The Omeza Protocol for Chronic Ulcers

A Randomized, Multicenter, Open Label Study Comparing the Omeza® Products Bundle to Standard of Care for Chronic Venous Leg Ulcers and Chronic Diabetic Foot Ulcers

Sponsor:	**OMEZA, LLC** 25 South Osprey Avenue Sarasota, FL 34236 Phone: (888) 886-6392
Clinical Research Organization:	**Palm Beach CRO, LLC** 400 Columbia Drive, Suite 111 West Palm Beach, FL 33409 Phone: (561) 200-3344 Fax: 561-828-8157
Protocol Number:	**100**
Palm Beach CRO Protocol No.	**489.0219**
Study Name:	**Omeza Protocol for Chronic Ulcers**
Date of Protocol:	**February 10, 2021**
Final Protocol Version:	**5.0**

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and with other applicable regulatory requirements

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Confidentiality Statement

The confidential information in the following document is provided to you as an Investigator, potential Investigator, or Consultant for review by you, your staff and an appropriate Institutional Review Board or Independent Ethics Committee. By accepting the document, you agree that the information contained herein will not be disclosed to others without written authorization from Omeza LLC, except to the extent necessary to obtain informed consent from those persons to whom the TEST product may be administered.

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SIGNATURE PAGE

Declaration of Sponsor

Title: A Randomized, Multicenter, Open Label Study, Comparing the Omeza® Products Bundle to Standard of Care for Chronic Venous Leg Ulcers and Chronic Diabetic Foot Ulcers

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product.

Omeza, LLC Chief Executive Officer

02.12.2021
Date

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SIGNATURE PAGE

Declaration of the Investigator

Title: A Randomized, Multicenter, Open Label Study Comparing the Omeza® Products Bundle to Standard of Care for Chronic Venous Leg Ulcers and Chronic Diabetic Foot Ulcers

All documentation for this study that is supplied to me, and that has not been previously published, will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, Electronic Case Report Forms (eCRFs), and other scientific data.

The study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB) and signed informed Consent Form of all subjects participating in the study. No changes will be made to the study protocol without the prior written approval of the sponsor and the IRB, except where necessary to eliminate an immediate hazard to the subjects.

I have read, understand, and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Study Site:

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

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Protocol Synopsis

Title	A Randomized, Multicenter, Open Label Study Comparing the Omeza® Products Bundle to Standard of Care for Chronic Venous Leg Ulcers and Chronic Diabetic Foot Ulcers
Sponsor	OMEZA, LLC
Study No.	Protocol #100
Study Site(s)	The study will be conducted in up to 3 clinical study sites in different regions of the United States

Introduction:

Venous leg ulcers (VLU) and Diabetic Foot Ulcers (DFU) are common and complicated ulcers to treat [1], and result in high morbidity [2] and significantly reduced quality of life [3]. Normal wound healing consists of four overlapping phases: hemostasis, inflammation, proliferation, and remodelling [4]. Most ulcers heal when the cause is eliminated, and the ulcer is treated with standard wound care. Some ulcers, however, are for various reasons locked in the inflammatory stage and do not heal [5].

This study will compare the Omeza® Products Bundle to standard of care (SOC) in subjects with chronic venous leg ulcers and subjects with diabetic foot ulcers.

Objectives

Primary

- To compare the efficacy of Omeza® Products Bundle to standard of care in the treatment of chronic venous leg ulcers and diabetic foot ulcers.

Secondary

- To evaluate the safety profile of the Omeza® Products Bundle compared to standard of care in the treatment of chronic venous leg ulcers and diabetic foot ulcers.
- To obtain cost benefit data comparing the Omeza® Products Bundle compared to standard of care in the treatment of chronic venous leg ulcers and diabetic foot ulcers.

Exploratory

- To measure the Quality of Life (QoL) of the subjects with chronic venous leg ulcers and with diabetic foot ulcers.

Study Design

This is a randomized, multicenter, open-label study comparing the Omeza® Products Bundle versus standard of care treatments for 2 different types of chronic ulcers (venous leg ulcers and diabetic foot ulcers). The treatment period will be 12 weeks, with subjects coming into the study site weekly for evaluations, photography and formal measurements of the target wound, and dressing changes. There will be a total of 13 study site visits. The Screening Visit (Day 0) will occur 1 week prior to randomization and will include routine labs and vascular assessment to determine inclusion/exclusion of the potential subject from the study; followed by weekly treatment visits (Week 1 through Week 11); randomization will occur at Treatment Visit Week 1; the Treatment Visit Week 12/End of Study Visit will include end of study labs. Target wounds will be photographed and measured, and vascular assessment will be done at each of the 13 visits. Standard of care will be billed to subject's insurance for both TEST and SOC control.

If the wound closes before Week 12, the subject will continue to come in for all the remaining study visits until study completion. If the wound does not close by Week 12, the subject will be immediately exited from the study and no further follow-up will occur as part of the study.

Key Entry Criteria

- The target wound appears to be healthy vascularized tissue at time of placement of treatment product. The wound is free from clinical signs of infection or ischemic changes. Target wound does not have presence of local active soft tissue infection.

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- No known allergy to the study treatment or SOC materials or components of the multi-layer compression bandaging, or who cannot tolerate multi-layer compression therapy
- Presence of any condition(s) which seriously compromises the subject's ability to complete this study or has a known history of poor adherence with medical treatment.

Treatments

STANDARD OF CARE:

Venous Leg Ulcer

1) Apply topical anesthetic
2) Perform appropriate sharp debridement as indicated
3) Clean wound with saline
4) Apply collagen alginate as primary dressing
5) Apply foam as secondary dressing
6) Soft roll and compressive wrap (Dynaflex™ or Profore or any other preferred multi-layer compression bandage system)

Diabetic Foot Ulcer

1) Apply topical anesthetic
2) Perform appropriate sharp debridement as indicated
3) Clean wound with saline
4) Apply collagen alginate as primary dressing
5) Apply foam as secondary dressing
6) Offloading of the DFU using standard of care practices at the clinical study site

TEST/ OMEZA® PRODUCTS BUNDLE:

Venous Leg Ulcer

1) Apply Omeza® Lidocaine Lavage and after 5 minutes wipe out debris
2) Perform appropriate sharp debridement as indicated
3) Apply additional Omeza® Lidocaine Lavage and wipe out debris
4) Apply Omeza® Collagen Matrix as primary dressing
5) Apply Omeza® Skin Protectant on periwound and surrounding intact skin from knee to toes
6) Apply foam as secondary dressing
7) Soft roll and compressive wrap (Dynaflex™ or Profore or any other preferred multi-layer compression bandage system)

Diabetic Foot Ulcer

1) Apply Omeza® Lidocaine Lavage and after 5 minutes wipe out debris
2) Perform appropriate sharp debridement as indicated
3) Apply additional Omeza® Lidocaine Lavage and wipe out debris
4) Apply Omeza® Collagen Matrix as primary dressing
5) Apply Omeza® Skin Protectant on periwound and surrounding intact skin from knee to toes
6) Apply foam as secondary dressing
7) Offloading of the diabetic foot ulcer using standard of care practices at the clinical study site

Number of Subjects and Population

Sample Size: Approximately 78 randomized at 2:1 ratio (39/indication, with 26 TEST/13 SOC for each

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indication).
Subjects who are diagnosed with one of the following chronic ulcers and who meet the entry criteria will be randomized into the study: 1) venous leg ulcer or 2) diabetic foot ulcer
Each indication will require 26 TEST subjects and 13 SOC control subjects assigned for a combined total of 78 randomized subjects.

Population:

Male and Female subjects suffering from chronic venous leg ulcers or diabetic foot ulcers

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Eligibility Criteria Venous Leg Ulcer (VLU):

Inclusion Criteria:

1. Male or female 21-80 years of age
2. Participated in the informed consent process and signed study specific informed consent document
3. Willing and able to comply with study procedures, including study visits and study dressing regimens
4. Confirmation of venous disease by non-invasive venous studies with either Doppler-confirmed venous reflux or having ≥ 2 clinical characteristics of venous insufficiency (varicose veins, lipodermatosclersosis, venous dermatitis, atrophie blanche, edema). Biopsy done to exclude other skin conditions e.g. cancer on ulcers ≥ 6 months
5. HbA1c of ≤ 10%
6. Have a venous ulcer between the knee and ankle, at or above the malleolus
7. Target wound size ≥ 4 cm^2 to ≤ 150 cm^2 in area without exposed tendon, muscle or bone
8. Target wound duration of at least 3 months and less than or equal to 12 months as of the date the subject signs consent for study
9. VLU may have characteristics that include yellow/white slough with or without fibrous/scar tissue and/or non-viable tissue, but not mandatory
10. Be willing and able (or have family member/friend willing and able) to apply required dressing changes as well as the ability of the subject to tolerate limb compression bandage

Exclusion Criteria:

1. Subjects with a BMI ≥ 65
2. Subject is medically unable to consent (due to head trauma, coma, etc.) or cognitively impaired (due to being mentally challenged, having Alzheimer's, etc.)
3. Subject is an active smoker
4. Subject has any history of fish allergy or a known sensitivity to any of the SOC materials which come into contact with the skin
5. Ankle-Branchial Index (ABI) less than 0.80 or greater than 1.3
6. Presence of any monophasic waveforms
7. Subject has the following abnormal lab values: Albumin < 2.5 g/dL; Total Protein < 5 g/dL; BUN above 25 mg/dL; Creatinine > 3.0 mg/dL
8. Any active cancer other than a nonmelanoma skin cancer; any previous cancer must be in remission for at least 1 year; bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or has had chemotherapy within the last 12 months

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9. Suspicion of malignancy within VLU. Any wound that has been present for ≥ 6 months and hasn't previously been biopsied, a biopsy must be performed. Also, if a clinical suspicion of malignancy exists in the opinion of the Investigator, a biopsy should be performed regardless of duration of wound
10. Life expectancy < 6 months
11. Subject has received within 28 days of screening a treatment which is known to interfere with or affect the rate and quality of wound healing (e.g., thrombolysis, systemic steroids, immunosuppressive therapy, autoimmune disease therapy, dialysis, radiation therapy, chemotherapy) to the leg or who may receive such medications during the screening period or who are anticipated to require such medications during the course of the study.
12. History of immunodeficiency or any illness or condition that could interfere with wound healing e.g., lymphedema, end-stage renal disease, severe malnutrition, liver disease, aplastic anemia, Raynaud's Syndrome, connective tissue disorder, acquired immune deficiency syndrome, HIV positive, or sickle cell anemia
13. Ulcers due to non-venous etiology and leg ulcers associated with mixed etiology
14. Untreated osteomyelitis
15. Hepatitis
16. Acute deep venous thrombosis
17. Allergy to lidocaine and/or epinephrine
18. Subject's inability to successfully tolerate compression therapy that is changed weekly
19. Suspected or confirmed gangrene or wound infection of the study ulcer, as evidenced by tissue necrosis, redness, pain, and/or purulent drainage and/or receiving systemic antibiotics for the treatment of such
20. Target wound has received hyperbaric therapy or wound dressings that include growth factors, engineered tissues, or skin substitutes within 28 days of randomization or is scheduled to receive treatment during the study e.g., Apligraf, PriMatrix, AMNIOEXCEL (first generation), Regranex, Dermagraft, EpiFix, GraftJacket, OASIS, Omnigraft, or Integra BMWD

Eligibility Criteria Diabetic Foot Ulcer (DFU):

Inclusion Criteria:

1. Male or female 21-80 years of age
2. Participated in the informed consent process and signed study specific informed consent document
3. Willing and able to comply with study procedures, including study visits and study dressing regimens
4. Diagnosed as having Type 1 or Type 2 diabetes
5. HbA1c of ≤ 10%
6. Presence of a DFU, Wagner 1 or 2 (see **Appendix 7** for definitions), extending at least through the dermis provided it is below the level of the medial or lateral malleolus. Any wound that has been present for ≥ 6 months and hasn't previously been biopsied, a biopsy must be performed to exclude other skin conditions e.g. cancer for ulcers. Also, if a clinical

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suspicion of malignancy exists in the opinion of the Investigator, a biopsy should be performed regardless of duration of wound

7. The target wound will be located on the foot or ankle and will be the largest ulcer if two or more DFUs are present with the same Wagner grade and will be the only one evaluated in the study. If other ulcerations are present on the same foot, they must be more than 1 cm distant from the target wound
8. Target wound (i.e. current episode of ulceration) has been present for greater than 4 weeks prior to screening visit and less than 12 months, as of the date the subject consents for study
9. Target wound size ≥ 0.25 cm^2 to ≤ 150 cm^2 post debridement at Screening Visit and Treatment Visit Week 1/Randomization

Exclusion Criteria:

1. Subject with a BMI ≥65
2. Subject is medically unable to consent (due to head trauma, coma, etc.) or cognitively impaired (due to being mentally challenged, having Alzheimer's, etc.)
3. Subject is an active smoker
4. Subject has any history of fish allergy or a known sensitivity to any of the SOC materials which come into contact with the skin
5. Target wound(s) deemed by the investigator to be caused by a medical condition other than diabetes or subject has wounds secondary to a disease other than diabetes (e.g. vasculitis, neoplasms, or hematological disorders)
6. Ankle-Branchial Index (ABI) less than 0.80 or greater than 1.3
7. Presence of any monophasic waveforms
8. Subject has the following abnormal lab values: Albumin < 2.5 g/dL; Total Protein < 5 g/dL; BUN above 25 mg/dL; Creatinine > 3.0 mg/dL
9. The subject is unable to safely ambulate with the use of a study required offloading method
10. Any active cancer other than a nonmelanoma skin cancer; any previous cancer must be in remission for at least 1 year; bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or has had chemotherapy within the last 12 months
11. Subject has received within 28 days of screening a treatment which is known to interfere with or affect the rate and quality of wound healing (e.g., thrombolysis, systemic steroids, immunosuppressive therapy, autoimmune disease therapy, dialysis, radiation therapy, chemotherapy) to the foot or during the screening period or who are anticipated to require such medications during the course of the study
12. Subject on any investigational drug(s) or therapeutic device(s) within 28 days preceding randomization
13. History of radiation at the ulcer site (regardless of time since last radiation treatment)
14. Target wound has received hyperbaric therapy or wound dressings that include growth factors, engineered tissues, or skin substitutes within 28 days of randomization or is scheduled to receive treatment during the study (e.g., Apligraf, PriMatrix, AMNIOEXCEL (first generation), Regranex, Dermagraft, EpiFix, GraftJacket, OASIS, Omnigraft, or Integra BMWD
15. Presence of any condition(s) which seriously compromises the subject's ability to complete this study or has a known history of poor adherence with medical treatment
16. Osteomyelitis or bone infection of the affected foot as verified by x-ray within 30 days prior to randomization. (In the event of an ambiguous diagnosis, the subject will not be enrolled)
17. Suspected or confirmed gangrene or wound infection of the study ulcer, as evidenced by

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tissue necrosis, redness, pain, and/or purulent drainage and/or receiving systemic antibiotics for the treatment of such

18. History of immunodeficiency or any illness or condition, other than diabetes, that could interfere with wound healing e.g., excessive lymphedema, end-stage renal disease, severe malnutrition, liver disease, aplastic anemia, Raynaud's Syndrome, connective tissue disorder, acquired immune deficiency syndrome, HIV positive, or sickle cell anemia
19. Subject has unstable Charcot foot or Charcot with bone exposed that could inhibit wound healing

Criteria for Evaluation of Efficacy and Safety

Objective efficacy endpoints comparing the Omeza® Products Bundle vs Standard of Care are:

- Percent change from baseline in target wound measure at Week 4, Week 8 and by Week 12/ End of Study.
- Ulcer size closure rate at Week 4, Week 8 and by Week 12/ End of Study.
- Time to maximum closure or complete closure.
- Incidence of DFU and VLU subjects healing at Week 12/ End of Study.

Safety and tolerability will be evaluated by assessing treatment-emergent adverse events, compliance, concomitant medications, Labs, Vital Signs and Physical Examinations.

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Vascular Assessment
Ankle-Branchial Index (ABI) of ulcers/wounds will be measured using the MESI ABPI MD device. It is an automated machine that uses oscillometry and volume plethysmography for accurately calculate the ABI. This device can also automatically collect pulse volume waveform readings (mediUSA).

Method of Target Wound Measurement and Photography
Swift Medical wound platform will be used for the measurement and imaging of ulcers/wounds (SWIFT MEDICAL Inc.).

Statistical Methods
Efficacy analyses will be conducted under the intent to treat principle. Analyses will be performed on each of the two indications (venous leg ulcers and diabetic foot ulcers) and overall.
Analyses to include the primary endpoint of:

- % change from baseline (Treatment Visit Week 1) in ulcer measure at Treatment Visit Week 4, Week 8 and by Week 12/End of Study using a mixed model repeated measure (MMRM)
- Ulcer size closure rate will be reported at Treatment Visit Week 4, Week 8 and by Week 12/End of Study.
- Time to maximum closure or complete closure will be assessed using Kaplan-Meier estimation, with medians, quartiles, and 95% confidence intervals (CIs).
- Incidence of DFU and VLU will be analyzed by comparing the proportion of subjects healing at week 12/End of Study.
  Further analysis may also be conducted using age category as a subgroup.

Descriptive statistics will be provided for subject demographics, safety, and exposure data and will include the number of observations, mean, standard deviation (SD), median, and range for continuous variables and number and percent for categorical variables; 95% CIs will be presented where appropriate.

Sample Size Analysis:
The power of the study is computed for the primary endpoint of “percent change from baseline in target wound measure by Week 12” comparing the two means. The combined sample size of 78 subjects (randomized 2:1) will provide over 80% power to detect a difference of about 14 units (percent change from baseline in wound measure by Week 12), assuming a standard deviation of 20 units, and a 2-sided significance level of 5%.

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LIST OF STUDY PERSONNEL

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Contents

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List of Abbreviations

Abbreviation or Term	Definition:
ABI	Ankle Branchial Index
ADL	Activities of Daily Living
AE(s)	Adverse Event(s)
CI	Confidence Interval
CFR	Code of Federal Regulations
CLU	Chronic Lower Extremity Ulcers
CRF(s)	Case Report Form(s)
CRO	Clinical Research Organization
CSR	Clinical Study Report
DFU	Diabetic Foot Ulcer
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measure
PI	Principal Investigator
QoL	Quality of Life
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	Standard of Care
TEAE	Treatment Emergent Adverse Event
VLU	Venous Leg Ulcer

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1 Background Information and Scientific Rationale

1.1 Chronic Lower Extremity Ulcers

Chronic lower extremity ulcers (CLU) are a common and complicated disease to treat [1], and result in high morbidity [2] and significantly reduced quality of life [3]. Normal wound healing consists of four overlapping phases: hemostasis, inflammation, proliferation, and remodeling [4]. Most ulcers heal when the cause is eliminated, and the ulcer is treated with standard wound care. Some ulcers, however, are for various reasons locked in the inflammatory stage and do not heal [5].

1.2 Rationale

Omeza is a medical technology and consumer healthcare products company specializing in the treatment of chronic hard to heal wounds such as venous leg ulcers, diabetic foot ulcers and pressure ulcers. The Omeza® Products Bundle consists of the Omeza® Lidocaine Lavage, Omeza® Collagen Matrix, Omeza® Skin Protectant. Omeza® oil is the company's platform technology, included in all its products. Omeza oil is unique, because it is anhydrous and contains a proprietary formulation of Omega-3, 6 and 9 oils plus nutrients in a rapidly penetrating delivery system. Omeza is the first value-based wound care company, and the Omeza® bundle of products sets a new standard of care.

The goal of this study is to compare this new line of products, the Omeza® Products Bundle, when used together as directed (see **Appendix 4**) to the standard of care in terms of efficacy and safety for the treatment of chronic venous leg or diabetic foot ulcers.

2 Overview of Study Objectives

Primary Objective

1. To compare the efficacy of Omeza® Products Bundle to standard of care in the treatment of chronic venous leg ulcers and diabetic foot ulcers.

Secondary Objective

1. To evaluate the safety profile of the Omeza® Products Bundle compared to the standard of care.
2. To obtain cost benefit data comparing the Omeza® Products Bundle compared to standard of care in the treatment of chronic venous leg ulcers and diabetic foot ulcers.

Exploratory Objective

To measure the Quality of Life (QoL) of the subjects with chronic venous leg ulcers and with diabetic foot ulcers.

3 Study Design

3.1 Description of the Study Design

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This is a randomized, multicenter, open-label study comparing the Omeza® Products Bundle versus standard of care treatments for 2 different types of chronic ulcers (venous leg ulcers and diabetic foot ulcers). The treatment period will be 12 weeks, with subjects coming into the study site weekly for evaluations, photography and formal measurements of the target wound, and dressing changes. There will be a total of 13 study site visits. The Screening Visit (Day 0) will occur 1 week prior to randomization and will include routine labs and vascular assessment to determine inclusion/exclusion of the potential subject from the study; followed by weekly treatment visits (Week 1 through Week 11); randomization will occur at Treatment Visit Week 1; the Treatment Visit Week 12/End of Study Visit will include end of study labs. Target wounds will be photographed and measured, and vascular assessment will be done at each of the 13 visits. Standard of care will be billed to subject's insurance for both TEST and SOC.

If the wound closes before Week 12, the subject will continue to come in for all the remaining study visits until study completion. If the wound does not close by Week 12, the subject will be immediately exited from the study and no further follow-up will occur as part of the study.

Table 1: Study Plan

Study Period	Visit	Purpose
Screening	Screening (Day 0)	Determine eligibility, routine labs, vascular assessment, photos and measures
Baseline / Randomization	Treatment Visit Week 1	Review eligibility, randomization, Wound-QoL questionnaire, vascular assessment, photos and measures, begin study treatments.
Treatment	Treatment Visits Week 2 - Week 11	Study treatments, vascular assessment, photos and measures
End of Study Visit	Treatment Visit Week 12	End of Study routine labs, vascular assessment, photos and measures, Wound-QoL questionnaire

For subject to be eligible they must meet entry criteria. If the subject is not found eligible at Treatment Visit Week 1, the subject may be re-screened once or may be replaced.

3.2 Study Endpoints

Primary Endpoint:

1. Percent Change from Baseline in target wound measure at Week 4, Week 8 and by Week 12.
2. Ulcer Size Closure rate at Week 4, Week 8 and by Week 12.
3. Time to maximum closure or complete closure.
4. Incidence of DFU and VLU healing at Week 12.

Secondary Endpoint:

1. Safety and tolerability will be evaluated by assessing Treatment Emergent Adverse Events, Treatment Compliance, Concomitant Medications, Clinical Laboratory Findings, Vital Signs and Physical Examinations.
2. To obtain cost benefit data comparing the Omeza Product Bundle and Standard of Care in treatment of the ulcers.

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Exploratory Endpoint:

A questionnaire called “Wound-QoL” will be used to measure the quality of life.

4 Study Population

4.1 Recruitment Plan

The subjects will be enrolled at up to 3 study sites from the patient population of board certified actively licensed physicians, who have demonstrated clinical research experience and/or possess an NIH or CITI training certificate and who have been qualified as Principal Investigators (PI) by the Contract Research Organization (CRO).

4.2 Subject Entry Criteria

Population: Male and Female subjects suffering from chronic venous leg ulcers or Diabetic foot ulcers

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Eligibility Criteria Venous Leg Ulcer (VLU):

Inclusion Criteria:

1. Male or female 21-80 years of age
2. Participated in the informed consent process and signed study specific informed consent document
3. Willing and able to comply with study procedures, including study visits and study dressing regimens
4. Confirmation of venous disease by non-invasive venous studies with either Doppler-confirmed venous reflux or having ≥ 2 clinical characteristics of venous insufficiency (varicose veins, lipodermatosclersosis, venous dermatitis, atrophie blanche, edema). Biopsy done to exclude other skin conditions e.g. cancer on ulcers ≥ 6 months
5. HbA1c of ≤ 10%
6. Have a venous ulcer between the knee and ankle, at or above the malleolus
7. Target wound size ≥4 cm^2 to ≤ 150 cm^2 in area without exposed tendon, muscle or bone
8. Target wound duration of at least 3 months and less than or equal to 12 months as of the date the subject signs consent for study
9. VLU may have characteristics that include yellow/white slough with or without fibrous/scar tissue and/or non-viable tissue, but not mandatory
10. Be willing and able (or have family member/friend willing and able) to apply required dressing changes as well as the ability of the subject to tolerate limb compression bandage

Exclusion Criteria:

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1. Subject with a BMI ≥ 65
2. Subject is medically unable to consent (due to head trauma, coma, etc.) or cognitively impaired (due to being mentally challenged, having Alzheimer's, etc.)
3. Subject is an active smoker
4. Subject has any history of fish allergy or a known sensitivity to any of the SOC materials which come into contact with the skin
5. Ankle-Branchial Index (ABI) less than 0.80 or greater than 1.3
6. Presence of any monophasic waveforms
7. Subject has the following abnormal lab values: Albumin < 2.5 g/dL; Total Protein < 5 g/dL; BUN above 25 mg/dL; Creatinine > 3.0 mg/dL
8. Any active cancer other than a nonmelanoma skin cancer; any previous cancer must be in remission for at least 1 year; bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or has had chemotherapy within the last 12 months
9. Suspicion of malignancy within VLU. Any wound that has been present for ≥ 6 months and hasn't previously been biopsied, a biopsy must be performed. Also, if a clinical suspicion of malignancy exists in the opinion of the Investigator, a biopsy should be performed regardless of duration of wound
10. Life expectancy < 6 months
11. Subject has received within 28 days of screening a treatment which is known to interfere with or affect the rate and quality of wound healing (e.g., thrombolysis, systemic steroids, immunosuppressive therapy, autoimmune disease therapy, dialysis, radiation therapy, chemotherapy) to the leg or who may receive such medications during the screening period or who are anticipated to require such medications during the course of the study.
12. History of immunodeficiency or any illness or condition that could interfere with wound healing e.g., lymphedema, end-stage renal disease, severe malnutrition, liver disease, aplastic anemia, Raynaud's Syndrome, connective tissue disorder, acquired immune deficiency syndrome, HIV positive, or sickle cell anemia
13. Ulcers due to non-venous etiology and leg ulcers associated with mixed etiology
14. Untreated osteomyelitis
15. Hepatitis
16. Acute deep venous thrombosis
17. Allergy to lidocaine and/or epinephrine
18. Subject's inability to successfully tolerate compression therapy that is changed weekly
19. Suspected or confirmed gangrene or wound infection of the study ulcer, as evidenced by tissue necrosis, redness, pain, and/or purulent drainage and/or receiving systemic antibiotics for the treatment of such
20. Target wound has received hyperbaric therapy or wound dressings that include growth factors, engineered tissues, or skin substitutes within 28 days of randomization or is scheduled to receive treatment during the study e.g., Apligraf, PriMatrix, AMNIOEXCEL (first generation), Regranex, Dermagraft, EpiFix, GraftJacket, OASIS, Omnigraft, or Integra BMWD

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Eligibility Criteria Diabetic Foot Ulcer (DFU):

Inclusion Criteria:

1. Male or female 21-80 years of age
2. Participated in the informed consent process and signed study specific informed consent document
3. Willing and able to comply with study procedures, including study visits and study dressing regimens
4. Diagnosed as having Type 1 or Type 2 diabetes
5. HbA1c of ≤ 10%
6. Presence of a DFU, Wagner 1 or 2 (see **Appendix 7** for definitions), extending at least through the dermis provided it is below the level of the medial or lateral malleolus. Any wound that has been present for ≥ 6 months and hasn't previously been biopsied, a biopsy must be performed to exclude other skin conditions e.g. cancer for ulcers. Also, if a clinical suspicion of malignancy exists in the opinion of the Investigator, a biopsy should be performed regardless of duration of wound
7. Target wound will be located on the foot or ankle and will be the largest ulcer if two or more DFUs are present with the same Wagner grade and will be the only one evaluated in the study. If other ulcerations are present on the same foot, they must be more than 1 cm distant from the target wound
8. Target wound (i.e. current episode of ulceration) has been present for greater than 4 weeks prior to screening visit and less than 12 months, as of the date the subject consents for study
9. Target wound size ≥0.25 cm^2 to ≤ 150 cm^2 post debridement at Screening Visit and Treatment Visit Week 1/Randomization

Exclusion Criteria:

1. Subject with a BMI ≥ 65
2. Subject is medically unable to consent (due to head trauma, coma, etc.) or cognitively impaired (due to being mentally challenged, having Alzheimer's, etc.)
3. Subject is an active smoker
4. Subject has any history of fish allergy or a known sensitivity to any of the SOC materials which come into contact with the skin
5. Target wound(s) deemed by the investigator to be caused by a medical condition other than diabetes or subject has wounds secondary to a disease other than diabetes (e.g. vasculitis, neoplasms, or hematological disorders)
6. Ankle-Branchial Index (ABI) less than 0.80 or greater than 1.3
7. Presence of any monophasic waveforms
8. Subject has the following abnormal lab values: Albumin < 2.5 g/dL; Total Protein < 5 g/dL; BUN above 25 mg/dL; Creatinine > 3.0 mg/dL
9. Subject is unable to safely ambulate with the use of a study required offloading method
10. Any active cancer other than a nonmelanoma skin cancer; any previous cancer must be in remission for at least 1 year; bone cancer or metastatic disease of the

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affected limb, radiation therapy to the foot, or has had chemotherapy within the last 12 months

11. Subject has received within 28 days of screening a treatment which is known to interfere with or affect the rate and quality of wound healing (e.g., thrombolysis, systemic steroids, immunosuppressive therapy, autoimmune disease therapy, dialysis, radiation therapy, chemotherapy) to the foot or during the screening period or who are anticipated to require such medications during the course of the study
12. Subject on any investigational drug(s) or therapeutic device(s) within 28 days preceding randomization
13. History of radiation at the ulcer site (regardless of time since last radiation treatment)
14. Target wound has received or hyperbaric therapy or wound dressings that include growth factors, engineered tissues, or skin substitutes within 28 days of randomization or is scheduled to receive treatment during the study (e.g., Apligraf, PriMatrix, AMNIOEXCEL (first generation), Regranex, Dermagraft, EpiFix, GraftJacket, OASIS, Omnigraft, or Integra BMWD)
15. Presence of any condition(s) which seriously compromises the subject's ability to complete this study or has a known history of poor adherence with medical treatment
16. Osteomyelitis or bone infection of the affected foot as verified by x-ray within 30 days prior to randomization. (In the event of an ambiguous diagnosis, the subject will not be enrolled)
17. Suspected or confirmed gangrene or wound infection of the study ulcer, as evidenced by tissue necrosis, redness, pain, and/or purulent drainage and/or receiving systemic antibiotics for the treatment of such
18. History of immunodeficiency or any illness or condition, other than diabetes, that could interfere with wound healing e.g., excessive lymphedema, end-stage renal disease, severe malnutrition, liver disease, aplastic anemia, Raynaud’s Syndrome, connective tissue disorder, acquired immune deficiency syndrome, HIV positive, or sickle cell anemia
19. Subject has unstable Charcot foot or Charcot with bone exposed that could inhibit wound healing

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4.3 Subject Identification and Randomization

4.3.1 Subject Identification

At the Screening Visit, a unique 5-digit subject number will be assigned consecutively for each subject after he or she signs the Informed Consent Form (ICF). Unique subject numbers will begin with the clinical site number, e.g., 01 followed by a 3-digit number starting with 001. For example, for clinical site number 02, the unique subject numbers will be as follows: 02-001, 02-002, 02-003, etc.

4.3.2 Randomization Scheme

It will be determined if a subject is eligible to participate in the study at Treatment Visit Week 1, and the subject will be randomized 2:1 to Omeza® Products Bundle or SOC. Randomization numbers will be generated in blocks and consist of the 2-digit site number, followed by a 4-digit subject number. Randomization numbers will be assigned consecutively to each subject in the order in which they become eligible for randomization. Since this is an open label study, a randomization schedule indicating if the subject is assigned to TEST or SOC will be provided to each study site.

The subject will keep this unique randomization number for the duration of the study. Once a subject is randomized, the randomization number will be the identifying number for that subject.

4.3.3 Subject Withdrawal

It is planned to randomize approximately 78 subjects, with 39 subjects per indication (VLU or DFU), at up to 3 clinical sites for this study. See **Section 10.4**, for a discussion of sample size. PIs may choose to discontinue a subject's participation in the study if they believe it is in the subject's best interest clinically. The reason(s) for withdrawal must be recorded on the eCRF. If a subject is prematurely withdrawn from the study for any reason, the PI must make every effort (with proper documentation) to perform the evaluations described for the End of Study Visit. A subject may also be withdrawn from study by the sponsor or the IRB. Subjects who fail to qualify for enrollment during Screening Period will be considered Screen Failures and the reason for failure will be documented.

5 Study Agent/Interventions

5.1 Identity

Omeza® Products Bundle includes use of the following products (see **Appendix 1**) applied in the same manner as SOC for each indication VLU or DFU.

- Omeza® Lidocaine Lavage
- Omeza® Collagen Matrix
- Omeza® Skin Protectant

The lot numbers and expiration dates of the investigational products will be provided in the certificate of analysis and recorded in the eCRF and accountability log. A sample of

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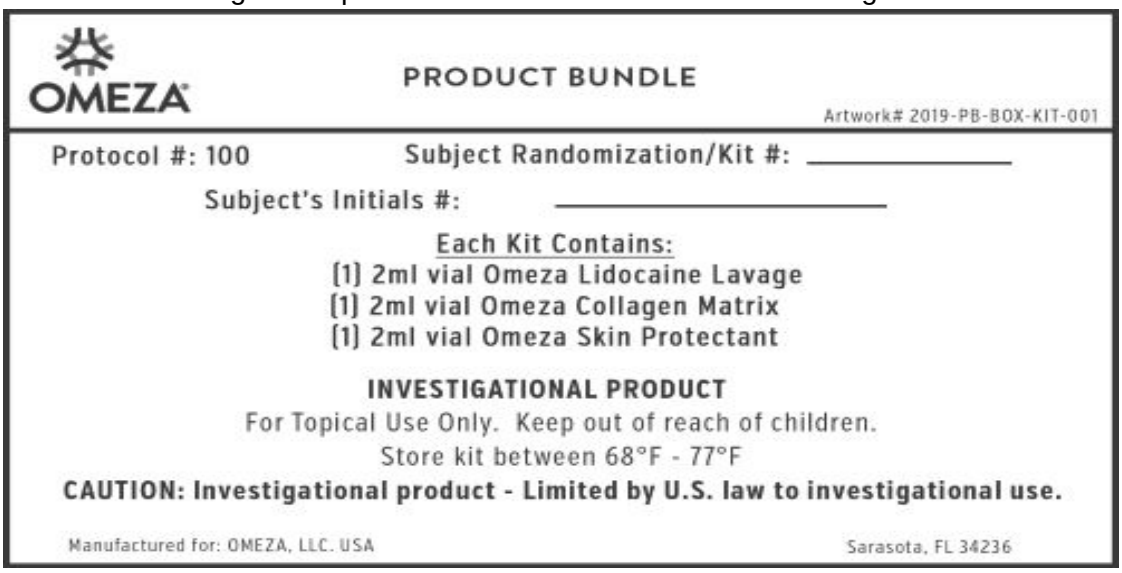
the label will be filed in the clinical site study files. All investigational TEST products will be prepared in accordance with current Good Manufacturing Practices (GMP).

Standard of Care (SOC): See **Appendix 2**: SOC for VLUs and **Appendix 3**: SOC for DFUs

5.2 Packaging

Each kit of investigational products will be labeled with the following information:



TEST product kits will be supplied to the clinical sites by Omeza, LLC. Each kit will contain one 2 mL vial of Omeza® Lidocaine Lavage, one 2 mL vial of Omeza® Collagen Matrix and one 2 mL vial of Omeza® Skin Protectant.

5.3 Storage

Supplies of the TEST products should be stored at room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP controlled room temperature]. Do not freeze.

The PI, or qualified designee, is responsible for the proper storage of the study products according to the manufacturer's recommendations and all applicable Federal/State regulatory guidelines.

5.4 Dosage and Administration of Study Agent

At each treatment visit (Weeks 1 through Week 12), each subject will undergo the wound care procedure as outline in the assigned randomized treatment i.e. either the Omeza® Products Bundle (TEST) or the standard of care (SOC). In all cases each treatment will be applied according to the diagnosed indication. If the wound closes before Week 12, the subject will continue to come in for all the remaining study visits until study completion, but the TEST subjects will be treated with the Omeza® Skin Protectant only.

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The TEST treatment will be labeled with a subject's unique randomization number, (which is also the kit number). In addition, the visit number will be hand-written on the label at the site. The adhesive label will be placed on the subject's chart (source) and documented in the eCRF.

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5.5 Accountability

The PI, or qualified designee, will dispense the study product only to randomized subjects during the study visits described in this protocol. At each treatment visit, each subject will undergo wound care corresponding to the treatment group to which they were randomized. The subject's unique randomization number, subject's initials, visit number and date of treatment will be written on the TEST product label and documented in the eCRF at the clinical site.

The PI, or qualified designee, will maintain an accurate inventory in the form of study product accountability logs beginning with recording the receipt of the study product as shipped by the sponsor (or designee) and the date received. In addition, accurate records of study product applied to subjects will be kept by the PI, or qualified designee, specifying the kit number, the subject number, and the date applied, for the subject and the master product accountability logs for the overall study. At the completion of the study, the PI will provide copies of this accountability log to the sponsor. At the completion of the study, following full accountability and reconciliation of all investigational product supplies, all unused/partially used investigational product kits will be returned and/or destroyed in accordance with the sponsor's (or designee's) written instructions. The PI must verify the accuracy of the accountability logs, and that no remaining supplies are in the PI's possession.

5.5.1 Subject Compliance with Study Agent

Subjects will be considered treatment compliant, if the % compliance is calculated to be between 80% and 120%. Compliance will be calculated, as follows: % Compliance = (# study treatments divided by # the number of treatments that should have taken place based on the number of days the subject was in the trial) x 100. Compliance will be summarized "as treated".

5.6 Concomitant Medications

All concomitant prescription medications, over-the-counter medications and non-prescription medications taken at the start of and during study participation will be reported on the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dose or regimen of a concomitant medication must also be recorded in the eCRF. At the Screening Visit, subjects will be asked what medications they have taken during the last 30 days. Concomitant medications will be summarized "as treated".

5.7 Prohibited Medications and Treatments

The following are medications that are prohibited at enrollment, during screening, and during the course of the study unless discussed with and approved by the medical monitor:

History of treatment 28 days prior to enrolment with immunosuppressants including:

- systemic corticosteroids >10 mg daily dose,

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- autoimmune therapy,
- hydroxyurea,
- application of topical steroids to the ulcer surface within 1 month prior to Screening Visit,

OR

Radiation therapy to the leg or foot, or chemotherapy within the last 12 months

OR

Skin ulcer previously treated within the last 4 weeks with biologic therapies e.g. cell therapy, growth factors

OR

Receive above medications during the screening period

OR

Are anticipated to require above medications during the course of the study

OR

Target wound has received wound dressings that include:

- growth factors
- engineered tissues
- skin substitutes (e.g., Apligraf, PriMatrix, AMNIOEXCEL (first generation), Regranex, Dermagraft, EpiFix, GraftJacket, OASIS, Omnigraft, or Integra BMWD)

5.8 Permitted Concomitant Medications

Other than the medications listed above in **Section 5.7**, all medication will be permitted provided that the subject has been on a stable dose for at least one month prior to the Screening period and/ or the medical monitor agrees.

6 Study Schedule

The study will be conducted in 13 visits (see **Appendix B**)

6.1 Screening Visit (Day 0)

Seven (7) days prior to baseline and initiation of study treatment, subjects will present for a screening visit where they will undergo the following procedures:

- Informed consent process/HIPAA authorization
- Review of inclusion/exclusion criteria
- Medical history / Concomitant medications
- Demographic information (include Fitzpatrick Skin Type[11] see **Appendix 8**)

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- If female, document subject confirmed lack of pregnancy (for women of childbearing potential)
- Routine laboratory evaluations (see details in **Section 7.1.4**)
- Physical exam (All systems) and vital signs
- Target wound identification and wound examination
- Vascular assessment (see **Appendix 6A**)
- Target wound measurement and photography (see **Appendix 6B**)
- Assignment of unique subject screening number
- Schedule Treatment Visit Week 1

6.2 Treatment Visit Week 1/Randomization/Baseline

Subjects will return for review of eligibility, baseline assessments, randomization and initiation of assigned treatment:

- Review of inclusion/exclusion criteria
- Subject to complete Baseline Wound-QoL questionnaire
- Concomitant medications
- Adverse event monitoring
- Wound examination
- Vascular assessment
- Target wound measurement and photography
- Randomization
- Wound Care, including the application of treatment (either TEST or SOC depending on randomization assignment see **Appendices 2-4** for method)
- Schedule Treatment Visit Week 2

6.3 Treatment Visits Week 2 - Week 11

Subjects will return to the study site once a week for a total of 11 Treatment Visits. These visits will include wound care and follow-up assessments. Every attempt will be made to schedule each Treatment Visit within the study day window of 7 days +/- 1 day, to assure proper wound care.

- Concomitant medications
- Adverse event monitoring
- Wound examination
- Vascular assessment
- Target wound measurement and photography
- Wound Care, including the application of treatment (either TEST or SOC depending as randomization assignment)
- Schedule the next weekly treatment visit

Note: If the wound closes before Week 12, the subject will continue to come in for all the remaining study visits until study completion, but the TEST subjects will be treated with the Omeza® Skin Protectant only.

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6.4 End of Study Visit/ Treatment Visit Week 12

Subjects will return to the study site for the End of Study Visit on Week 12. If the wound has not closed by Week 12, the subject will be immediately excited from the study and no further follow-up will occur as part of the study.

- Routine laboratory evaluations
- Subject to complete end of Study Wound-QoL questionnaire
- Concomitant medications
- Adverse event monitoring
- Wound examination
- Vascular assessment
- Target wound measurement and photography
- Wound Care, including the application of treatment (either TEST or SOC depending on randomization assignment)

6.5 Early Termination Visit

Subjects who no longer wish to participate in the study or who become ineligible to participate will be asked to return for final assessments (End of Study Visit).

7 Study Procedures/Evaluations

7.1 Medical History

A complete medical history will be taken from all subjects to cover all of the inclusion and exclusion criteria. Source documentation for previous treatment (to include SOC during screening), diagnosis, and interventions should be included in the subject's records to facilitate source documentation monitoring.

7.2 Physical Examination

Full physical examination (all systems) must be performed by the principal investigator or sub-investigator (medically qualified professional per the local guidelines) at the Screening Visit. Wound examinations shall be performed at every visit. The examination should include examination of body systems where there are symptom complaints by the subject.

7.3 Adverse Event Monitoring

The PI will assess adverse events (AEs) by spontaneous, unsolicited reports of subjects, by observation, and by routine non-leading questions (e.g., "How have you felt since I last saw you?").

7.4 Laboratory Evaluations

Blood will be collected at the Screening Visit and End of Study Visit for routine laboratories:

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- Albumin
- BUN/Creatinine/ Total protein
- Hemoglobin A1C
- Complete Blood Count
- Liver Function Tests (Alanine AminoTransferase, Aspartate AminoTransferase AST, Alkaline Phosphatase) and
- Urine Pregnancy test (for women of childbearing potential) – only done at Screening

7.5 Target Wound Evaluations

Vascular Assessment: Ankle-Branchial Index (ABI) of ulcers/wounds will be measured using the MESI ABPI MD device. It is an automated machine that uses oscillometry and volume plethysmography for accurately calculate the ABI. This device can also automatically collect pulse volume waveform readings (see **Appendix 6A** for details).

Wound Measurement and Photography: Swift Medical wound platform will be used for the measurement and imaging of ulcers/wounds (see **Appendix 6B** for details).

7.6 Quality of Life Assessment

The Wound-QoL is a short questionnaire that measures the quality of life in subjects with chronic wounds. It contains the core content of three established wound questionnaires but is much shorter, and relates explicitly to the wound in each item, thereby measuring disease specific quality of life information. Results of a virtual validation indicate good reliability and validity.

The questionnaire will be completed by the subject during Treatment Visit Week 1 and the End of Study Visit (see **Appendix 5** for details).

The quality of life data will be summarized by average score at Week 1 (Baseline) and End of Study (Week 12) for each indication (DFU/VLU) and subscale (Body, Psyche and Everyday Life). Change from baseline will also be summarized. Also, the average score will be compared for both the TEST and SOC for each indication by the subscale.

8 Potential Risks and Benefits

8.1 Potential Risks

During a preliminary clinical evaluation of the Omeza® Products Bundle, a variety of subjects and wounds received treatment with the lidocaine lavage, the collagen matrix and the skin protectant.

No serious or adverse effects have been observed to date, including hypersensitivity reactions, infection or pain. One patient stated the odor was a bit strong but tolerable. Potential concerns include hypersensitivity reaction, maceration due to combination of wound exudate with Omeza® components, or sensitivity to odor from the products.

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8.2 Potential Benefits

There is a public health need for products for the treatment of chronic lower extremity ulcers. The incidence of ulceration is rising as a result of the ageing population and increased risk factors for atherosclerotic occlusion such as smoking, obesity, and diabetes. Chronic ulceration of the lower extremities is a relatively common condition amongst adults, and ulcer symptoms usually include increasing pain, friable granulation tissue, foul odor, and wound breakdown instead of healing. This results in social distress and considerable healthcare and personal costs.[8] Faster and more effective treatment protocols are needed to improve the quality of life for these subjects.

It is the goal of this trial to demonstrate that the TEST product (Omeza® Products Bundle) can be an effective addition to provide a clinical benefit for the treatment of chronic leg ulcers.

Over the past two plus years, clinical evaluation of Omeza products has been conducted in private physician office, hospital based wound center and patient home settings. The products that have been evaluated include the lidocaine lavage, collagen matrix, slow release hydrocolloid and emollient skin protectant.

In the time frame mentioned, encouraging results have been observed over a range of subjects and with a variety of wound types. Additionally, no adverse effects have been observed and subjects have generally expressed strongly favorable opinions of the products, including ease of application and overall tolerability.

9 Assessment of Safety

9.1 Adverse Event Recording/Documentation

At each contact with the subject, information regarding adverse events will be elicited by appropriate questioning and examinations. All events, both expected/unexpected and related/unrelated will be recorded on a source document. Source documents will include progress notes, laboratory reports, consult notes, phone call summaries and data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable adverse events that are identified will be recorded on the eCRF. The start date, the stop date, the severity of each reportable event, the PI's judgment of the AEs relationship and expectedness to the TEST products and the outcome will also be recorded. Adverse event reporting will extend from signing of ICF until completion of final visit.

9.2 Definitions

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a TEST product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, or study

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procedure whether or not considered related to the TEST product. All AEs that occur prior to administration of study TEST product (blinded medical product) will not be considered a Treatment Emergent Adverse Event (TEAE) but will be recorded in the medical history.

A TEAE is defined as an AE that begins or that worsens in frequency and/or severity after at least one dose of study agent has been administered.

9.3 Assessment of Adverse Events

Each AE will be assessed by the investigator with regard to the following categories.

Seriousness

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening; (This means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

Intensity (Severity)

Investigators should assess the severity of AEs according to CTCAE, provided to each clinical site before the start of the study. In general, CTCAE version 4.0 Severity Grades are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL) (Instrumental ADL include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL include bathing, dressing and

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undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is a regulatory definition as per the CTCAE **Section 6.2.1.2**. An AE of severe intensity may not necessarily be considered serious (by definition) or a mild AE (mild stroke) may be considered as an SAE.

Causality

The investigator will assess the causality/relationship between the study TEST product and the AE and record that assessment on the eCRF. The causal relationship of the AE to study TEST product will be described in terms of the following:

Related:

This category applies to those AEs that, after careful medical consideration are felt to be related to the administration of the study agent. The relationship of an AE to the TEST study agent can be considered related if:

It follows a reasonable temporal sequence from administration of the TEST product.

It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.

It follows a known response pattern to the suspected TEST product.

It reoccurs upon re-challenge with the study TEST product.

Probable:

This category applies to those AEs that, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of the study TEST product. The relationship of an AE to the study TEST product can be considered probable if:

It follows a reasonable temporal sequence from administration of the TEST product.

It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.

It follows a known response pattern to the investigational TEST product.

Possible:

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This category applies to those AEs that, after careful medical consideration, are felt unlikely to be related to the administration of the study TEST product, but the possibility cannot be ruled out with certainty. The relationship of an AE to the study TEST product can be considered possible if:

It follows a reasonable temporal sequence from administration of the study TEST product.

It could be reasonable explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.

It follows a known pattern of response to the investigational TEST product.

Unlikely:

This category applies to those AEs that, after careful medical consideration, are felt unlikely to be related to the administration of the study TEST product. The relationship of an AE to the study TEST product can be considered unlikely if:

It does not follow a reasonable temporal sequence from administration of the study TEST product.

It could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administrated to the subject.

It does not follow a known pattern of response to the investigational TEST product.

Not related:

The AE does not meet any of the above criteria for relatedness.

There is sufficient information that the etiology of the AE is not related to the study TEST product.

Not assessable/unclassifiable:

The AE cannot be judged because of insufficient or contradictory information, which cannot be supplemented or verified.

The study conduct relatedness for SAEs will also be assessed and documented. The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated on the CRF with details of the concomitant disease or medication or other cause.

9.4 Reporting Procedures

Any AE that meets the criteria for serious outlined in the protocol must be reported to the Medical Monitor within 24 hours from the time site personnel becomes aware of the event. The Medical Monitor Contact Information is:

Medical Monitor
Mira Baron, MD

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Palm Beach CRO
400 Columbia Drive. Suite 111
West Palm Beach, FL 33409
Telephone: (561) 200-3344
SAE Fax Line: 561-828-8157
Cell Phone: 561-670-7883
Email: mbaron@palmbeachcro.com

A written report must be submitted and should consist of the Serious Adverse Event Report Form, accompanied by the following eCRF pages: demographics, medical history AEs, and concomitant medications. If the subject is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary *with identifying information removed* should be faxed to SAE Fax line at 561-828-8157 or scanned and e-mailed to **Mira Baron, MD to** *mbaron@palmbeachcro.com* and/or Luba Lavrik at: llavrik@palmbeachcro.com as soon as it becomes available.

Withdrawal from the study and all therapeutic measures will be at the discretion of the PI, sub-investigator or medical monitor. All SAEs (related or with an unknown relationship to the study TEST product) will be followed until satisfactory resolution or until the PI or sub-investigator deems the event to be chronic or the subject to be stable. All SAEs will be recorded from signing of ICF until the end of the study.

Serious AEs occurring after the end of the study and coming to the attention of the PI must be reported only if they are considered (in the opinion of the PI) causally related to the study TEST product. After receipt of the initial report, the Medical Monitor will review the information and, if necessary, contact the PI, to obtain further information for assessment of the event. The Sponsor or their designated representative will be responsible for all information processing and reporting according to local legal requirements.

9.5 Pregnancy

If a female subject is or should become pregnant during the study (i.e., from the date the ICF was signed until the subject's last visit), the PI (or authorized delegate) should notify the Medical Monitor on the initial Pregnancy Report Form within 24 hours of the PI or site personnel first becoming aware of the pregnancy. Pregnancy itself is not an AE, unless there is suspicion that the investigational TEST product may have interfered with the effectiveness of a contraceptive medication.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. However, elective abortion without complications should not be handled as SAEs.

All outcomes of pregnancy must be reported by the PI to the Medical Monitor on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.

9.6 Premature Termination of the Study

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If the PI, the sponsor, and/or the Medical Monitor become aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the sponsor's discretion in the absence of such a finding. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- Failure to enroll subjects at an acceptable rate.
- A decision on the part of the sponsor to suspend or discontinue development of the study TEST product.

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor, in consultation with its advisors, will issue prompt notification to all PIs and IRBs. A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

9.7 Early Withdrawal of a Subject

If a subject is prematurely withdrawn from the study for any reason, the PI should record the reason(s) for withdrawal and make every effort to perform the evaluations described for the end of study visit.

9.8 Replacement of a Subject Who Discontinues Study Treatment

Subjects who met entry criteria and have been randomized will not be replaced if they drop out from the study for any reason.

9.9 Cost Benefit Assessment

The acquisition price from a supplier may be the most basic cost of a product but is not the complete cost of product utilization. When choosing between different products of the same category for Medical Policy development, the Med Tech Committee will want to know the overall cost of using the product, not merely the price of an individual application. There are three types of cost associated with product use in a health-care system: direct, indirect and intangible.

1. The Direct costs include:
    - Acquisition cost of the device (Omeza® Lidocaine Lavage, Omeza® Collagen Matrix and Omeza® Skin Protectant)
    - Supplies to administer the medicine
    - Standard of Care, topical anaesthetic, saline, collagen alginate, foam, soft roll, compressive wrap
    - Pharmacist salary, preparation and dispensing of medications, clinical pharmacy activities, nursing salaries, physician fees

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2. The Other Direct costs include:

    - Treating adverse reactions
    - Inpatient and outpatient treatment of poor response to therapy, emergency room use
    - Hospital overhead costs, for example electricity laboratory services

3. The Indirect costs include:

    - Cost of illness to the patient
    - Lost time from work

4. The intangible costs include:

    - Quality of life

10 Statistical Considerations (See Statistical Analysis Plan [SAP])

10.1 General Considerations and Populations

The primary endpoint is percent change from baseline in target wound measure by Week 12/End of Study.

All statistical testing will be performed at a two-sided alpha=0.05 level of significance. A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock.

All subjects who are randomized and receive at least one study treatment will be included in the Safety Population. All summaries of safety data will be based on this population and reported “as treated” – in case there are subjects that were not treated as per the randomization outcome.

All subjects who are randomized, receive at least one study treatment and have at least one post-baseline measure assessment will be included in the Intent-to-Treat Population (ITT). All efficacy summaries will be based on this population and will be reported according to the intent to treat principle (as randomized).

A review of major protocol violations will be performed. Major violations will include, but not be limited to, an assessment of compliance, use of concomitant medications and intercurrent illnesses. Subjects and data points without major protocol violations will be included as part of the Per-Protocol Population. If fewer than 10% of the subjects have major protocol violations, these analyses may not be performed.

All analyses and summaries will be reported overall and for each indication (venous leg ulcers and diabetic foot ulcers).

10.2 Efficacy Analyses

Primary and Secondary Efficacy Analysis

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1. The null hypothesis to be tested for the primary efficacy endpoint is: No differences between the TEST (Omeza® Products Bundle) and the Standard of Care.
   The primary efficacy endpoint, percent change of wound measure from baseline at Week 4, Week 8 and by Week 12 will be analyzed using mixed model repeated measure (MMRM) with fixed effects factors of treatment and visit and subject as a random effect in the statistical model.

2. Time to maximum closure or complete closure can be defined as the time taken from the start of treatment till the closure (complete or maximum) of the ulcer. Time to closure data will be analyzed using Kaplan Meier Product Life Estimate with median, quartiles and 95% CI.

3. Wound reduction rate will be calculated at Week 4, 8 and by Week 12.

4. Proportion of subjects healed at Week 12 will be compared between TEST (Omeza® Products Bundle) and SOC.

10.3 Safety Analyses

The number and percent of subjects reporting treatment-emergent adverse events (TEAEs) will be tabulated as treated. Subjects discontinuing study product due to adverse events will be listed as will subjects reporting any serious adverse events. TEAEs will also be summarized according to severity and for the subset with at least possible relationship to study product.

Physical examination and laboratory results will also be summarized as treated. Descriptive statistics on the data at each visit and changes from baseline at each visit will be presented.

10.4 Sample Size Rationale

The power of the study is computed for the primary endpoint of “percent change from baseline in target wound measure by Week 12” comparing the two means. The combined sample size of 78 subjects (randomized 2:1) will provide over 80% power to detect a difference of about 14 units (percent change from baseline in wound measure by Week 12), assuming a standard deviation of 20 units, and a 2-sided significance level of 5%.

11 Ethics/Protection of Human Subjects

11.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation between the human research subject and the researchers which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the

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study and include purpose, duration, experimental procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will sign the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IRB and signed by all subjects subsequently screened for the study as well as those currently enrolled in the study.

11.2 Subject Confidentiality

All study findings and documents will be regarded as confidential. The PI and members of his/her research team must not disclose such information without prior written approval from the sponsor. The study data and the analysis or resulting claims will be owned by the sponsor. The anonymity of participating subjects must be maintained. Subjects will be identified on eCRFs and other documents submitted to data management by their subject number, initials, and/or birth date, not by name. Documents not to be submitted to data management that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the PI. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the U.S. Food and Drug Administration (FDA), the sponsor or the sponsor's designee.

12 Data Handling and Record Keeping

12.1 Data Quality Assurance

Standardized and validated procedures and systems will be used to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

The sponsor or sponsor's designee will conduct a clinical site visit to verify the qualifications of each PI, inspect the clinical site facilities, and inform the PI of responsibilities and the procedures for ensuring adequate and correct documentation, as outlined on the Form FDA 1572.

The PI is required to prepare and maintain adequate and accurate case histories (source documentation) designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRF for this study must be consistent with the subjects' source documentation (i.e., medical records).

12.2 Database Management and Quality Control

Data from source documents will be entered into the electronic case report forms (eCRFs) by clinic staff, verified by study monitors and approved by the PI.

A data management plan will be prepared to describe the processes and data flow within the clinical study. Timelines, versions for the computer systems and coding will be

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defined in the plan, and if applicable, Sponsor-specific requests will also be documented within. The plan will be finalized before any treatment if possible but before database lock.

A data validation specification will be created to outline the validation checks to be performed during the study and finalized before data validation. After the data has been monitored by the responsible study monitor, all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the data validation specification. Queries will be generated and sent to the Investigator for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms. This process will be repeated until no further discrepancies are found. The data will then be declared as clean and applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and any change in the data will have a full audit trail.

Electronic Case Report Forms (eCRF) and Source Documentation

The data collection tool for this study will be a sponsor-approved eCRF. A list of all persons who are allowed to make entries in the eCRF, must be personally approved by the PI and made available in each study site. The PI must verify that all data entries in the eCRF are accurate and correct. Entries are to be checked against appropriate source documentation by the monitor. After review by the site monitor any missing or uninterpretable data will be discussed with the PI for resolution.

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

The PI is responsible for maintaining adequate and accurate electronic or hard copy source documents for all observations and data generated during the study. Such documentation is subject to inspection by the sponsor and/or the applicable regulatory authorities.

12.3 Data Collection

An electronic data capturing (EDC) and information management system will be used for data collection. The system should combine all aspects of source data gathering with process control and clinical study management. All clinical and laboratory data, should be collected and subjected to data entry, as needed.

The study (clinical research) monitor is responsible for checking the data during monitoring visits to the clinical unit. The Investigator will ensure that the data collected

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are accurate, complete and legible. Data will be monitored within the electronic data management system by the study monitor. Any changes made during monitoring will be documented with a full audit trail.

12.4 Access to Source Data

During the course of the clinical study, a clinical research monitor will conduct clinical unit visits to review protocol compliance, compare data entries and individual subject's personal records, assess drug accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. Data entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject's anonymity.

Checking of the data entries for completeness and clarity and verifying with source documents, will be required to monitor compliance with Good Clinical Practice (GCP) and other regulations. Moreover, regulatory authorities of certain countries, IECs/IRBs can request to carry out source data inspections on-site, and the Sponsor's clinical quality assurance group can request to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The Investigator will ensure the Sponsor always has the necessary support.

12.5 Data Processing

All data from source documents will be entered into the eCRFs by the respective study coordinators or designee and verified by the PIs. The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/corrections are managed electronically within the study specific database, as described above. There is no paper transmission between Clinical Research Organization (CRO) Monitor, Data Management, or the Site Coordinator. The PI will review and approve the final eCRF data, prior to database lock. Medical history, current medical conditions and AEs will be coded using the MedDRA terminology. The versions of the coding dictionaries will be provided in the Clinical Study Report (CSR).

12.6 Archiving Study Records

Documents will be retained as mutually agreed between the sponsor and the CRO. The sponsor will be the final authority on the documents after two years have elapsed following the data lock date. However, the sponsor may request that these documents should be retained for a longer period if required by the applicable legal requirements. Sponsor has the right to freely access the data for examination or sub analysis at any time and for communication to external audiences. The Data Lock protocol will be decided mutually by the sponsor and the CRO.

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12.7 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the sponsor and PI abide by the principles of the GCP guidelines.

12.8 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. Study records will be maintained by the PI for a minimum of 3 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

13 Legal, and Administrative Aspects

13.1 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB, in accordance with local legal requirements. The sponsor must ensure that all ethical and legal requirements have been met before the first subject is screened in the study. This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB approval prior to implementation (if appropriate). Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment but may still require IRB review and approval. All amendments will be distributed to all protocol recipients, with appropriate instructions.

13.2 Liability and Insurance

The sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the PI, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the study products being tested or by medical steps taken in the course of the study.

13.3 Publication Policy

By signing the study protocol, the PI agrees with the use of results of the study for the purposes of national and international registration, publication, and information for various interested groups, and medical professionals. If necessary, Regulatory Authorities will be notified of the PI's name, address, qualifications, and extent of involvement.

A PI shall not publish any data (poster, abstract, paper, etc.) without having prior written permission with the sponsor in advance.

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Appendix A. Scientific References

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Appendix B. Schedule of Study Procedures/Evaluations

Period	Screening	Treatment		
Duration (Window)	1 week	12 weeks		
Visit	Screening (Day -7 +/-1 day)	Treatment Visit Week 1 Randomization/ Baseline	Treatment Visit Week 2,3,4,5,6,7,8,9,10,11[#] (7 days apart +/-1 day)	Treatment Visit Week 12 End of Study Visit[##] (+/-1 day)
Visit Number	**1**	**2**	**3-11**	**13**
Informed Consent Form/HIPAA Authorization	X			
Demographics (including Fitzpatrick Skin Type)	X			
PE (All systems) / Vital Signs	X			
Medical History	X			
Urine Pregnancy Test**	X			
Concomitant Medications	X	X	X	X
Study Eligibility (I/E)	X	X		
Labs	X			X
Wound QoL Questionnaire		X		X
Randomization		X		
Target Wound Identification	X			
Vascular Assessment	X	X	X	X
Wound Examination	X	X	X	X
Target Wound Measure and Photography	X	X	X	X
Ulcer Care Treatment Applied as Randomized		X	X	X
Safety Assessments/Adverse Events/Intercurrent Illnesses		X	X	X

** Pregnancy testing is for females of childbearing potential

If wound closes before Week 12, the subject will continue to come in for all the remaining study visits until study completion, but the TEST subjects will be treated with the Omeza® Skin Protectant only.

If wound does not close by Week 12, the subject will be immediately exited from the study and no further follow-up will occur as part of the study.

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Appendix 1. Omeza® Ulcer Care Product Information


Omeza Products Bundle Protocol Ove


Omeza Lidocaine Lavage.pdf


Omeza Collagen Matrix.pdf


Omeza Skin Protectant.pdf

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Appendix 2: Standard of Care Venous Leg Ulcers

1) Apply topical anesthetic
2) Perform appropriate sharp debridement as indicated
3) Clean wound with saline
4) Apply collagen alginate as primary dressing
5) Apply foam as secondary dressing
6) Soft roll and compressive wrap (Dynaflex™ or Profore or any other preferred multi-layer compression bandage system)

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Appendix 3: Standard of Care Diabetic Foot Ulcers

1) Apply topical anesthetic
2) Perform appropriate sharp debridement as indicated
3) Clean wound with saline
4) Apply collagen alginate as primary dressing
5) Apply foam as secondary dressing
6) Offloading of the diabetic foot ulcer using standard of care as practiced at the study site

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Appendix 4: Omeza® Products Bundle Instructions

Venous Leg Ulcer

1) Apply Omeza® Lidocaine Lavage and after 5 minutes wipe out debris
2) Perform appropriate sharp debridement as indicated
3) Apply additional Omeza® Lidocaine Lavage and wipe out debris
4) Apply Omeza® Collagen Matrix as primary dressing
5) Apply Omeza® Skin Protectant on periwound and surrounding intact skin from knee to toes
6) Apply foam as secondary dressing
7) Soft roll and compressive wrap (Dynaflex™ or Profore or any other preferred multi-layer compression bandage system)

Diabetic Foot Ulcer

1) Apply Omeza® Lidocaine Lavage and after 5 minutes wipe out debris
2) Perform appropriate sharp debridement as indicated
3) Apply additional Omeza® Lidocaine Lavage and wipe out debris
4) Apply Omeza® Collagen Matrix as primary dressing
5) Apply Omeza® Skin Protectant on periwound and surrounding intact skin from knee to toes
6) Apply foam as secondary dressing
7) Offloading of the diabetic foot ulcer using standard of care as provided by the clinical study site

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Appendix 5: Wound-QoL

The 'Wound-QoL': A Short Questionnaire Measuring Quality of Life in Patients with Chronic Wounds

Christine Blome[1], Katrin Baade[1], Patricia Price[2], Eike Sebastian Debus[3], Matthias Augustin[1]

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[3] Cardiff

BACKGROUND

University, UK

Chronic wounds can heavily impair the patients' quality of life by causing for example severe pain, social isolation, restricted mobility, and sleeping problems.

Evaluation of health related quality of life (HRQoL) has become a standard in wound research and wound care [1]. Three wound-specific HRQoL questionnaires have been developed in, or translated to, German language and are currently being used in treatment evaluation: The **Freiburg Quality of Life Assessment for wounds** (FLQA-w) [2] consisting of 3 pages and 30 questions; the **Cardiff Wound Impact Schedule** (CWIS) [3] with 7 pages and 57 questions; and the **Würzburg Wound Score** (WWS) [4] with 4 pages and 21 questions.

For the CWIS, no global score can be calculated. The WWS, in contrast, provides no possibility of evaluating different domains of HRQoL by calculating subscale scores.

Furthermore, all three instruments are quite long and comprise a lot of text. This increases the patient burden for completing the questionnaires which may impair acceptance and increase the number of missing values. This is of particular relevance in chronic wounds, where the majority of affected patients are elderly [5] and benefit from short and easy-toread questionnaires [6].

In this study, a short questionnaire measuring health-related quality of life in patients with chronic wounds was developed on the basis of the three established instruments.

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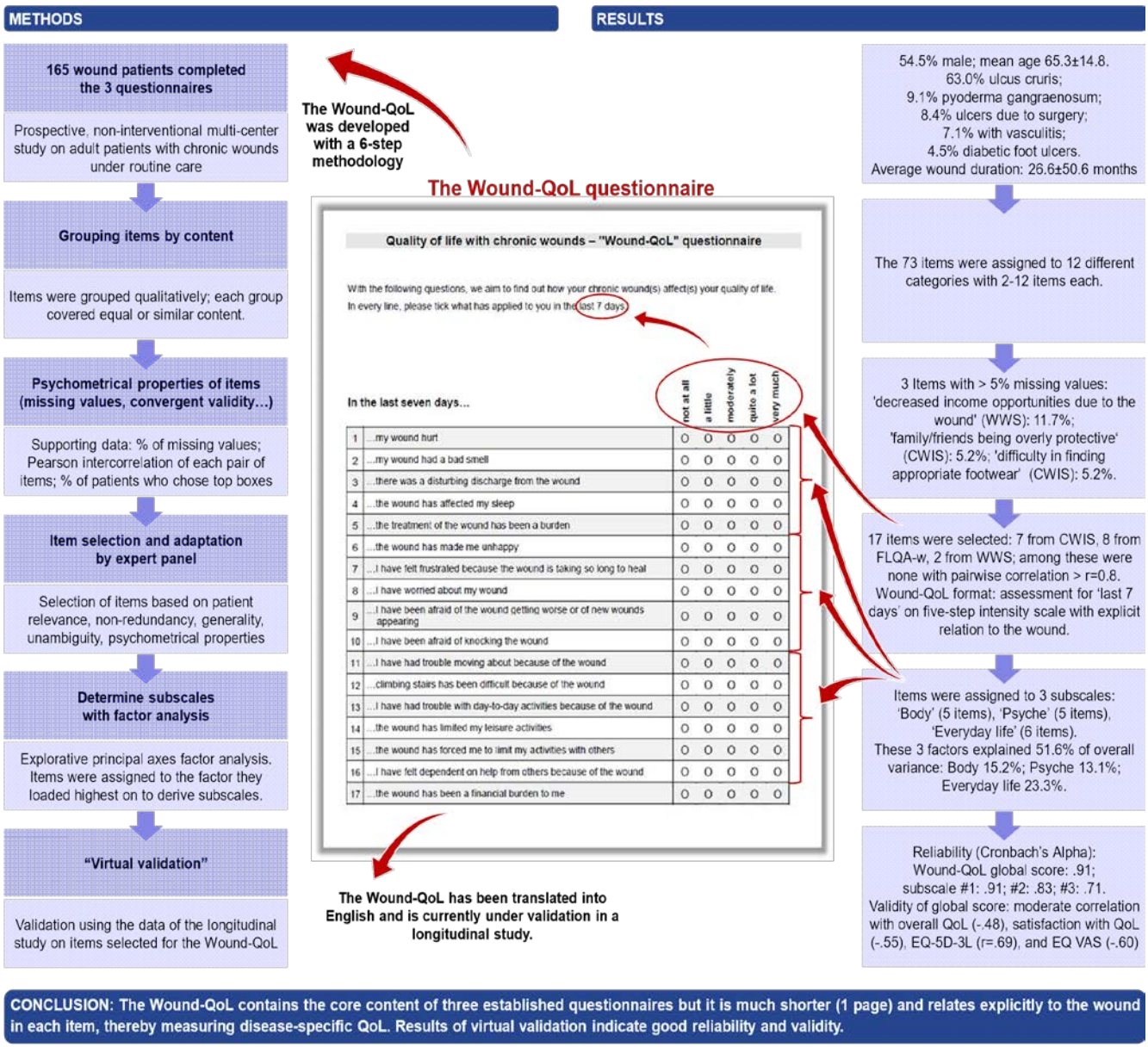

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Questionnaire on quality of life with chronic wounds

Short Manual

Date: June 2019

1. Description and use

The Wound-QoL measures the disease-specific, health-related quality of life of patients with chronic wounds. It consists of 17 items on impairments which are always assessed in retrospect to the preceding seven days.
The Wound-QoL can be used in clinical and observational studies and in daily practice.

2. Development

The Wound-QoL was developed on the basis of three validated instruments assessing HRQoL in chronic wounds: the Freiburg Life Quality Assessment for wounds (FLQA-w, Augustin et al. 2010), the Cardiff Wound Impact Schedule (CWIS, Price et al. 2004), and the Würzburg Wound Score (WWS, Spech 2003; Engelhardt et al. 2014).
These three questionnaires were filled in by 165 leg ulcer patients in a prospective study under routine care. For implementation in the Wound-QoL those of all 92 items were selected that showed the best psychometric properties and that were not redundant in content. Item and instruction wording of the Wound-QoL were harmonized and improved by an expert panel. Wound-QoL subscales have been determined with factor analysis.

3. Languages

Validated translations of the original, German version of the Wound-QoL have been performed as follows:

1. independent translations by 2 native speakers
2. independent back-translations by 2 native speakers
3. tabulation of all translations (sentence by sentence) with listing of all differences between translations and differences between back translations and original
4. translators' and methodologists'/authors' conference (sentence by sentence) to find a consensus on the final translation
5. proof reading of the final questionnaire by a native speaker.

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To date, validated translations of the Wound-QoL have been performed for:

- Arabic (Israel)
- Czech (Czechia)
- Danish (Denmark)
- Dutch (Netherlands)
- English (Canada)
- English (UK)
- English (US)
- German (Germany and Austria) [original version]
- German (Switzerland)
- Hebrew (Israel)
- French (France)
- Italian (Italy)
- Latvian (Latvia)
- Lithuanian (Lithuania)
- Polish (Poland)
- Portuguese (Portugal)
- Portuguese (Brasil)
- Russian (Russia)
- Slovakian (Slovakia)
- Spanish (Spain)
- Spanish (Central America)
- Standard Chinese (China)
- Swedish (Sweden)
- Turkish (Turkey)
- Ukrainian (Ukraine)

4. Instructions

The Wound-QoL is filled in by the patient himself. The questionnaire is self-explanatory; yet, patients can be supported if they are not able to fill it in by themselves. In this case, the support has to be documented.

5. Data entry

For statistical analyses, the data are entered into a spread sheet (e.g. Excel) or statistics program (e.g. SPSS). The spread sheet matrix must be structured as follows: Each row corresponds with one patient and each column corresponds with one variable (=item).

6. Data analysis

If more than one box is ticked within an item or if a patient has ticked between two checkboxes, the item is treated as missing.
Answers to each item are coded with numbers (0='not at all' to 4='very much').

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A Wound-QoL **global score** on overall disease-specific quality of life is computed by averaging all items. A global score can only be computed if at least 75% of the items have been answered (i.e., at least 13 in 17 items are valid).
In addition, **subscales** of the Wound-QoL can be calculated representing different dimensions of disease specific quality of life by averaging the respective items. A subscale can only be computed if no more than 1 item of the subscale is missing. The items are assigned to subscales as follows:

1. Subscale 'Body': Items #1 to #5
2. Subscale 'Psyche': Items #6 to #10
3. Subscale 'Everyday life': Items #11 to #16

Item #17 does not belong to either of the subscales.

7. Psychometric properties of the Wound-QoL
The Wound-QoL has been tested for internal consistency, convergent validity regarding four generic HRQoL measures such as the EQ-5D, and responsiveness in a so-called virtual validation using the longitudinal study data on the three questionnaires FLQA-w, CWIS and WWS (Blome et al. 2014). A further validation has been conducted in a cross-sectional study (Augustin et al. 2014).
In a prospective validation study (Augustin et al. 2017), patients completed the Wound-QoL and two other QoL questionnaires (European Quality of Life-5 Dimensions, EQ-5D, and Freiburg Life Quality Assessment for wounds, FLQA-wk) at baseline and at two more time points (4 and 8 weeks). Wound status was assessed with an anchor question. 227 patients (48.5% women) participated in the study. Mean age was 66.9 years (range 17–96, median 69.5). Indications were venous leg ulcers (40.1%), pyoderma gangraenosum (14.1%), diabetic or ischemic foot ulcers (5.3%), pressure ulcers (2.6%), and other etiologies (30.0%). The Wound-QoL showed good internal consistency, with high Cronbach's alpha in all the subscales and in the global scale on all time points (>0.8). Convergent validity was indicated by moderate-to-high correlations with the EQ-5D (range 0.5–0.7, $p<0.001$) and FLQA-wk global score ($r>0.8$, $p<0.001$) at every time point. Responsiveness was high, too.
In a study on the test–retest reliability of the Wound-QoL (Sommer et al. 2017), patients were asked to complete the Wound-QoL twice within 3–7 days. Intraclass correlation coefficients (ICCs) ranged 0.79 and 0.86, which can be considered evidence of excellent reliability. Another indicator of very good reliability was high internal consistency of both global score (0.92) and subscale scores (body: 0.91; psyche: 0.88; everyday life: 0.90).

8. The Wound-Act Implementation Tool
In order to identify areas of need for action, a panel of wound specialists and patients developed a one-page implementation tool called Wound-Act. The Wound-Act is a decision aid for taking further action once quality of life problems at the level of single items are identified with the Wound-QoL. Within the Wound-
Act, each Wound-QoL item answered with "quite a lot" or "very much" by the patient is regarded an important area of need for action.

9. Contact and license information
PD Dr. Christine Blome, **c.blome@uke.de**

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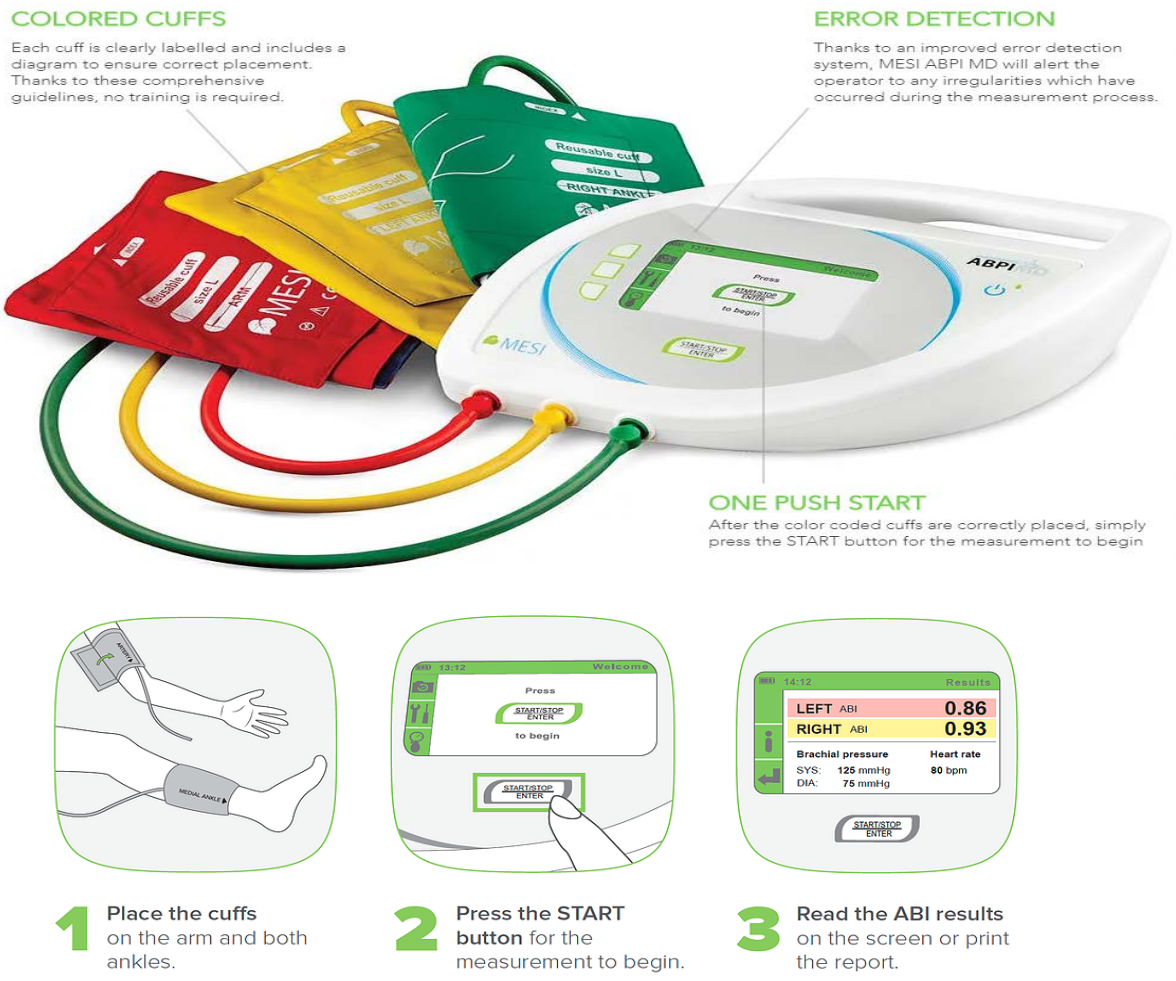
Appendix 6A: Vascular Assessment

MESI ABPI MD Device

- Automated device that uses Device uses oscillometry and volume plethysmography to accurately calculate a patient's Ankle-Branchial Index (ABI).
- It uses a unique algorithm to automatically measure both left and right ankle-branchial pressures
- Includes blood pressure cuffs with sensors that can automatically collect pulse volume waveform readings
- Report Printouts using the MESIresults computer software

https://www.mediusa.com/Our-Brands/MESI/



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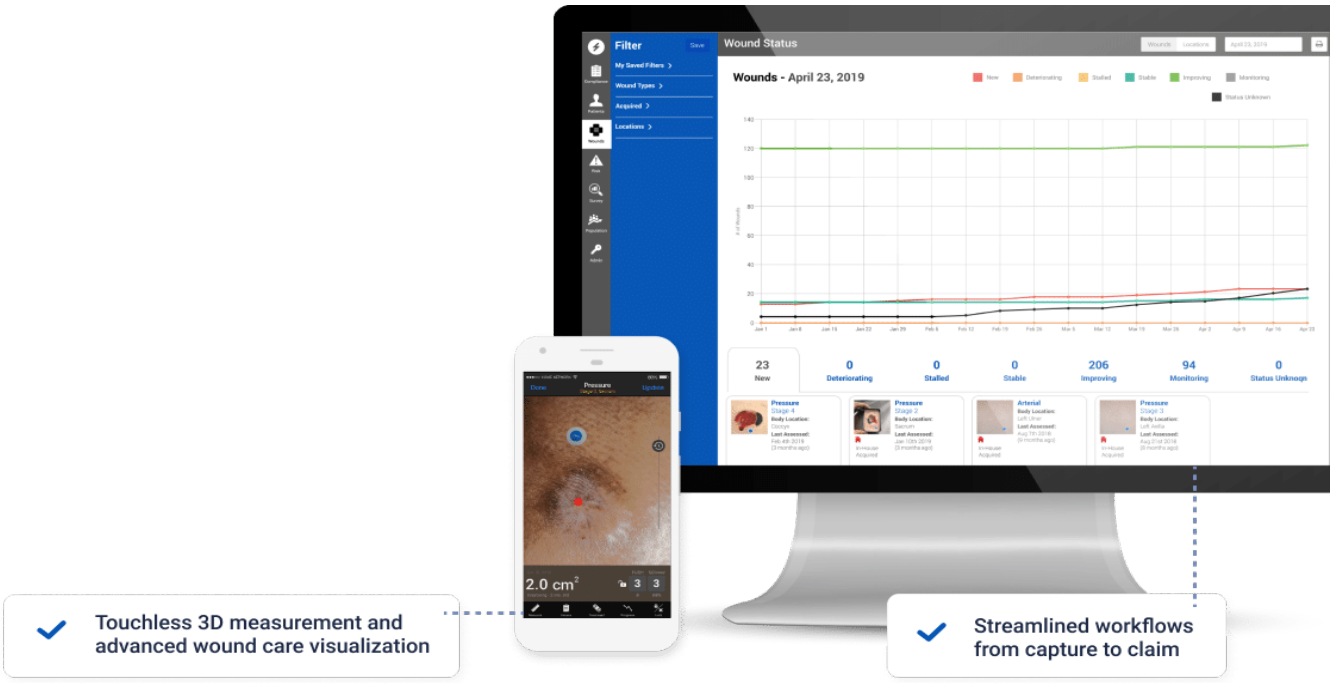
Appendix 6B: Wound Measurement and Photography

Swift Skin and Wound

- A Smartphone App that captures wound measurement and images
- More accurate measure than the ruler method
- Allows for wound depth which is calibrated automatically

https://swiftmedical.com/



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Appendix 7: The Wagner Diabetic Foot Ulcer Grade Classification System

The Wagner diabetic foot ulcer classification system assesses ulcer depth and the presence of osteomyelitis or gangrene by using the following grades:

- Grade 0 – intact Skin
- Grade 1 – superficial ulcer of skin or subcutaneous tissue
- Grade 2 – ulcers extend into tendon, bone, or capsule
- Grade 3 – deep ulcer with osteomyelitis, or abscess
- Grade 4 – partial foot gangrene
- Grade 5 – whole foot gangrene

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Appendix 8: Fitzpatrick Skin type Classification Scale

Skin Type	Skin Color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark brown; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

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