material is biocompatible and will eventually be fully absorbed at the wound site. This resorption process is initiated by the exposure of the dressing to fluid at the wound site.

Indications for Use

The MIRRAGEN™ Advanced Wound Matrix is intended for use in the management of wounds. Wound types include:

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

The product is designed for single patient/single treatment use only. DO NOT reuse.

Warnings MIRRAGEN™ Advanced Wound Matrix is sterile only if the packaging is unopened and undamaged. **DO NOT re-sterilize. DO NOT use expired product.**

Precautions MIRRAGEN™ Advanced Wound Matrix dressings are intended to be used under the supervision of a healthcare professional.

Adverse Reactions Possible adverse reactions may include local irritation, swelling, inflammation, excessive redness, or pain.

Contraindications The use the MIRRAGEN™ Advanced Wound Matrix should be discontinued if any adverse reactions are observed.

How Supplied MIRRAGEN™ Advanced Wound Matrix is supplied sterile. The dressing is packaged in a two-piece disposable tray that is sealed in a foil pouch.

Instructions for Use The MIRRAGEN™ Advanced Wound Matrix is sterile. Use aseptic techniques when applying the dressing.

1. Prepare the wound bed using standard wound cleaning and debridement procedures.

2. Dry the area surrounding the wound.

3. Cut or shape the MIRRAGEN™ Advanced Wound Matrix dressing to fit the size of the wound bed. Place the dressing directly in contact with the wound, ensuring the entire wound area and wound margins are covered.

4. If applying MIRRAGEN™ Advanced Wound Matrix to a dry wound, moisten the dressing with sterile saline to aid in maintaining a moist wound environment.

5. Place a suitable secondary dressing over the MIRRAGEN™ Advanced Wound Matrix to manage the wound environment and protect the wound area. The secondary dressing should completely cover the MIRRAGEN™ dressing.

6. Dressing changes are conducted according to standard wound care practices every 3 to 7days. As healing occurs, new tissue may grow into the MIRRAGEN™ Advanced Wound Matrix. Do not forcibly remove or debride areas of the MIRRAGEN™ dressing that are embedded or adhered to the wound site. The MIRRAGEN™ dressing is 100% bioabsorbable and will eventually be absorbed at the wound site.

7. Loose sections of the MIRRAGEN™ Advanced Wound Matrix may be removed. Apply additional MIRRAGEN™ dressing to fill and cover the wound. Moisten the dressing with sterile saline, as needed.

8. Secondary dressings should also be replaced at each dressing change.

9. Heavy exuding wounds may require more frequent dressing changes.

Storage Do not expose to excessive heat and humidity.

Shelf-life Refer to pouch label.

Sterilization This device has been sterilized with gamma irradiation

Manufactured and Distributed by:

ETS Wound Care, LLC
13210 Dillon Outer Road
Rolla, MO 65401 USA
P h o n e + 1 - 573-202-2550
Fax: + 1 - 573-755-0588
support@etswoundcare.com
www.etswoundcare.com

6.3 FIBRACOL™ Product Information (provided from IFU)

Product Description

FIBRACOL™ Plus Collagen Wound Dressing with Alginate is an advanced wound care device composed of collagen and calcium alginate fibers. FIBRACOL™ Plus dressing contains 80% more collagen than our traditional FIBRACOL™ Dressing. Its unique combination of natural biopolymers created by a patented process combines the structural support of collagen and the gel forming properties of alginates into a sterile, soft, absorbent, conformable topical wound dressing. In the presence of wound fluid FIBRACOL™ Plus dressing maintains a physiologically moist microenvironment at the wound surface that is conducive to granulation tissue formation, epithelialization, and enables healing to proceed at a rapid rate.
FIBRACOL™ Plus dressing is versatile as a primary wound dressing, it can be cut to the exact size of the
wound, multi-layered for the management of deep wounds and used in combination with either a semi-occlusive or non-occlusive secondary dressing.

Indications

FIBRACOL™ Plus dressing is indicated for the management of exuding wounds including:

- Full-thickness and partial-thickness wounds
  Pressure ulcers
- Venous ulcers
- Ulcers caused by mixed vascular etiologies
  Diabetic ulcers
- Second-degree burns
- Donor sites and other bleeding surface wounds
  Abrasions
- Traumatic wounds healing by secondary intention
  Dehisced surgical incisions

Precautions

FIBRACOL™ Plus dressing may be used when visible signs of infection are
present in the wound area only when proper medical treatment addresses the underlying cause. FIBRACOL™ Plus dressing may be used under compression therapy with healthcare professional supervision.

Contraindications

FIBRACOL™ Plus dressing is not indicated for wounds with active vasculitis, third-degree burns, or patients with known sensitivity to collagen or alginates.

Adverse Reactions

FIBRACOL™ Plus dressing should not be used on patients with known sensitivities to collagen or alginates. Discontinue use if signs of sensitivity appear.

Directions for Use

Debride when necessary and irrigate the wound site with normal saline solution. Remove excess solution from surrounding skin. For heavily exuding wounds, apply to wound bed directly. For wounds with minimal exudate, apply to moistened wound bed; this will initiate the gel forming process.

Pack deep wounds loosely. The dressing can be cut to size with sterile scissors. The amount of FIBRACOL™ Plus dressing to be used depends on the size of the wound and the amount of exudate.

FIBRACOL™ Plus dressing may be covered with either a non-occlusive secondary dressing and fixed to the skin with a non-irritating tape or a semi-occlusive dressing. Reapply FIBRACOL™ Plus dressing when the secondary dressing has reached its absorbent capacity or whenever good wound care practice dictates that the dressing should be changed. A heavily exuding wound may require daily or twice daily dressing changes. More moderately exuding wounds will require less frequent changes

Following the initial application, irrigate the wound with saline solution. Reapply FIBRACOL™ Plus dressing as previously instructed.

Dressing Removal

After gently removing the secondary dressing, lift any FIBRACOL™ Plus dressing that has not formed a gel and discard. Using normal saline, gently irrigate the wound to remove any residual gel.

Do not re-use.

Do not re-sterilize.

Do not use it if the package is damaged.

The use by date of this product is printed on the packaging.

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

7 Standard of Care, Concomitant Medications, Excluded/Allowed Therapies/Medications and Allowed Dressings

Beginning at the screening visit, ALL subjects must have their index ulcer managed using the SOC procedures noted below.

7.1 SOC Procedures

7.1.1 Cleaning the Index Ulcer

Remove all dressings and wash the foot. The leg should be elevated for as much time as possible during this process. Wash the foot with sterile water or saline solutions. Gently irrigate the index ulcer prior to each dressing change with the same solution. Wound cleansers containing antiseptics (examples: Hypochlorous Acid, Vashe, ExSept, PrepIt, etc.) are prohibited for use during the duration of this study.

During the Treatment Phase, the washing and cleaning of the DFU must be done prior to application of SOC primary dressing

7.1.2 Debridement of the Index Ulcer

Debridement is an essential technique and SOC in the treatment of DFU. It is important to remove all non-viable and necrotic material from the index ulcer prior to enrolling the patient. Debridement is allowed during the treatment phase at the treating Investigator's discretion. For detailed guidelines please see Appendix E.

7.1.3 Offloading

Offloading is essential if the wound is to heal. A diabetic offloading CAM boot will be given to each subject or if the subject cannot be accommodated into a CAM boot, a TCC will be provided.

Subjects will be educated on the importance of using the device to offload their DFU and instructed on keeping dressings dry and to call or visit the study site if the dressing becomes soiled, wet or is removed. In addition, subjects should be educated on wound infection and if they observe infection, to call or visit the study site.

7.2 Concomitant Medications

The subject may be administered any necessary medications, at the discretion of the Investigator; provided such medications are not applied topically to the index ulcer surface (topical medication can be applied to other surfaces around the ulcer or other non-reference ulcers).

All medications and therapies administered or taken by the subject beginning 30 days prior to signing the ICF and throughout the study will be recorded in the source documents and for randomized subjects, on the appropriate CRF.

7.3 Prohibited Medications and Therapies

The following treatments and medications are prohibited 30-days prior to screening period and throughout the trial:

- Any cellular and/or tissue-based products or wound dressings that include growth factors (e.g., EpiFix, Regranex, Dermagraft, Apligraf, GraftJacket, OASIS, Primatrix, Matristem)
- Revascularization surgery on the lower extremity with the index ulcer

- Radiation therapy to the foot

Excluded at SVI

- Topical antibiotics* or other topical agents, including or containing silver, honey, hydrofera blue, etc. (with the exception of anesthetics used during debridement)
- Systemic steroids/oral corticosteroids in excess of 10mg daily dose. (Note: inhaled steroids are acceptable)
- Other immunosuppressive agents and chemotherapy
- Cytotoxic therapies
- Negative pressure wound therapies
- Hyperbaric oxygen
- Any other investigational treatment/medications in the Investigator's opinion are likely to seriously impact wound healing
- Heat lamps
- UV lights
- Whirlpool baths
- Water Piks™
- Jet water streams (other than gentle water irrigation)
- Wound cleansers that contain active ingredients and are not just normal saline (e.g., Hypochlorous Acid, Vashe, ExSept, PrepIt, etc.)
- Selective COX-2 inhibitors (such as Celecoxib)

*Topical antibiotics must be stopped at the first screening visit.

7.4 Allowable Medications and Therapies

The following medications and therapies are allowed during the study, if in the opinion of the Investigator, they are required for proper care of the study subject:

- Use of anesthetics for debridement
- Treatment with systemic antibiotics for acute or chronic infection, however, prophylactic use of systemic antibiotics is not allowed
- Other medications/therapies that are not otherwise prohibited and in the opinion of the Investigator, are required for proper medical care

7.5 Approved Dressings

The following is a list of approved dressings suitable for study DFUs receiving SOC treatment:

SOC FIBRACOL™ Group

- FIBRACOL™ – Collagen / Calcium alginate
- Plain foam (e.g., Allevyn gentle, Mepilex)
- Three-layer dressing, (4x4 gauze, soft cast roll, ace bandage / coban)

SOC MIRRAGEN™ Group

- MIRRAGEN™ – Wound Matrix
- Plain foam (e.g., Allevyn gentle, Mepilex)
- Three-layer dressing, (4x4 gauze, soft cast roll, ace bandage / coban)

8 Description of Protocol Assessments and Procedures

8.1 Informed Consent

Written informed consent will be obtained for this study by the Investigator or suitably qualified designee from all subjects before the collection of any protected health information and performance of any protocol-specific procedure.

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to Good Clinical Practice (GCP). The Investigator, or designee, must fully inform subjects of all pertinent aspects of the study. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the study, the ICF must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. For screen failure subjects who rescreen at a later date, re-consenting is required.

8.2 Assessment of Eligibility

At each visit during the Screening Period, the Investigator must assess a subject's continued suitability and eligibility for the study, especially with regard to the Inclusion and Exclusion criteria. If the subject is no longer suitable or eligible for the study, the subject will be considered a screen failure. Screen failure subjects may be re-entered into the study at a later time and re-screened.

Further, a panel of three board-certified plastic surgeons will review each wound, as well as inclusion/exclusion criteria, in a blinded fashion to ensure that randomizations are appropriate. The review will occur between SV2 and the day of randomization. The plastic surgeon will provide correspondence to the trial manager that the subject is appropriate for randomization, prior to the site being able to randomize the patient.

8.3 Re-Screening

If a subject initially fails to meet Inclusion/Exclusion criteria 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 again (i.e., up to two screenings) and may be enrolled if they are found to meet all Inclusion and none of the Exclusion criteria at the second screening visit.

8.4 Subject Demographics, Medical History and Ulcer History

8.4.1 Demographics

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

- Date of ICF signature
- Date of birth
- Gender
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

- Use of tobacco products

8.4.2 Medical History

A medical history will be recorded during the Screening Period and will include:

- All ongoing medical conditions
- All previously resolved medical conditions related to diabetes or foot ulceration or which are relevant in the opinion of the Investigator

Events that emerge prior to the randomization visit will be recorded in the medical history and not as Adverse Events. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions that occur prior to randomization

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

- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal
- Hepatic
- Neurological
- Endocrine
- Lymphatic
- Hematologic
- Immunologic
- Dermatologic
- Psychiatric
- Genitourinary
- Other
- DFU History

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (resolved or ongoing)

8.4.3 Foot Ulcer History

- Duration of the current DFU

  Note: "Duration" is defined as the length of time that the index ulcer has been open at this location since the last time it was fully closed.

- Current offloading system used for the DFU (if any) and length of time that this has been used
- Prior treatments that have been used on the DFU for up to 1-year
- Age when the subject developed his/her first DFU
- Total number of previous DFUs
- Location of the current DFU

  Note: "Index ulcer location" is defined by the ulcer being on the left or right foot, by the location of the ulcer on the foot, dorsal or plantar, toe (which toe), forefoot, midfoot, hind foot, ankle heel and by the positioning of the ulcer as lateral, medial, dorsal, or plantar located.

- Number of additional DFUs and location of each present at the screening visits
- History of DFU recurrence

Note: "Recurrence" is defined as the re-opening of the index ulcer after complete healing.

- History of any amputations in the study foot and contralateral foot or leg
- History of any significant foot deformities, dermatological abnormalities, fungal lesions, or other findings.

8.4.4 Physical Exam

The physical examination will include routine examinations for the following:

- Head, ears, eyes, nose, and throat
- Abnormalities of the extremities
- Neurologic abnormalities
- Heart/cardiovascular abnormalities
- Musculoskeletal abnormalities
- Dermatologic abnormalities
- 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 safety or efficacy results for the subject, i.e., the abnormality is clinically significant

Each abnormality will be recorded, and the Investigator will record an assessment of its clinical significance.

8.4.5 Vital Signs

The following vital signs will be collected:

- Height
- Weight
- Body mass index (BMI)
- Seated blood pressure (take after the subject has been seated for at least 5 minutes)
- Pulse
- Temperature

8.4.6 Pregnancy test

Females who are of childbearing potential must have a urine or blood pregnancy test at SV1 and at TV6.

8.5 ABI or Arterial Doppler Ultrasound

ABI, also known as the Winsor Index and the Ankle Brachial Pressure Index, is the ratio of blood pressure measured at the ankle to that measured at the arm. Details of the procedure can be found in Appendix B. An ABI < 0.8 indicates that there is a high probability that arterial insufficiency is present (positive predictive value 95% in a general practice population).

It should be noted that incompressible, calcified arteries may occur in diabetes causing a falsely elevated ABI, so if the subject has other signs or symptoms that could suggest peripheral arterial disease, further investigations to determine vascular status may be warranted.

A documented record of an ABI test performed using the index ulcer leg, within one month of SV1 is acceptable for the purposes of this study, otherwise this must be completed in the Screening Period.

As an alternative arterial Doppler ultrasound can be performed evaluating for biphasic dorsalis pedis and posterior tibial vessels at the level of the ankle.

8.6 SPP

SPP provides another noninvasive method for measuring microcirculatory pressure of the artery at the skin level. It measures the pressure at which perfusion first returns to the cutaneous microcirculation following a controlled release of occlusion. SPP is useful in assessing the ischemic severity of lower limb and predicting ulcer healing in chronic critical limb ischemia with a value of <30 mmHg. See Appendix C for the appropriate technique of assessment.

8.7 TCOM

A TCOM assesses the partial pressure of oxygen molecules dissolved in the blood plasma. The amount of oxygen detected by the sensor is a balance of the oxygen delivery and local physiologic demands and reflects the metabolic status of the skin; it indicates the level of oxygen available at the ulcer site to assist in the ulcer healing process. A TCOM less than 30 mmHg of oxygen indicates impaired ulcer healing and ischemic disease. An appropriate technique for a TCOM assessment is provided in Appendix D.

8.8 WOUND-Q Assessment

The WOUND-Q will be administered to all subjects on SV1, TV3, TV7 and EOS1. This tool will document the impact of the wound on the subject's life and whether the treatment interventions helped to return them to improved functioning.

If a subject discontinues the study, every effort should be made to contact them to complete the WOUND-Q tool on their EOS1 visit.

Further details and the tool itself can be found in Appendix E.

8.9 Pain Assessment: NPRS

Pain intensity of the reference DFU is to be assessed before any dressing changes or other ulcer manipulations at all screening and treatment visits.

The subject will be asked to indicate a numerical value that best represents the current pain intensity at the index ulcer site on a scale of 0 to 10, anchored by word descriptors at each end, as "no pain" on the left side and "worst possible pain" on the right side of the number line. The number 0 represents "no pain," the number 5 represents "moderate pain", and the number 10 represents the "worst possible pain." The subject indicates the level of pain intensity by selecting a number on the line shown in Figure 3 below that represents their perception of their current state.

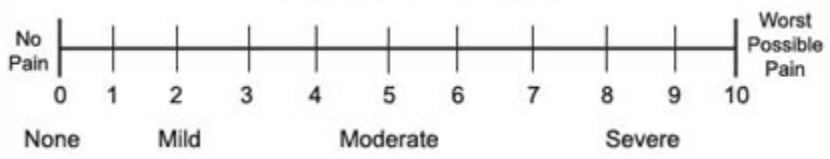

FIGURE 3: SUBJECT PAIN SCALE (NPRS)

8.10 Ulcer Assessments

A number of different index ulcer assessments are required, including appearance, exudate characteristics, infection, and peri-wound characteristics.

8.10.1 Index Ulcer Appearance Assessment (Pre-debridement)

Index Ulcer Appearance Assessment (pre-debridement) categories includes:

- % Granulating *(red/brown bumpy tissue that bleeds upon light debridement)*
- % Non-viable tissue
- % Epithelialized Skin

Note: the categories should add to 100%.

8.10.2 Index Ulcer Exudate Assessments

The Investigator will determine the amount and type, if any, of index ulcer exudate. In determining the amount of index ulcer exudate, the Investigator must take into account the amount of exudate absorbed into the index ulcer dressing. Table 2 below details the categories will be used to quantify the amount and describe the type of index ulcer exudate:

TABLE 2: INDEX ULCER EXUDATE ASSESSMENT

Index Ulcer Exudate Assessment	
Volume	• No exudate • Minimal amount • Light (scant) or small amount • Moderate amount • Heavy/large/copious amounts
Type	• Not applicable: no exudate present • Serous: clear or light-yellow watery plasma • Serosanguinous: pink to light-red watery plasma • Sanguineous: red with fresh bleeding • Purulent: thick and opaque exudate, of creamy yellow, green, white, or tan color

8.10.3 Index Ulcer Infection Assessments

The presence/absence of the following signs of infection at the index ulcer site will be documented at each visit. Infection of the index ulcer will be assessed using the STONEES method developed by Woo and Sibbald.[19] Table 3 below lists the criteria for considering an index ulcer infected:

TABLE 3: INDEX ULCER INFECTION ASSESSMENT

Index Ulcer Infection Assessment
Three or more of the following signs or symptoms are present: • Increased surface area • Increased peri-wound margin temperature by more than 3^0F difference between two mirror image sites • Exposed bone or can be probed to the bone

- New areas of breakdown or satellite lesions
- Presence of swelling or reddened skin in peri-wound area
- Increased wound drainage
- Unpleasant, sweet, or sickening odor present

NOTE: An ulcer that Is deemed to be infected with three or more of the following signs will undergo a wound culture to confirm the presence of infection and identify the pathogenic organism, so the study subject receives the most appropriate antibiotic treatment

Infection at Index Ulcer site prior to Randomization

If the infection occurs prior to randomization i.e., prior to TV1, then the subject will be ineligible to be randomized.

Infection at Index Ulcer site after Randomization

If infection of the index ulcer site occurs after randomization *i.e.*, after the Randomization visit, record the infection as an adverse event and treat it as appropriate with oral antibiotics at the discretion of the Investigator.

Note: application of topical antibiotics and anti-microbial dressings to the index ulcer site are prohibited.

A subject with an infected index ulcer that is being treated by the Investigator will remain in the study unless the situation requires an alternative methodology that violates the protocol. Antibiotic interventions will be recorded on the Concomitant Medications CRF, and the event will be categorized as an Adverse Event, serious if it meets the definition of that category. All subjects who show evidence of an ulcer infection must have it reported on an Adverse Event CRF.

All subjects will be instructed to contact the Investigator if signs or symptoms of infection develop prior to their next scheduled visit.

During an episode of infection, the Investigator should not continue TCC, if it is being used, until the infection is resolved, and dressings should be changed at least every 72 hours.

Evaluate the skin surrounding the index ulcer for presence of signs such as erythema, edema, and cellulitis.

8.10.4 Investigator Assessment of Index Ulcer Closure

"**Complete healing**" of the index ulcer is defined as 100% re-epithelialization without drainage. At each visit, the Investigator will assess the ulcer by answering the following questions:

- Index ulcer 100% re-epithelialized?
- Drainage is absent?

Both questions must be answered "yes" for the index ulcer to be considering having reached "complete closure."

The date of complete healing is defined as the date of the first assessment of 100% re-epithelialization.

Confirmation of Wound Healing

Note that if a wound is initially judged as healed, it must be confirmed as healed with one healing confirmation visit at two weeks (plus or minus three days, HCV 1). The assessment details can be found in section 4.3.2.

Index Ulcer Photographs and Measurements

The index ulcer will be digitally imaged with a Sony digital camera that is at least 20 (twenty) megapixels, with the photo taken at a focal distance of 18 inches and a two-dimensional calibration scale. The Investigator will also take a planimetry photo for appropriate wound measurement.

8.11 Randomization

Subjects who are eligible to participate in the study will be randomized to one treatment group at the time of completion of screening.

8.12 Assessment of Offloading

The following questions will be asked to assess the performance of the offloading during the Screening and Treatment Phase visits and at selected follow-up visits:

- Did the subject have the offloading device with him or her or is the TCC cast still present? (Yes/No)
- What percentage of the time is the subject using the offloading device while not sleeping? (Note: heel ulcers might still need to be offloaded while sleeping.)

8.13 Semmes Weinstein Monofilament Test for Peripheral Neuropathy

This is a non-invasive topical evaluation of neuropathy with a monofilament wire and with vibratory evaluation. The test will be performed in a standard manner with 10 points being evaluated on each visit. At each point, the Investigator asks the subject whether they can feel the filament and / or vibration (yes or no). Note: If a subject is missing a body part called out in the Semmes Weinstein test and with vibratory, the most skin in the area where the missing body part is located is used for the test.

8.14 SnapshotNIR

SnapshotNIR imaging for tissue perfusion will be obtained at SV1, TV1 pre-randomization, TV2, TV4, TV7, and EOS1. The procedure is described in Appendix H.

9 Data and Statistical Analyses

9.1 Data Analysis

This study consists of primary, secondary and exploratory/tertiary (research) endpoints. Data analysis of study endpoints includes use of validated DFU wound healing measures, quantitative and qualitative analyses, as well as exploratory methodologies. Table 4 below details each study endpoint, corresponding data, and planned analyses.

TABLE 4: ETS WOUND CARE, LLC DFU ENDPOINT DATA ANALYSIS

Endpoint	Endpoint Description	Supporting Study Data	Endpoint Analysis
Primary	Comparison of the proportion of index ulcers "healed" at 12 weeks	Investigator assessment of healing (100% epithelization w/no drainage), measurements of ulcer size using digital imaging and photos	Adjudication panel will determine using photographs of the DFU
Secondary	Proportion of Index Ulcers healed at 6 weeks		
	PAR at 6 and 12 weeks	Digital imaging	Mathematical wound area change
	Time to healing within 6 and 12 weeks	Primary endpoint	Mathematical time based on healing
	Changes in peripheral neuropathy	Semmes Weinstein with vibratory	Mathematical change in scores
	Changes in wound quality of life	WOUND-Q (Quality of life tool)	Mathematical change in scores
	Change in pain levels during trial	NPRS	Mathematical change in scores
	Difference in cellulitis and/or infection at 12 weeks	Observation	Count of positive and negative responses
Exploratory/Tertiary	Changes in tissue perfusion of wound bed and periphery with treatment	SnapshotNIR	Exploratory

9.2 Statistical Analysis

Descriptive statistical methods will be used to summarize the data from this study with hypothesis testing performed for the primary and other selected efficacy endpoints. All testing for endpoints will be two-sided with alpha set at .05 level of significance if no statistical testing is done at the interim analysis at 0.044 if statistical testing is done at N=240.

A formal Statistical Analysis Plan (SAP) will be created prior to database lock. The primary endpoint analysis will be at 12 weeks and a series of secondary and exploratory/tertiary

endpoints will be analyzed at 6 and 12 weeks. The SAP will provide a more technical and detailed description of the proposed data analysis methods and procedures. Any deviation from the analyses outlined in the protocol will be described in the most current version of the SAP. All statistical analyses will be conducted using PASW 28.

The primary study hypothesis is that the proportion of wounds healed at 12 weeks, after up to 12 weeks of SOC with MIRRAGEN™ and SOC with FIBRACOL™, will be equal for Groups 1 and 2. Formally, H0: I1–I2 = 0; HA: I1–I2 = D1≠0, where I1 is the proportion of wounds healed in Group 1, I2 is same metric for Group 2, D1 is the difference (I1–I2); assuming the alternative hypothesis and statistical test used is chi square/Fisher exact test. Analysis may be adjusted using generalized linear modeling based on available variables at baseline known to affect wound healing.

Group sequential trials with sample sizes of 120 and 120 at the final look achieve 100% power to detect a difference of 0.35 between group 1 (the MIRRAGEN™ group) (proportion 0.70) the control group (SOC with FIBRACOL™) proportion of 0.35 at the 0.049 significance level (alpha) using a two-sided Z-Test (Pooled).

The populations defined for analysis will include the intent-to-treat (ITT) and per protocol (PP). Additional analysis populations may be defined to evaluate study results. Any additional analysis populations will be defined in the SAP.

Envelopes will be created with a random allocation sequence, which will be composed of a random sequence of block sizes of 10 designed to achieve a balanced design.

One interim analysis will be performed (N~100). The object of the interim analysis is to assess subject outcomes between the groups, in particular to assess any adverse effects or events, such as infection and to recalculate sample size for the primary endpoint.

Primary analysis: Proportion of index wounds closed at 12 weeks (group 1 versus group 2) using chi square. Analysis will be adjusted using logistic regression.

Secondary analysis: (1) proportion of Index Wounds closed at 6 weeks (group 1 versus group 2) using chi square; (2) time to heal within 6 and 12 weeks using Kaplan-Meier analysis; (3) PAR at 6 and 12 weeks (group 1 versus group 2) using the Mann-Whitney test; (4) mean difference between groups 1 and 2 of change in weekly peripheral neuropathy score surrounding the DFU using the Semmes Weinstein monofilament with vibratory procedure based on GLM repeated measures; (5) mean difference between groups 1 and 2 of change in WOUND-Q score based on difference between baseline and 12 weeks using t test if data are normal or Kolmogorov–Smirnov test if data are non-normal; and (6) mean difference between groups 1 and 2 of change in weekly wound pain VAS score based on GLM repeated measures.

Control of the familywise error rate (all endpoints) will be achieved through the Hochberg step-up procedure.

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized and treated. Subjects who are withdrawn or lost to follow-up will be included in the ITT analysis of primary and secondary endpoints using data imputation methods detailed in the SAP. Sensitivity analysis will also be conducted for the primary endpoint using different imputation algorithms.

10 Adverse Effects and Events (Definitions and Reporting)

The Investigator is responsible for the detection and documentation of any events meeting the criteria and definition of an adverse effect or adverse event (AE), as described in this protocol.

During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting any adverse effect or adverse event, as detailed in this Section of the protocol.

10.1 SOC Adverse Events

Since this a post market study involving commercially available SOC dressings of FDA cleared and approved medical devices; adverse events associated with their use may also require reporting to FDA.

An AE is defined as any unfavorable or unintended sign, symptom or disease that occurs or is reported by the subject to have occurred, or a worsening of a pre-existing condition related to the procedure or medical treatment (device/drug) used. All AEs related to the study procedure or medical treatment, including intercurrent illnesses, must be recorded in the subject's medical records and on the CRF. CTCAE v4.0 will be used for AE reporting.

AEs will be defined as those events that occur after the first study treatment is applied at TV1, through the final study visit. A description of the AE along with the onset date, end date, severity, action taken, treatment, outcome, likely cause and relationship to the study procedure or products will be recorded in the CRF.

AEs associated with each treatment arm will be tabulated and compared at the end of the study. AEs will be elicited through direct questioning, subject reports, and physical examination.

An abnormal laboratory test result is not by itself considered to be an AE unless the Investigator considers the finding of clinical significance that should be reported in such a manner**.**

The Investigator is responsible for assessing the relationship of the AE to the procedure or medical treatments used and the seriousness and expectedness of the AE at the time of occurrence. A medically qualified person appointed by the Sponsor will also assess this once the Sponsor has been notified of an AE. All AEs that occur during the trial will be documented on the AE CRF.

AEs reported during the study should be followed to resolution of the AE or within thirty days from the end of the study. A final assessment of the outcome will be made at that time.

Each AE related to the study procedure or medical treatment used will be categorized as "serious" or "not serious," based on the definition of a serious adverse event (SAE). An SAE is defined as an AE resulting in at least one of the outcomes described in Section 10.1.3.

10.1.1 AE Severity Assessments

The guidelines outlined in CTCAE v4 will be used for severity assessments. Note: the term "severe" is a measure of intensity and that a severe AE is not necessarily serious. Table 5 below provides guidance on determining the severity of an AE.

TABLE 5: AE SEVERITY GRADING SCALE

Severity Grade	Description
Mild (1)	Awareness of sign, symptom, or event, but easily tolerated; does not interfere with usual daily activities or tasks.
Moderate (2)	Discomfort is enough to cause interference with usual daily activity. It may warrant therapeutic intervention.
Severe (3)	Incapacitating: inability to perform usual activities and daily tasks; significantly affects clinical status; requires therapeutic intervention.
Life-threatening (4)	Emergency treatment required, life-threatening, death.

A grade of 1-4 is assigned by the Investigator to each AE.

10.1.2 AE Causality Assessments

AEs will be assigned a relationship (causality) to the study procedure or medical treatments. The Investigator will be responsible for determining the relationship between an AE and the study procedure or medical treatment. The type of event, organ system affected and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study procedure or medical treatment. The relationship of AEs to study procedures or medical treatments will be classified as follows:

- Not Related: No relationship exists between the AE and the study procedure or medical treatment. The event is attributed to a pre-existing medical condition or an inter-current event unrelated to the study procedure or medical treatments.
- Possibly Related: Follows the study procedure or medical treatment but may have developed as a result of an underlying clinical condition or treatments/interventions unrelated to the study.
- Probably Related: Follows the study procedure or medical treatment but is unlikely to have developed as a result of the subject's underlying clinical condition or other treatment or other interventions.
- Definitely Related: Follows the study procedure or medical treatment and physical evidence shows a convincing relationship to the study procedure or medical treatment.
- Unknown: Follows the study product or medical treatment, but unable to determine the relationship to the study procedure or medical treatment.

10.1.3 Serious Adverse Events

A SAE is any untoward medical incident that occurs during the course of the study beginning after informed consent has been executed.

A 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

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment,

they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.1.3.1 Reporting of Serious Adverse Events

The Investigator or delegated site personnel is required to report all SAEs that occur during the study. Once the Investigator or delegated site personnel becomes aware of an SAE, he/she must report the SAE to the CRO and/or ETS Wound Care, LLC, the study Sponsor, within 24 hours.

The study sponsor contact is: Zachary Davis: ETS Wound Care. LLC, (573) 201-4023 email: Zachary.davis@heraeus.com

The CRO contact information is listed on the SAE reporting form.

A written SAE report must follow and must include a full description of the event and all supporting documentation available at the time (e.g., lab reports, culture reports, etc.). Additional follow-up information as it becomes available must be reported to the CRO and / or Sponsor.

The Investigator or delegated site personnel is also responsible for reporting all SAEs to the IRB in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

10.1.3.2 SAE Follow-up

All SAEs will be monitored for a minimum of 30 days until they are resolved, have stabilized, or are clearly determined to be due to a subject’s stable or chronic condition or intercurrent illness (es).

11 Direct Access to Source Data/Documentation

Subjects will be identified on CRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The monitors, auditors, personnel authorized by the Sponsor, the local IRB and applicable regulatory bodies are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research and will be given direct access to source data and documentation (e.g., medical charts/records, printouts, 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 while remaining compliant with institutional requirements.

12 Quality Control and Quality Assurance

12.1 Acceptability of CRF

CRF must be completed for each subject who has signed an ICF. For subjects who are screen failures, this would be limited to the Screening or other applicable forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

12.2 Modification of Protocol

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator's IRB must also be obtained prior to implementation of the change, with two exceptions:

When necessary to eliminate apparent immediate hazard to the subject, or

When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the ICF. The Investigator will provide an approval letter for the amendment and revised ICF, if applicable, to the Sponsor. An amendment must be made in writing, and it must be dated by both the Sponsor and the Investigator. All material must be approved by the IRB.

12.3 Reporting Protocol Deviations

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. Any time there is deviation from any protocol requirements, a protocol deviation is required to be reported. If the deviation may impact subject participation, the Sponsor should be notified and 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 CRFs. Protocol deviations will be tracked at the site level and (by the Sponsor) at the study level for the duration of the trial.

13 Ethics and Regulatory Requirements

This study is to be conducted in accordance with the requirements of this protocol and in accordance with principles consistent GCP, ICH E6, HIPAA regulations (45 CFR Part 164) and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without prior review and approval of the IRB, except where it may be necessary to eliminate an immediate hazard to a study subject. In such a case, the change will be reported to the IRB as soon as possible, according to IRB requirements. Additionally, all products used in this study are manufactured, handled, and stored in accordance with their FDA labeling.

13.1 IRB

The Investigator at each center will provide the IRB with study materials, including but not limited to the clinical study protocol, ICF and any advertising materials. The study will not be initiated until the IRB provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The site Investigator will not participate in the decision. If the Investigator is an IRB member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Investigator will be made to the IRB 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 and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without IRB prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to subjects or when the change involves only logistics or administration.

13.2 Investigator's Responsibilities

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the ICH GCP Consolidated Guideline 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.

13.3 Subject Informed Consent Requirements

Written and oral information about the study in a language understandable by the patient will be given to all patients by the Investigator and/or designee. Written informed consent will be obtained from each patient before any procedures or assessments that would not otherwise be required for the care of the patient are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained, and the patient has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the patients 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 21 CFR § 50.27 and GCP requirements. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB. A copy of the ICF to be used will be submitted by the Investigator to the IRB for review and approval prior to the start of the study. Each study site must provide the Sponsor with an unsigned copy of the IRB-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.

14 Data Handling and Record Keeping

14.1 Recording and Collection of Data

The primary source document for this study will be the subject's medical record. If separate research records are maintained by Investigators, the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to the approved CRF. The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review CRFs 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. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database, designed in accordance with the clinical data manager.

14.2 Clinical Data Management and Monitoring

The CRO will be responsible for the processing and quality control of the data. The study will be monitored by the CRO. Monitoring may consist of either on site or remote review of any and all applicable study records. All study CRFs and background source documents will be made available for monitoring. The study monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

14.3 Archiving

All study documentation at the Investigator site will be archived in accordance with PERI SOPs.

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
- Laboratory results, ranges, and certifications
- Product (SOC dressing supplies) and accountability records
- Study personnel signature log
- Correspondence to and from the Sponsor, designee, and IRB
- Investigator and sub-Investigator CVs
- Signed ICF and HIPAA consent forms
- Subject screening and randomization log
- AE or SAE event reports

- IRB approval, re-approval letters and reports
- Any 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.

15 Publication Plan

Manuscripts and abstracts will be prepared by both the Investigators 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 Principal 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 agreed upon submission of a manuscript for 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.

Publication and Disclosure: Because this is a multi-center study, sites and Investigators shall not independently publish, publicly disclose, present or discuss any results or information pertaining to site's and Investigator's activities conducted under this agreement, until such a multi-center publication is released under Sponsor's direction; provided, however, that if a publication is not released within eighteen (18) months after completion of analysis of all study data from all sites within the multi-center study, site and Investigator shall have the right to publish the results of and information pertaining to site's and Investigator's activities conducted under this protocol and the clinical trial agreement with sponsor permission. Site and Investigator agree to submit any proposed manuscript, presentation, or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. Site and Investigator shall not publish, publicly disclose, present, or discuss any results of or information pertaining to sites and Investigator's activities prior to completion of the trial, even if the study is terminated before its completion and the final clinical study report is signed off or with respect to any endpoints or analyses, other than those specified in this protocol.

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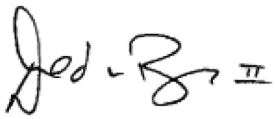
17 SIGNATURES

The Protocol has been reviewed in respect to compliance with ISO 14155: 2020, applicable national regulations and with ETS Wound Care LLC SOPs.

May 15, 2023

Nicolas Guggenheim, PhD
Chief Executive Officer
ETS Wound Care LLC

Date



May 15, 2023

Donald W. Buck II, M.D.
Chief Medical Officer
ETS Wound Care LLC

Appendices

Appendix A: Wagner Grades

Grade 1: Superficial diabetic ulcer

Grade 2: Ulcer extension

- Involves ligament, tendon, joint capsule, or fascia
- No abscess or osteomyelitis

Grade 3: Deep ulcer with abscess or osteomyelitis

Grade 4: Gangrene to portion of forefoot

Grade 5: Extensive gangrene of foot

Appendix B: ABI or Arterial Doppler Ultrasound

ABI Technique

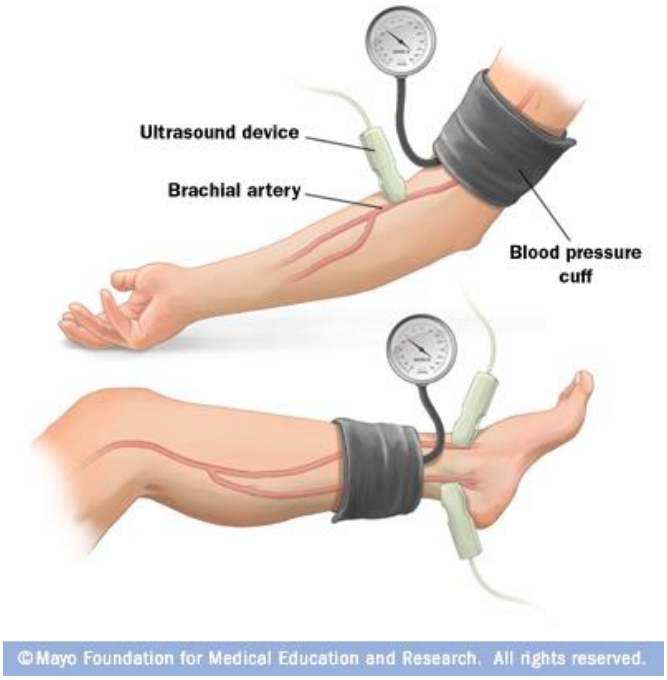
Place the subject in the supine position, with the arms and legs at the same level as the heart, for a minimum of 10 minutes before measurement,

Select an appropriately sized blood pressure cuff for both the ankle and the arms (see figure below), the cuff width should be, at a minimum, 20% greater than the diameter of the extremity. The ankle cuff should be placed on the leg between the malleolus and the calf. Enough room should be left below both cuffs to permit placement of the ultrasound gel, so that the Doppler device can adequately detect the brachial, dorsalis pedis and posterior tibial arteries.

Obtain the brachial systolic pressures of both arms. Use the higher of the arm pressures in the ABI calculation. Obtain the pressure in the dorsalis pedis and posterior tibial arteries for the extremity with the target ulcer. Use the highest pressure for the ABI calculation.

Ankle-Brachial Index = Highest ankle pressure/ Highest brachial pressure.

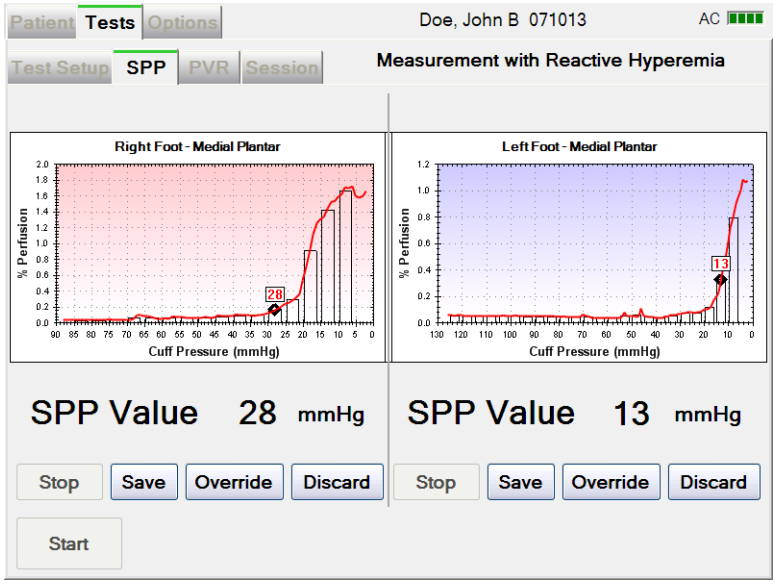
Care should be taken to cover the index ulcer during the ABI measurement. In addition, subjects should be informed that they may experience discomfort during the test, secondary to the pressure exerted by the cuff in the area of skin breakdown.



Arterial Doppler Ultrasound Technique

Place the subject in the supine position, with the arms and legs at the same level as the heart. Ultrasound gel will be applied at the ankle level to the anatomic position of the dorsalis pedis and posterior tibial vessels. The Doppler will then be applied to each vessel until a waveform is established, a printer will be used to document the Doppler waveform and at least five waveforms will be printed for each vessel. The clinician will verify biphasic or triphasic waveforms.

Appendix C: SPP



SPP can be employed to evaluate the subject's vascular status. SPP is obtained using a laser Doppler.

Technique

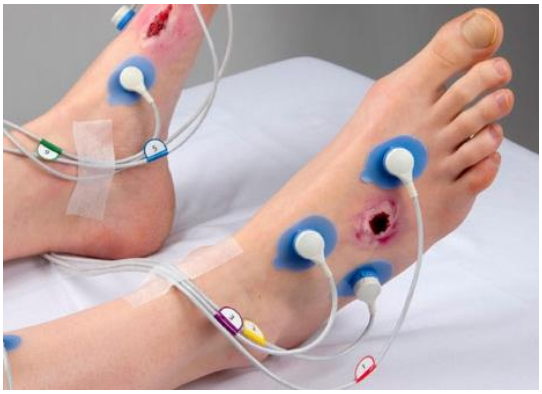
1. Secure the laser Doppler flow sensor within the bladder of a blood pressure cuff equipped with a transparent polyvinyl chloride window for measuring microcirculatory perfusion during cuff inflation and deflation.
2. Place the subject in supine position and keep still for five minutes.
3. Apply the cuff to the proximal margin of the ulcer and inflate to 20 mmHg above the brachial systolic pressure. A stable laser Doppler output value near zero (< 0.1 volume %) should be reached before deflating.
4. Deflate the cuff, first in 10 mmHg-stepwise decrements every five seconds to a pressure of 50 mmHg, and then in 5-mmHg decrements every 15 seconds until the laser Doppler output increased for two consecutive pressure values.
5. The pressure at which this first occurred is considered the SPP value.

Subjects with SPP less than 30 mmHg have vascular insufficiency and are not candidates for enrollment.

Appendix D: TCOM

Technique

Place the subject in the supine position, with the arms and legs at the same level as the heart. Electrodes must be in contact with the tissue through the contact liquid. If there is air between the tissue and an electrode, TCOM values will be questionable. Erroneous readings may also occur if electrodes are placed directly over a bone or there is severe edema around the wound. For the best results, tests should be conducted at ambient temperature (21-23^0) and the subject should not have smoked, nor had caffeine for several hours prior.



1. Calibrate the TCOM electrode—this takes about 15-20 minutes.
2. Clean the selected measuring site with alcohol or other skin-preparation solution.
3. Dry the site well with a gauze pad.
4. Take a standard fixation ring.
5. Remove the fixation ring from the protective film.
6. Apply the fixation ring to the measuring site as follows:
   - Press the center of the fixation ring onto the measuring site with a finger.
   - Run a finger around the rim circumference.
   - Press firmly to prevent leaks.
7. Fill the hole in the fixation ring with 3-5 drops of the contact liquid.
8. Affix the electrode into the fixation ring as follows:
   - Align the arrow on the electrode with one of the marks on the fixation ring.
   - Turn the electrode 90° clockwise to fasten it in the fixation ring.
9. Repeat steps 1 to 8 if more electrodes are to be applied; note: several electrodes can be calibrated at the same time.

It is sometimes advantageous to simultaneously use several electrodes placed strategically around the wound and calculate mean values from individual readings.

The normal sequence of events for TCOM is measurement in air, the leg elevation test (optional) and the oxygen challenge. Shah et al[20] determined that the optimal times for these events in terms of measurement time are 20, 5 and 10 minutes, respectively.

Appendix E: Debridement

Many chronic wounds contain necrotic tissue that has a black or dark gray appearance. Wound eschar is usually full-thickness, dry devitalized tissue arising from prolonged ischemia and slough is an adherent fibrous material commonly creamy yellow in appearance. Chronic wounds can also have colonized bacteria in the form of biofilm or cells, particularly along the margins of a wound, which have stopped dividing - a process known as senescence. Finally, devitalized tissue and biofilms can harbor high levels of cytokines or cellular remnants that maintain the wound in the inflammatory or proliferative stages of healing, through cellular trafficking processes. Any of these factors can disrupt the normal stages of wound healing.

Debridement is the process by which these elements are removed to permit healing, in effect changing the stalled chronic wound into an acute wound. In this clinical study, we have restricted the type of debridement to sharp debridement.

Technique

Sharp debridement comprises the following elements:

1. The index ulcer and the surrounding skin are prepped with water or Saline.
2. Anesthesia, topical or injected, is applied to the ulcer as necessary to reduce subject discomfort.
3. Using a sterile technique, all non-viable tissue in the wound bed is excised using a scalpel and scissors.
4. Excessive bleeding is controlled by using direct pressure, but cautery may be employed if necessary.

If extensive surgical debridement is necessary during the run-in period (e.g., general anesthesia is required), the patient is not a candidate for this trial. Likewise, if other forms of debridement (e.g., enzymatic) are required during run-in, based on the opinion of the treating clinician, the subject should be screen failed. During the Treatment Phase of the trial, other forms of debridement are NOT permitted. If this should happen, the type of debridement should be noted in the CRF, using other forms of debridement besides sharp debridement more than once during the treatment phase will result in the subject being withdrawn from the trial.

Although there is increasing evidence that more frequent debridement results in faster healing on average, the frequency and level of debridement in this trial is left up to the treating physician’s judgment. Excessive debridement can be as deleterious to healing as too little debridement.

For wound bed preparation, follow the TIME principles: Tissue management (primarily debridement in this trial), control of Infection and Inflammation (management of infection, control of edema, management of exudate, etc.), Moisture imbalance (ensuring that the wound is at all times in a moist healing environment, as well as dealing with excessive wound exudate), and advancement of the epithelial Edge of the wound (addressing hypoxia, infection, desiccation, dressing trauma, hyperkeratosis and calluses, and cell senescence at the wound margin). (Dowsett C, Newton H. Wounds UK 2005; 1:58-70).

Appendix F: WOUND-Q Instrument

SCALE STRUCTURE

Protocols for interventions to treat and prevent wounds have typically overlooked the patient perspective of outcomes and have focused instead on objective measures. The WOUND-Q is a rigorously developed patient-reported outcome measure that can be used with all types of chronic wounds in any anatomical location. The WOUND-Q measures 4 overarching domains. Each domain includes 2 or more independently functioning scales. Clinicians and researchers are able to administer the subset of scales relevant to their situation.

WOUND CHARACTERISTICS

Three scales measure wound characteristics. The first scale measures how concerned someone is with their chronic wound(s) in the past week. The other two scales measure how bothered people are with drainage and smell.

HEALTH-RELATED QUALITY OF LIFE

Four scales measure health-related quality of life. The first scale measures life impact and the other three measure specific concerns, i.e., how chronic wound(s) affect sleep, psychological, and social function.

EXPERIENCE OF CARE

Four scales measure patients' experience of healthcare. The first scale measures satisfaction with information and the other three measure satisfaction with members of the health care team, i.e., home care nurses, wound team, and office staff in a wound clinic.

WOUND TREATMENT

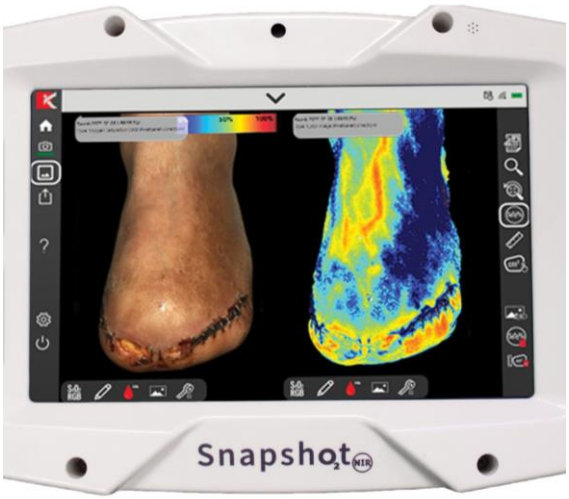
Two scales measure common treatments for chronic wounds. One scale measures satisfaction with dressing and the other scale measures satisfaction with the use of a suction device (e.g., vacuum pump device, negative pressure therapy dressing).

Data analysis

WOUND-Q Instrument

1. **Wound – Assessment**
2. **Wound – Drainage**
3. **Wound – Smell**
4. **Health-Related Quality of Life**
5. **Treatment - Dressing**

Appendix G: SnapshotNIR



SnapshotNIR is a near-infrared (NIR), reflectance-based technology that measures tissue oxygen saturation (StO2) in superficial tissue. Using multiple wavelengths of NIR light, SnapshotNIR measures relative amounts of oxygenated and deoxygenated hemoglobin in the microcirculation where oxygen exchange is happening. SnapshotNIR provides users with a tissue oxygenation map that can be used in medical decision making, for tracking and trending oxygenation, and for evaluating tissue viability.

The imaging device is completely non-invasive, eliminating the need for patient contact or injected dyes. Accurately capture diagnostic insight into the availability of oxygenated blood in tissue. SnapshotNIR's actionable data is helping to provide insight for improved decision-making, forging a path in advanced diagnostic-driven wound care throughout the continuum of care.

THE SCIENCE BEHIND SNAPSHOT

Chronic wounds are a health problem with significant reductions in quality of life and can have devastating consequences such as limb amputations and premature death. SnapshotNIR is an imaging device that visualizes and maps tissue oxygen saturation in the capillary network.

Ability to treat nearly all patients, regardless of melanin content for universal peace of mind and care for everybody. Portable and lightweight technology fits easily into your workflow. Both Doctors and nurses can operate it.
Ability to image the actual wound bed and surrounding tissue for a more accurate and precise reading of the wound area.

Precise visualization of oxygen saturation for faster assessments and healing trajectory predictions. A means to track and document patient progress to improve clinical outcomes and mitigate risks early.