A single site randomized, clinical trial comparing the concomitant use of MicroMatrix® and Cytal™ Wound Matrix 2-Layer to Standard of Care in patients with Stage 3 or 4 pressure injuries

Unique Protocol ID: CA2016-001

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Version 5.0

08 June 2018

A single site randomized, clinical trial comparing the concomitant use of MicroMatrix® and Cytal™ Burn Matrix 2-Layer to Standard of Care in patients with Stage 3 or 4 pressure injuries

CA2016-001

ACell, Inc.
6640 Eli Whitney Drive
Columbia, MD 21046

Version 5.0

08 June 2018

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LIST OF ABBREVIATIONS

ABI	Ankle Brachial Index
ADL	Activities of Daily Living
AE	Adverse Event
BMI	Body Mass Index
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
NPUAP	National Pressure Ulcer Advisory Panel
NPWT	Negative Pressure Wound Therapy
PUSH	Pressure Ulcer Scale for Healing
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SF	Short Form
SID	Subject Identification Number
SNF	Skilled Nursing Facility
SOC	Standard of Care
UADE	Unanticipated Adverse Device Effect
VPS	Visual Pain Scale

PROTOCOL SUMMARY

Title:	A single site randomized, clinical trial comparing: • Concomitant use of MicroMatrix® and Cytal™ Burn Matrix 2-Layer • MicroMatrix® and Cytal™ Burn Matrix 2-Layer with a negative pressure wound therapy (NPWT) system • A NPWT alone in the management of Stage 3 or 4 pressure injuries (as defined by the National Pressure Ulcer Advisory Panel [NPUAP]).
Protocol Number:	CA2016-001
Study Design:	A three arm, parallel-design, randomized study comparing 2 experimental arms to a single control arm. The primary comparison will be Group 1 (MicroMatrix® with Cytal™ Burn Matrix 2-Layer vs. Group 3 (NPWT) to determine if Group 1 is superior to Group 3. NPWT is the standard of care (SOC) for patients with Stage 3 or 4 pressure ulcers and is the active control arm for the study. A secondary comparison will be conducted comparing Group 2 (MicroMatrix® with Cytal™ Burn Matrix 2-Layer plus NPWT) vs. Group 3 (NPWT) to determine if Group 2 is superior to Group 3. Patients who meet the inclusion and exclusion criteria for the study will be randomized (1:1:1) to Group 1, 2, or 3 using a permuted block randomization scheme.
Objectives:	1. To compare the incidence of complete epithelization at 12 weeks between Group 1 and Group 3, and Group 2 to Group 3. 2. To compare the time to complete epithelization between Group 1 and Group 3, and Group 2 to Group 3.

	3. To compare the rate of wound epithelization between Group 1 and Group 3, and Group 2 to Group 3 over time in cm^2/week. 4. To evaluate improvements in the clinical efficacy and impact of MicroMatrix® and Cytal™ Burn Matrix 2-Layer treatments as compared to NPWT. 5. To compare direct and indirect pressure ulcer related costs by subject. 6. To compare the treatment-emergent adverse event (AE) safety profile between Cytal™ Burn Matrix 2-Layer, MicroMatrix®, and NPWT.
Endpoints:	**Primary Endpoint** Incidence of complete epithelization at 12 weeks between Group 1 and Group 3, and Group 2 to Group 3. **Secondary Endpoints** 1. Time to complete wound epithelization between Group 1 and Group 3, and Group 2 to Group 3. 2. Compare rate of wound epithelization, measured by change in pressure ulcer area over time, in cm^2/week. 3. Impact of the treatments, measured by: a. Patient satisfaction using the Short Form (SF)-20 Health Survey, Wong-Baker FACES® Visual Pain Scale (VPS), and Katz Index of Independence in Activities of Daily Living (ADL) b. Type of tissue developed (Pressure Ulcer Scale for Healing [PUSH] Tool) i. Ulcer area changes and decrease in wound margins ii. Granulation, epithelization, and exudates changes iii. Time to healing c. Pain evaluation and narcotic use d. Nursing contact time (time required for dressing changes) e. Length of hospital stay for in-patient patients f. Length of stay at skilled nursing facilities (SNF) for patients who are discharged to SNF

	Tertiary Endpoints 1. Cost Analysis a. Direct and indirect pressure ulcer related costs by subject. This is measured by total inpatient and outpatient expenses, stratified by product and care cost b. Current employment status and return to work status c. Frequency (and associated expenses) of pressure ulcer specific AEs, UADEs and SAEs
Number of Subjects:	60 patients who present to the physician in the hospital or wound care clinic with at least one Stage 3 or 4 pressure ulcer will be considered for enrollment and randomization. Given that the primary endpoint is dichotomous, patients who withdraw prematurely (<12 weeks from randomization and treatment assignment) without complete wound epithelialization will be considered in the analysis as not having met the definition for epithelialization.
Study Criteria	**Inclusion Criteria** 1. Provision of signed and dated informed consent form by subject or legally authorized representative. 2. Stated willingness to comply with all study procedures and availability for the duration of the study. 3. Male or female patients that are ≥ 21 years of age. 4. Body Mass Index (BMI) <45. 5. At least one Stage 3 or 4 pressure injury (NPUAP Staging Guidelines) present at the Screening and/or Treatment Visit located in any of the following regions: a. Occipital b. Back c. Flank d. Upper Extremity i. Arm ii. Elbow iii. Wrist iv. Hand e. Sacral f. Hip

g. Gluteal
h. Ischial
i. Lower Extremity
    i. Leg
    ii. Knee
    iii. Ankle
    iv. Heel
    v. Foot

6. Surface dimensions of pressure injury must be between 9 to 64 cm^2 inclusive (as measured prior to treatment using a cm-scale ruler). The longest dimension must not exceed 10 cm; depth must not exceed 5 cm.
7. Wound must be >5 cm from the anus if colostomy not performed.
8. For lower extremity ulcers: Adequate arterial blood flow and perfusion near the site of the injury (the foot is warm to the touch and has palpable pulses), per Investigator judgement.
9. Confirmed pressure injury versus moisture-associated skin damage or friction injury.
10. Ability to maintain an intact occlusive dressing for 4-7 days with reinforcement without contamination of urine or stool.
11. Confirmed fecal (Colostomy) and/or urine incontinence (Foley) maintenance/management, if necessary.
12. Consent to off-loading (turns) from pressure sites a minimum of every 2 hours (if possible).
13. Consent to sharp debridement of necrotic tissue in the wound bed unless the wound has already undergone debridement within 5 days prior to the Treatment Visit.
14. For females of reproductive potential (defined as females ≤ 55 years of age): Negative pregnancy test required prior to surgical debridement per hospital procedures.

Exclusion Criteria

1. Surgical treatment of pressure injury 30 days prior to the Treatment Visit and/or pressure injury in previously irradiated areas.
2. Inability to manage fecal and/or urine incontinence or patient refusal of its maintenance/management (as

	determined medically necessary). Patient may be rescreened and enrolled if urinary and/or fecal continence status or management change after failure to comply with requirement. 3. Allergy or hypersensitivity to materials in porcine-based study products (per subject report) or personal preference. 4. Currently treated for an active malignant disease. 5. Prior diagnosis of active malignant disease, and is less than 1 year disease-free. 6. History of malignancy within the wound. 7. Presence of any conditions that are contraindicated with NPWT. 8. Any condition associated with a wound healing abnormality (e.g.: connective tissue disorder or immune disorder). 9. Dermatologic comorbid disease (e.g., cutis laxa or collagen vascular disease). 10. Bleeding diathesis. 11. Patients with primary treatment ulcers from burns (from exposure to high heat) or venous leg ulcers. A patient may have concomitant non-pressure ulcers present in non-pressure ulcer treatment regions. 12. Received biological-based therapy in any pressure wound within 3 months of the Treatment Visit. 13. Severe or significant hypoalbuminemia (albumin <2.5 g/dL, and/or pre-albumin <5 mg/dL), or hypoproteinemia (protein <6 g/dL). 14. Moderate to severe anemia (Hgb <7 g/dL). 15. Severely uncontrolled diabetes mellitus (defined as HA1C >12%). 16. Subject report of concurrent participation in another clinical trial that involves an investigational drug or device that would interfere with this study. 17. Subject report of previous participation in other interventional wound healing clinical investigation within 60 days prior to the Screening Visit. 18. The subject has any physical or psychiatric condition that in the Investigator's opinion would warrant exclusion from the study or prevent the subject from completing the

	study.
Number of Sites:	1
Site Locations:	**Saint Vincent's Medical Center Riverside** 1 Shircliff Way Jacksonville, FL 32204 **Saint Vincent's Medical Center Southside** 4201 Belfort Road Jacksonville, FL 32216 **Wells Surgical Services, LLC** 1395 Cassat Avenue, Suite 1 Jacksonville, FL 32205 11512 Lake Mead Avenue Suite 531 Jacksonville, FL 32256 3 Shircliff Way Dillon Building Suite 630 Jacksonville, FL 32204
ACell Study Product(s):	1. MicroMatrix® 2. Cytal™ Burn Matrix 2-Layer
Participant & Study Duration:	The duration of this study for each subject will be a maximum of up to 27 weeks. Subject recruitment is planned to last for 6-9 months, starting in early 2017. The study will end in mid-2018 after the database has been locked. The actual overall study duration or subject recruitment period may vary.
Statistical Methodology:	All statistical tests will be conducted using a type 1 error rate of 5%. Simultaneous testing for the primary endpoint of Group 1 vs. Group 3 and Group 2 vs. Group 3 will be conducted. The analyses of the secondary endpoints will be conducted using a hierarchical plan: if the primary analysis is significant in favor of Group 1 over Group 3, the secondary and tertiary analyses can be conducted in sequential order using a type 1 error rate of 5%. If the primary analysis is

	significant in favor of Group 2 over Group 3, the secondary and tertiary analyses will be conducted in sequential order using a type 1 error rate of 5%. The testing will continue, provided the prior analysis was significant in favor of the study product. The analysis of the primary endpoint will be based on a generalized linear model specifying the distribution as binomial. If a patient withdraws prior to the 12-week wound evaluation visit and the last recorded observation revealed complete wound epithelialization, the patient will be counted in the primary analysis as having achieved complete wound epithelialization. If a patient withdraws prior to the 12-week wound evaluation visit and the last recorded observation revealed the wound had not closed, the patient will be counted in the primary analysis as not having achieved complete wound epithelialization. The analysis of the time of the initial observation of complete wound epithelialization will be conducted using a log rank test. If a patient withdraws prior to achieving complete wound epithelialization, the patient will be censored using the time of the last observation. To estimate the sample size for this clinical investigation, the difference in the incidence of patients who achieve complete wound epithelialization (primary endpoint) was used. Estimates were prepared considering complete closure in the NPWT arm of 20% to 40% and a type 1 and 2 error rate of 5% and 20%, respectively. Based on these estimates, if the incidence in Group 1 is 45% greater than the incidence in Group 3, the difference will be significant ($p<0.05$).

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

A pressure injury is localized damage to the skin and/or underlying soft tissue usually over a bony prominence or related to a medical or other device.[1] The injury occurs as a result of intense and/or prolonged pressure or pressure in combination with shear, and may present as intact skin or an open ulcer.[1] The staging of a pressure injury includes[1]:

Stage 1: Non-blanchable erythema of intact skin
Intact skin with a localized area of non-blanchable erythema, which may appear differently in darkly pigmented skin. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.

Stage 2: Partial-thickness skin loss with exposed dermis
Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible. Granulation tissue, slough and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel. This stage should not be used to describe moisture associated skin damage (MASD) including incontinence associated dermatitis (IAD), intertriginous dermatitis (ITD), medical adhesive related skin injury (MARSI), or traumatic wounds (skin tears, burns, abrasions).

Stage 3: Full-thickness skin loss
Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.

Stage 4: Full-thickness skin and tissue loss
Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining and/or tunneling often occur. Depth varies by

anatomical location. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.

Unstageable Pressure Injury: Obscured full-thickness skin and tissue loss
Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a Stage 3 or Stage 4 pressure injury will be revealed. Stable eschar (i.e. dry, adherent, intact without erythema or fluctuance) on an ischemic limb or the heel(s) should not be removed.

Deep Tissue Pressure Injury: Persistent non-blanchable deep red, maroon or purple discoloration
Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood filled blister. Pain and temperature change often precede skin color changes. Discoloration may appear differently in darkly pigmented skin. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury, or may resolve without tissue loss. If necrotic tissue, subcutaneous tissue, granulation tissue, fascia, muscle or other underlying structures are visible, this indicates a full thickness pressure injury (Unstageable, Stage 3 or Stage 4). Do not use Deep Tissue Pressure Injury to describe vascular, traumatic, neuropathic, or dermatologic conditions.

Pressure injuries have previously been called pressure ulcers, pressure sores, bedsores, and decubitus ulcers, terms that imply that only bed-bound, non-ambulatory patients develop pressure injuries.[1] However, patients who are ambulatory can also develop pressure ulcers, although reduced mobility is still a major risk factor.[1]

Pressure injury prevalence in health care setting ranges from 0%[2] to 72.5%,[3] with large variations observed between countries and clinical settings (e.g., acute care, aged care and community care).[1] Average prevalence in acute care settings is cited as approximately 10%.[4] In general acute care, there appears to be a gradual decline in pressure injury prevalence over the past decade, [5] due to the growing international health policy focus on prevention of pressure injuries.[1] However, there are no clear trends in other clinical settings.[1] Prevalence and incidence rates are generally higher in populations who are at elevated risk, [1] such as those receiving palliative care,[4] those with spinal cord injuries[6], and individuals in critical care. [7, 8]

In 2001, the National Pressure Ulcer Advisory Panel (NPUAP) described the incidence of pressure injuries as ranging from 0.4% to 38% in hospitals, from 2.2% to 23.9% in

skilled nursing facilities and from 0.0% to 17% for home health agencies.[5] Since then, hospitals have increased their efficiency in pressure ulcer prevention, and incidence rates have dropped from 7% in the 2000s to 4.5% in 2012.[9, 10]

Pressure injury treatment begins with an accurate diagnosis and the classification of pressure injury. Current treatments include wound bed preparation (cleansing, debridement and dressing), biophysical agents, surgery, and wound off-loading.

Pressure ulcers represent a major burden of sickness and reduced quality of life for patient consumers and their care givers.[1] Increased morbidity and mortality associated with pressure ulcer development in hospitalized patients is documented in multiple studies.[12,13] According to NPUAP, hospital lengths of stay, readmission rates, and hospital charges are greater in individuals who develop a pressure ulcer than in those remaining ulcer free.[1] The development of a single pressure ulcer in hospitals in the United States can increase the patients' length of stay five-fold.[14] Additionally, the personal burden associated with a chronic wound, including pain and discomfort; stress, anxiety and depression; lowered autonomy and security; and impaired social functioning is immeasurable.[1]

Pressure injuries acquired during hospitalization, evaluated as either Stage 3 or 4 are considered among the eight preventable conditions identified by the Centers for Medicare and Medicaid Services (CMS).[11] Since October of 2008, hospitals no longer receive higher Medicare payments related to the ulcer specific care of patients who acquire Stage 3 or 4 pressure injuries during their inpatient stay.[11]

Pressure injuries are often documented in hospitalized patients as a secondary diagnosis rather than the primary reason.[11] In 2007, CMS reported 257,412 cases of secondary, Stages 3 or 4 pressure injuries, at a cost per case of $43,180 (USD).[11] However, this may be a serious underestimation of the problem, because physician discharge diagnoses may not include presence of a pressure injury even when the patient has a Stage 3 or Stage 4 ulcer.[11] Physicians often see pressure injury detection and prevention as a nursing issue and fail to include this data in their discharge summaries, which are used by coders for billing purposes.[11]

2 OBJECTIVES AND PURPOSE

The primary objectives of the study are:

1. To compare the incidence of complete epithelization at 12 weeks between Group 1 and Group 3, and Group 2 to Group 3.

The secondary objectives of the study are:

1. To compare the time to complete epithelization between Group 1 and Group 3, and Group 2 to Group 3.
2. To compare the rate of wound epithelization between Group 1 and Group 3, and Group 2 to Group 3 over time in cm^2/week.
3. To evaluate improvements in the clinical efficacy and impact of MicroMatrix® and Cytal™ Burn Matrix 2-Layer treatments as compared to NPWT

The tertiary objectives of the study are:

1. To compare direct and indirect pressure ulcer related costs by subject measured by total inpatient and outpatient expenses.
2. To compare the treatment-emergent AE safety profile between Cytal™, MicroMatrix® and NPWT.

3 STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

A three arm, parallel-design, randomized study comparing 2 experimental arms to a single control arm. The primary comparison will be Group 1 (MicroMatrix® with Cytal™ Burn Matrix 2-Layer) vs. Group 3 (NPWT) to determine if Group 1 is superior to Group 3. NPWT is the SOC for patients with Stage 3 or 4 pressure ulcers and is the active control arm for the study.

A secondary comparison will be conducted comparing Group 2 (MicroMatrix® with Cytal™ Burn Matrix 2-Layer plus NPWT) vs. Group 3 (NPWT) to determine if Group 2 is superior to Group 3.

Patients who sign the informed consent form and meet all inclusion and exclusion criteria for the study will be randomized (1:1:1) to Group 1, 2, or 3 using a permuted block randomization scheme.

The duration of this study for each subject will be a maximum of up to 27 weeks.

Subject recruitment is planned to last for 6-9 months, starting in early-2017. The study will end mid-2018 after the database has been locked. The actual overall study duration or subject recruitment period may vary.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT

The primary endpoint of the study is the incidence of complete epithelization at 12 weeks between Group 1 and Group 3, and Group 2 to Group 3.

3.2.2 SECONDARY ENDPOINTS

The secondary endpoints of the study include:

1. Time to complete wound epithelization between Group 1 and Group 3, and Group 2 to Group 3.
2. Compare rate of wound epithelization, measured by changes in pressure ulcer area over time, in cm^2/week.
3. Impact of the treatments, measured by:
    a. Patient satisfaction using the Short Form (SF)-20 Health Survey, Wong-Baker FACES® Visual Pain Scale (VPS), and Katz Index of Independence in Activities of Daily Living (ADL)
    b. Type of tissue developed (PUSH Tool)
        i. Ulcer area changes and decrease in wound margins
        ii. Granulation, epithelization, and exudates changes
        iii. Time to healing
    c. Pain evaluation and narcotic use
    d. Nursing contact time (time to change dressing)
    e. Length of hospital stay for in-patient patients
    f. Length of stay at SNF for patients who are discharged to SNF

3.2.3 TERTIARY ENDPOINTS

Tertiary endpoints of the study include:

1. Cost Analysis
    1. Direct and indirect pressure ulcer related costs by subject. This is measured by total inpatient and outpatient expenses, stratified by product and care cost
    2. Current employment status and return to work status
    3. Frequency (and associated expenses) of pressure ulcer specific AEs, UADEs and SAEs

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Inclusion Criteria

1. Provision of signed and dated informed consent form by subject or legally authorized representative.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female patients that are ≥ 21 years of age.
4. Body Mass Index (BMI) <45.
5. At least one Stage 3 or 4 pressure injury (NPUAP Staging Guidelines) present at the Screening and/or Treatment Visit located in any of the following regions:
    a. Occipital
    b. Back
    c. Flank
    d. Upper Extremity
        i. Arm
        ii. Elbow
        iii. Wrist
        iv. Hand
    e. Sacral
    f. Hip
    g. Gluteal
    h. Ischial
    i. Lower Extremity
        i. Leg
        ii. Knee
        iii. Ankle
        iv. Heel
        v. Foot
6. Surface dimensions of pressure injury must be between 9 to 64 cm^2 inclusive (as measured prior to treatment using a cm-scale ruler). The longest dimension must not exceed 10 cm; depth must not exceed 5 cm.
7. Wound must be > 5 cm from the anus if colostomy not performed.

8. For lower extremity ulcers: Adequate arterial blood flow and perfusion near the site of the injury (the foot is warm to the touch and has palpable pulses), per Investigator judgement.
9. Confirmed pressure injury versus moisture-associated skin damage or friction injury.
10. Ability to maintain an intact occlusive dressing for 4-7 days with reinforcement without contamination of urine or stool.
11. Confirmed fecal (Colostomy) and/or urine incontinence (Foley) maintenance/management, if necessary.
12. Consent to off-loading (turns) from pressure sites a minimum of every 2 hours (if possible).
13. Consent to sharp debridement of necrotic tissue in the wound bed unless the wound has already undergone debridement within the previous 5 days of the Treatment Visit.
14. For females of reproductive potential (defined as females ≤ 55 years of age): Negative pregnancy test required prior to surgical debridement per hospital procedures.

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

Exclusion Criteria

1. Surgical treatment of pressure injury 30 days prior to the Screening Visit and/or pressure injury in previously irradiated areas.
2. Inability to manage fecal and/or urine incontinence or patient refusal of its maintenance/management (as determined medically necessary). Patient may be rescreened and enrolled if urinary and/or fecal continence status or management change after failure to comply with requirement.
3. Allergy or hypersensitivity to materials in porcine-based study products (per subject report) or personal preference.
4. Currently treated for an active malignant disease.
5. Prior diagnosis of active malignant disease, and is less than 1 year disease-free.
6. History of malignancy within the wound.
7. Presence of any conditions that are contraindicated with NPWT.
8. Any condition associated with a wound healing abnormality (e.g.: connective tissue disorder or immune disorder).
9. Dermatologic comorbid disease (e.g., cutis laxa or collagen vascular disease).
10. Bleeding diathesis.

11. Patients with primary treatment ulcers from burns (from exposure to high heat) or venous leg ulcers. A patient may have concomitant non-pressure ulcers present in non-pressure ulcer treatment regions.
12. Received biological-based therapy in any pressure wound within 3 months of the Treatment Visit.
13. Severe or significant hypoalbuminemia (albumin <2.5 g/dL, and/or pre-albumin <5 mg/dL), or hypoproteinemia (protein <6 g/dL).
14. Moderate to severe anemia (Hgb <7 g/dL).
15. Severely uncontrolled diabetes mellitus (defined as HA1C >12%).
16. Subject report of concurrent participation in another clinical trial that involves an investigational drug or device that would interfere with this study.
17. Subject report of previous participation in other interventional wound healing clinical investigation within 60 days prior to the Screening Visit.
18. The subject has any physical or psychiatric condition that in the Investigator's opinion would warrant exclusion from the study or prevent the subject from completing the study.

4.3 STRATEGIES FOR RECRUITMENT

Eligible subjects will be recruited and enrolled from the in-patient facility or from consult referrals to Wells Surgical Services, LLC, under the responsibility of the Principal Investigator.

4.4 PARTICIPANT WITHDRAWAL OR TERMINATION

4.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

A subject may be discontinued from the study at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of *possible* reasons for study treatment discontinuation:

- Screen Failure
- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse Event that in the opinion of the Investigator would be in the best interest of the subject to discontinue study participation
- Protocol violation requiring discontinuation
- Lost to follow-up
- Sponsor request for early termination of study

- Subject death

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and the Case Report Form (CRF).
If a subject is withdrawn from treatment due to an AE, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

The Investigator must make every effort to contact subjects who are lost to follow-up. Three (3) attempted telephone contacts should be documented by key research personnel in order to consider the participant lost to follow-up. Furthermore, a certified letter will be mailed to the participant's address. If the participant does not respond, the certified letter receipt should be filed in the individual's research record with a copy of the letter sent. Attempts to contact such subjects must be documented in the patients' records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, etc.).

4.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Although subjects may withdraw from the study at any time and for any reason, (or may be withdrawn at the Investigator's discretion), subject withdrawal should be avoided as much as reasonably possible. In any case, appropriate follow-up for endpoints should be continued.

Subjects who prematurely discontinue are not to be replaced. For subjects considered lost to follow-up, the CRF must be completed up to the last visit performed.

4.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

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

5 STUDY DEVICE

5.1 STUDY DEVICE DESCRIPTION

5.1.1 DEVICE DESCRIPTION

MicroMatrix®
MicroMatrix® is composed of a porcine-derived extracellular matrix known as urinary bladder matrix and is intended for the management of topical wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds. The device is intended for one-time use.

The devices are supplied in a particle form in masses up to 1000mg, and packaged in a glass vial and a peel-open pouch.

Refer to Instructions for Use for further details.

Cytal™ Burn Matrix 2-Layer
Cytal™ Burn Matrix 2-Layer is composed of a porcine-derived extracellular matrix also known as urinary bladder matrix. The device is intended for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence),

trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds. The device is intended for one time use.

The devices are supplied in a fenestrated sheet configuration in sizes up to 10 cm x 15 cm and packaged in double peel-open pouches.

Refer to Instructions for Use for further details.

Negative Pressure Wound Therapy
KCI, Inc.
The V.A.C.Via™ Negative Pressure Wound Therapy System is an integrated wound management system for use in acute, extended and home care settings. It is intended to create an environment that promotes wound healing by secondary or tertiary (delayed primary) intention by preparing the wound bed for closure, reducing edema, promoting granulation tissue formation and perfusion, and by removing exudates and infectious material. It is indicated for patients with chronic, acute, traumatic, subacute and dehisced wounds, partial-thickness burns, ulcers (such as diabetic, pressure or venous insufficiency), flaps and grafts.

GenaDyne, Inc.
Genadyne A4 Wound Vacuum System is indicated for patients who would benefit from a suction device, particularly as the device may promote wound healing by the removal of excess exudates, infectious material and tissue debris.

A4-XLR8 Foam Dressing is appropriate for use on the following wounds:

- Pressure ulcers
- Diabetic/Neuropathic ulcers
- Venous insufficiency ulcers
- Traumatic wounds
- Post-operative and dehisced surgical wounds
- Skin flap and grafts

Products used by the treating Investigator which are part of his/her SOC will be used as per manufacturer specific approved recommendations.

5.1.2 ACQUISITION AND ACCOUNTABILITY

The Sponsor (or designee) will ship MicroMatrix® (only) to the investigational site. The initial study product shipment will be shipped after site activation (i.e., when all required regulatory documentation has been received by the Sponsor and a contract has been

executed). Subsequent study product shipments will be made after the site requests for resupply.

Upon receipt of the MicroMatrix®, an inventory check must be performed against the device receipt log, filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The Investigator must notify the study Sponsor of any damaged or unusable study devices that were supplied to the Investigator's site.

Regular study device reconciliation will be performed to document device assigned and used. This reconciliation will be logged on the Device Accountability Log and Device Dispensing Log, each signed and dated by the PI.

5.1.3 STUDY DEVICE STORAGE

MicroMatrix® and Cytal™ Burn Matrix 2-Layer should be stored at room temperature in a clean, dry environment, in the unopened and undamaged package. The products should be protected from freezing temperatures, excessive heat, and high humidity.

5.1.4 RETURN OR DESTRUCTION OF STUDY DEVICE

All unused MicroMatrix® will be retrieved by the Sponsor. A detailed Device Accountability Log and a Storage Attestation Form of the returned study product(s) will be provided to the Sponsor at the end of the study.

5.2 POTENTIAL RISKS AND BENEFITS

5.2.1 POTENTIAL RISK AND PRODUCT WARNINGS

MicroMatrix® and Cytal™ Burn Matrix 2-Layer
Complications and reactions are possible with any soft tissue repair, including but not limited to:

- Infection
- Increased chronic inflammation

- Allergic reaction
- Unexplained fever or chills
- Excessive redness, pain or swelling
- Odor associated with the use of products during the healing phase
- Excessive drainage from the wound

Warnings for MicroMatrix®

- If active infection is present, treat patient to resolve infection prior to device implantation.
- Do not re-use or re-sterilize; can damage the device and lead to device failure and/or patient injury.
- Do not use after printed expiration date.
- Do not use if package is compromised, which may indicate loss of device sterility.
- Do not use device if cracked, broken or otherwise damaged.

Warnings for Cytal™ Burn Matrix 2-Layer

- Do not use if cracked, broken, or otherwise damaged.

Precautions for Cytal™ Burn Matrix 2-Layer

- Do not re-use or re-sterilize.
- Do not use after printed expiration date.
- Do not use device if package seal has been broken.
- Exposure to a contaminated or infected field can lead to rapid breakdown of device.
- If an active infection is present, treat.

Negative Pressure Wound Therapy
NPWT is contraindicated on the following situations:

- Exposed organs, blood vessels, vascular grafts, or unexplored enteric fistulas
- Active, untreated infection
- Necrotic tissue
- Malignancy tissue (within the wound)
- Fragile skin
- Active hemorrhage / coagulopathy / anticoagulation
- Adhesive allergy

Bleeding is the most common significant complication associated with NPWT. Minor hemorrhage from granulation tissue during dressing changes is common and easily

controlled using direct pressure. Severe hemorrhage may occur in patients who are anticoagulated or in patients with exposed blood vessels or grafts. Infection is most commonly due to inadequate debridement and control of the initial wound infection.

5.2.2 POTENTIAL BENEFITS

This study may not directly benefit participants but may provide information that will benefit future patients that develop pressure injuries.

MicroMatrix®
MicroMatrix® is constructed of a naturally-occurring biomaterial designed to manage wounds. The devices can be applied dried or hydrated prior to placement by adding room temperature sterile saline. The biomaterial is a resorbable extracellular matrix scaffold containing epithelial basement membrane which allows for tissue ingrowth and integration by the surrounding host tissue to facilitate wound healing by the body.

Cytal™ Burn Matrix 2-Layer
Cytal™ Burn Matrix 2-Layer is constructed of a naturally-occurring biomaterial designed to manage wounds. The devices may be cut to size and must be hydrated prior to placement by immersion in room temperature sterile saline. The biomaterial is a resorbable extracellular matrix scaffold containing basement membrane which facilitates constructive remodeling of host tissue by integration.

Negative Pressure Wound Therapy
NPWT is designed to potentially promote wound healing by applying a vacuum to a wound using a sealed dressing over the area being treated. The vacuum can draw fluid from the wound and may increase blood flow to the area. The vacuum may be applied continuously or intermittently, depending on the wound being treated and the judgement of the clinician treating the wound.

6 STUDY PROCEDURES AND SCHEDULE

6.1 STUDY PROCEDURES/EVALUATIONS

6.1.1 STUDY SCHEDULE

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix I. All Follow-Up Visits will occur relative to the Treatment Visit, as outlined below:

Screening Visit – between Study Days -5 – 0
Treatment Visit – Study Day 1
Follow-Up Visit 1 – between Study Days 2 – 7
Follow-Up Visit 2 – between Study Days 8 – 14
Follow-Up Visit 3 – between Study Days 15 – 21
Follow-Up Visit 4 – between Study Days 22 – 28
Follow-Up Visit 5 – between Study Days 29 – 35
Follow-Up Visit 6 – between Study Days 36 – 42
Follow-Up Visit 7 – between Study Days 43 – 49
Follow-Up Visit 8 – between Study Days 50 – 56
Follow-Up Visit 9 – between Study Days 57 – 63
Follow-Up Visit 10 – between Study Days 64 – 70
Follow-Up Visit 11 – between Study Days 71 – 77
Follow-Up Visit 12 – between Study Days 78 – 84
Follow-Up Visit 13 – between Study Days 85 – 91

6.1.2 SCREENING VISIT (STUDY DAY -5 TO 0)

The Screening Visit will occur up to 5 days prior to the Treatment Visit.

1. Obtain informed consent from the potential subject, or legally authorized representative.
2. Assign subject identification number (SID). SIDs will be assigned in consecutive order and not be re-used in the case of Screen Failures.
3. Collect demographic data including: date of birth, gender, race, ethnicity, employment status and ambulatory status (bed, wheelchair, independent [with or without assistance]).
4. Document weight, height, and BMI.
5. Review alcohol and tobacco use.
6. Review and record medical history, surgical history, and medication history to determine eligibility based on inclusion/exclusion criteria.
7. Record presence of medications associated with the pressure ulcer(s) for pain (narcotic, steroidal, non-steroidal, and opioids), antibiotics, nutritional supplements and anti-hypertensives. Indicate type, dose, frequency, duration, and indication for each medication).

8. Administer SF-20 Health Survey, Visual Pain Scale (VPS), and Katz Index of Independence in Activities of Daily Living (Katz ADL).
9. Perform physical examinations needed to determine eligibility based on inclusion/exclusion criteria.
10. Record the following information for all pressure ulcers present:
    - Classification
    - Anatomic location
    - Initial measurements of length, width, and depth in centimeters, and surface area
11. Collect blood sample(s) for pre-albumin, albumin, protein, and hemoglobin (only if these results are not documented in the subject's medical chart within 30 days of the Screening Visit).). HA1C levels will be drawn on known diabetics only (if this result is not documented in the subject's medical chart within 30 days of the Screening Visit). HA1C levels are not required for non-diabetic.

6.1.3 TREATMENT VISIT (DAY 1)

After all inclusion/exclusion criteria have met, the patient becomes eligible for randomization. Randomization assignment may be obtained from ACell any time after eligibility is verified and prior to device application.

1. Verify inclusion/exclusion criteria continue to meet.
2. Perform physical examination.
3. Perform urinary pregnancy test for women of childbearing potential.
4. Record changes to medications associated with the pressure ulcer(s) for pain (narcotic, steroidal, non-steroidal, and opioids), antibiotics, and anti-hypertensives. Indicate type, dose, frequency, duration for each medication).
5. Record the following information for all pressure ulcers present:
    a. Confirmation of length, width, and depth in centimeters
    b. Wound appearance and characteristics:
        i. Presence of epibole, eschar, undermining, tunneling, sinus tracts, adverse odor, and/or suspected infection.
        ii. Appearance of Exudate: Serous; Serosanguinous; Purulent; Bloody
        iii. Appearance of Wound Bed: Beefy Red; Red; Pink; White; Yellow
        iv. Categorize the pressure ulcer(s) with respect to surface area (length x width), exudate amount, and type of wound tissue using the PUSH Tool.
        v. Document volume of the wound(s) (length x width x depth).
6. Obtain photographs of the eligible wound(s) post debridement and prior to device application.

7. Treat eligible wound(s) based on randomization assignment to Group 1, Group 2, or Group 3.

    a. **Group 1 Procedures (ACell products)**
        i. Debride the eligible pressure ulcer(s). Wash the wound(s) and confirm hemostasis achieved.
        ii. Apply a thin contiguous layer of MicroMatrix® between the wound margins, covering the entire wound bed, to include any tunneling, sinus tracts, and/or undermining areas.
        iii. Place up to three (3) appropriately sized Cytal™ Burn Matrix 2-Layer sheets (previously hydrated in sterile saline, per the manufacturer's Instructions for Use) over the MicroMatrix®. The hydrated sheet should be cut to fit the interior of the wound (including any tunneling, sinus tracts, and/or undermining areas).
        iv. Cover the Cytal™ Burn Matrix 2-Layer sheet(s) with Mepitel® and secure the Mepitel® to the wound edges with staples.
        v. Apply Surgilube® to the Mepitel®, then cover with ABD and tape, or ABD Kerlix and Coban if on extremity.

    b. **Group 2 Procedures (ACell products and NPWT)**
        i. Debride the eligible pressure ulcer(s). Wash the wound(s) and confirm hemostasis achieved.
        i. Apply a thin contiguous layer of MicroMatrix® between the wound margins, covering the entire wound bed, to include any tunneling, sinus tracts, and/or undermining areas. The distribution of the initial powder application should be approximately 3.5-5 mg/cm^2 on the area to be covered.
        i. Place up to three (3) appropriately sized Cytal™ Burn Matrix 2-Layer sheet (previously hydrated in sterile saline per the manufacturer's Instructions for Use) over the MicroMatrix®. The hydrated sheet(s) should be cut to fit the interior of the wound (including any tunneling, sinus tracts, and/or undermining areas), with no overlap onto healthy skin. The trimmed pieces may be placed in the interior of the wound bed.
        ii. Cover the Cytal™ Burn Matrix 2-Layer sheet with Mepitel® wound contact layer and surgically staple the edges of the Mepitel®.
        iii. Apply Surgilube®, cover with GranuFoam™, and apply NPWT therapy to the treated wound(s) according to manufacturer's Instructions for Use. When NPWT is used in conjunction with

MicroMatrix® and Cytal™ Burn Matrix 2-Layer, vacuum should be applied at 100mg Hg, low intensity, and continuous therapy.

c. **Group 3 Procedures (NPWT)**
   i. Debride the eligible pressure ulcer(s). Wash the wound(s) and confirm hemostasis achieved.
   ii. Apply AQUACEL® AG, then a layer of Mepitel® wound contact sheet to the wound bed.
   iii. Cover the wound(s) with GranuFoam™, gauze dressing, and tape.
   iv. Apply NPWT to treated wound(s) according to manufacturer's Instructions for Use. When NPWT is used as the primary wound treatment, vacuum should be applied at 125mg Hg, low intensity, and continuous therapy.

8. Record wound-related, post-treatment adverse events as reported by subject or observed by Investigator.
9. Record the approximate amount of hands-on time spent on wound care (skin to skin time).
10. Provide instructions to nursing staff and/or subject regarding maintenance of protein levels at 80-100 grams/day using supplements per Investigator's choice (Ensure, Glucerna, Protein Powder, etc.).
11. Provide instructions to nursing staff and/or family member(s) regarding off-loading.
12. Confirm date of next visit with subject.

6.1.4 FOLLOW-UP VISITS 1 – 13

1. Record weight, if possible.
2. Record any changes to employment and ambulatory status.
3. Provide instructions to nursing staff and/or family member(s) regarding off-loading.
4. Record changes to pain medication associated with pressure ulcer(s) pain and update Medications Log. Also include protein supplement, antibiotics and anti-hypertensive medications documentation.
5. Administer SF-20 Health Survey, VPS, and Katz ADL prior to device application.
6. Perform a physical examination. (Follow-Up Visits 1, 5, and 13 only).
7. Record wound-related, post-treatment AEs as reported by participant or observed by Investigator.
8. Collect blood sample(s) on the following days:
   a. Albumin: Visit 3 and Visit 5

b. Pre-albumin: Visit 3, Visit 5, Visit 7, Visit 9, Visit 11, and Visit 13
c. Hemoglobin: PRN (only if a delay in healing [suspected infection] is noted by the Investigator)

9. Record the following information for each eligible wound:
    a. Length, width, and depth.
    b. Wound appearance and characteristics:
        i. Presence of epibole, eschar, undermining, tunneling, sinus tracts, and/or adverse odor
        ii. Appearance of Exudate: Serous; Serosanguinous; Purulent; Bloody
        iii. Appearance of Wound Bed: Beefy Red; Red; Pink; White; Yellow
        iv. Epithelialization: As calculated by change in surface area and volume of wound size.
        v. Categorize the pressure ulcer(s) with respect to surface area (length x width), exudate amount, and type of wound tissue using the PUSH Tool.
        vi. Document volume of the wound(s) (length x width x depth).

10. Record change in wound area and volume from the Screening Visit.
11. For lower extremity ulcers: record ABI value only if a delay in healing is noted by the Investigator.
12. Obtain photographs of the eligible wound(s), if possible.
13. Proceed with treatment procedures as outlined below, as needed, depending on randomization of the wound(s).

    a. **Group 1 Procedures (ACell products)**
        i. Do not disturb the Cytal™ Burn Matrix 2-Layer/MicroMatrix® or the Mepitel® wound covering, which is stapled to the perimeter of the wound.
        ii. Apply a new layer of Surgilube® on top of the Mepitel® sheet.
        iii. Replace gauze dressing and tape.
        iv. Record the approximate amount of hands-on time spent on wound care.

    b. **Group 2 Procedures (ACell products and NPWT)**
        i. Disconnect the NPWT system.
        ii. Remove the following material and/or any other dressing layers that are covering the wound: tape, gauze dressing, GranuFoam™, and Surgilube® layers.
        iii. Do not disturb the Cytal™/MicroMatrix® or the Mepitel® wound covering which is stapled to the perimeter of the wound.

iv. Clean wound bed and debride with curette, as needed.
v. Apply Tegaderm™ over GranuFoam™ and replace gauze dressing, tape, and NPWT system per manufacturer's Instructions for Use.
vi. When NPWT is used in conjunction with MicroMatrix® and Cytal™ Burn Matrix 2-Layer, vacuum should be applied at 100mg Hg, low intensity, and continuous therapy.
vii. Record the approximate amount of hands-on time spent on wound care.

c. **Group 3 Procedures (NPWT)**
   i. Disconnect the NPWT system.
   ii. Remove the following material and/or any other dressing layers that are covering the wound: tape, gauze dressing, GranuFoam™, Mepitel®, and AQUACEL® AG layers.
   iii. Clean wound bed and debride with curette as needed.
   iv. Replace the AQUACEL® AG layer, and cover with Mepitel®, GranuFoam™, and then Tegaderm™ to the periwound skin and bridge.
   v. Replace NPWT system per Manufacturer's Instructions for Use. When NPWT is used as the primary wound treatment, vacuum should be applied at 125mg Hg, low intensity and continuous therapy.
   vi. Record the approximate amount of hands-on time spent on wound care.

d. **For Groups 2 and 3 only:** If periwound maceration is observed, and the Investigator determines NPWT should not be continued, then the following procedures will be followed:

   i. **Group 2 Procedures (ACell products and NPWT)**
      1. Do not disturb the Cytal™ Burn Matrix 2-Layer/MicroMatrix® or the Mepitel® wound covering which is stapled to the perimeter of the wound.
      2. Apply Surgilube® and cover with gauze dressing and tape, or gauze dressing and medical bandage material as appropriate (the latter only if the wound is on the extremity).
      3. Record the approximate amount of hands-on time spent on wound care

4. Record the length of time the NPWT is disrupted. This time should be ≤ 1 week.

ii. **Group 3 Procedures (NPWT)**

1. Remove the NPWT system.
2. Remove the following material and/or any other dressing layers covering the wound: tape, gauze dressing, GranuFoam™, Mepitel®, and AQUACEL® AG layers.
3. Clean wound bed and debride with curette as needed.
4. Reapply AQUACEL® AG.
5. Cover the wound(s) with gauze dressing and tape, or gauze dressing and medical bandage material, as appropriate (the latter only if the wound is on the extremity).
6. Record the approximate amount of hands-on time spent on wound care.
7. Record the length of time the NPWT is discontinued. This time should be ≤ 1 week.

13. Confirm date of next visit with patient.
14. For Visit 13 only:
    a. **If complete wound healing is not observed by Visit 13:** The Investigator will determine and record the appropriate treatment method of the pressure ulcer(s) for the months preceding the Final Study Visit. Subjects will be evaluated at the Final Study Visit for wound progression.
    b. **If complete wound healing is observed by, or prior to, Visit 13:** Subjects will be evaluated for pressure injury recurrence at approximately 6 months from their initial Treatment Visit.

6.1.6 FINAL STUDY VISIT [± 2 WEEKS])

The Final Study Visit will occur approximately 24 weeks after the Treatment Visit .

The following procedures will be completed for all subjects:

1. Record weight (if possible) and BMI.
2. Record any changes to employment and ambulatory status.
3. Record changes to pain medication associated with pressure ulcer(s) pain and update Medications Log. Also include changes protein supplement documentation, antibiotics, and anti-hypertensive medications.
4. Administer SF-20 Health Survey, VPS, and Katz ADL.
5. Perform a physical examination.

6. Record wound-related AEs as reported by participant or observed by Investigator.
7. Collect blood sample(s) for pre-albumin, albumin, protein, and hemoglobin levels.
8. All efforts will be made to collect the total direct and indirect pressure ulcer related costs by subject, as measured by total inpatient and outpatient expenses, stratified by product and care cost.

For those subjects who <u>did not</u> achieve complete wound healing by Visit 13, the following procedures will be done for evaluation of wound progression:

1. Provide instructions to nursing staff and/or family member(s) regarding off-loading.
2. For lower extremity ulcers: record ABI value only if a delay in healing is noted by the Investigator.
3. Evaluate the pressure ulcer(s) which had not healed by Visit 13 using the PUSH tool.
4. Record the following information for the wound(s) which had not healed by Visit 13:
    a. Wound appearance and characteristics:
        i. Presence of epibole, eschar, undermining, tunneling, sinus tracts, and/or adverse odor
        ii. Appearance of Exudate: Serous; Serosanguinous; Purulent; Bloody
        iii. Appearance of Wound Bed: Beefy Red; Red; Pink; White; Yellow
        iv. Epithelialization: As calculated by change in surface area and volume of wound size.
    b. Length, width, and depth
    c. Change in wound area and volume from the Screening Visit
5. Obtain photographs of the eligible wound(s), if possible.

For subjects in whom <u>there was</u> complete wound healing by or prior to Visit 13, the following procedures will be completed:

1. Record if there has been a recurrence at the original anatomical location of the pressure ulcer(s). If recurrence is noted:
    a. Obtain photographs of the wound(s) if recurrence is noted
    b. For lower extremity wound(s): record ABI value

6.1.7 UNSCHEDULED VISIT

Unscheduled visits may occur at any time between the Treatment Visit and Follow-up Visit 13. Reasons for an Unscheduled Visit include, but are not limited to: pressure injury events, assessment and/or maintenance of adverse events, etc.

1. Document reason for the unscheduled visit.
2. Record weight, if possible.
3. Record any changes to employment and ambulatory status.
4. Record changes to pain medication associated with pressure ulcer(s) pain and update Medications Log.
5. Perform a physical examination.
6. Record wound-related AEs as reported by participant or observed by Investigator.
7. As applicable :
    a. Record if there has been a recurrence at the original anatomic location of the pressure ulcer(s).
    b. Evaluate the pressure ulcer(s) using the PUSH tool.
    c. Record the following information for the wound(s):
        i. Wound appearance and characteristics:
            1. Presence of epibole, eschar, undermining, tunneling, sinus tracts, and/or adverse odor
            2. Appearance of Exudate: Serous; Serosanguinous; Purulent; Bloody
            3. Appearance of Wound Bed: Beefy Red; Red; Pink; White; Yellow
            4. Epithelialization: < 25%; 25%-50%; >50%-75%; 75%-99%; Complete Epithelialization
        ii. Length, width, and depth
        iii. Change in wound area and volume from the Screening Visit
8. For lower extremity ulcers: record ABI value only if a delay in healing is noted by the Investigator.
9. Obtain photographs of the eligible wound(s), if possible.
10. Record treatment method of the wound(s).

7 ASSESSMENT OF SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

7.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse Event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Adverse events of interest under this protocol are those to be considered related to the occurrence or presence of Stage 3 or 4 pressure ulcers. They include but are not limited to:

- Infection
- Increased chronic inflammation
- Allergic reaction
- Unexplained fever or chills
- Excessive redness
- Pain – excessive or exacerbated
- Swelling - excessive or exacerbated
- Odor associated with the use of products during the healing phase
- Odor from the wound bed
- Puss drainage from the treated wound
- Bleeding
- Hematoma
- Seroma
- Skin ulcers – newly developed or worsening
- Necrotic tissue
- Wound dehiscence
- Osteomyelitis
- Cellulitis
- Periwound maceration
- Death
- Malnutrition (as defined by hypoalbuminemia on follow-up serum lab work [serum albumin < 2.5g/dL and/or serum pre-albumin < 5mg/dL])
- Uncontrolled hyperglycemia (PI determination)
- Wound recurrence (after closure)
- Hypergranulation of treated wound(s)

7.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical

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

7.1.3 DEFINITION OF UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.2 CLASSIFICATION OF AN ADVERSE EVENT

7.2.1 SEVERITY OF EVENT

The Investigator will be asked to assess the severity of the AE using the following categories:

Mild: Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely: The relationship of the AE and the study device or the study procedure

can definitely be established.

Probably: While a clear relationship to the study device or to the study procedure cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.

Possibly: There is no clear relationship between the AE and the study device or study procedure; however, one cannot definitely conclude that there is no relationship.

Unrelated: There is no relationship between the AE and the study device or study procedure. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced.

7.2.3 EXPECTEDNESS

The Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study products.

7.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits or upon review by a study monitor. All AEs (per Investigator discretion) that are possibly impactful to the development or healing of a pressure injury and those including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study products (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UADEs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.4 REPORTING PROCEDURES

7.4.1 ADVERSE EVENT REPORTING

Adverse Events will be documented on the appropriate Case Report Form (CRF) as the Investigator learns of the event. All AEs, not serious in nature, will be reviewed by the Sponsor during scheduled Interim Monitoring Visits (IMVs). The Investigator will follow all AEs until adequate resolution is achieved. The IRB should be notified of all AEs according to their notification policies.

7.4.2 SAE REPORTING

In the case of a SAE, the Investigator must immediately notify (within 1 working day) the study Sponsor (contact information is provided in **Section 1, Key Roles).** The IRB must also be notified according to their notification policies.

7.4.3 UADE REPORTING

The study Investigator must immediately notify the study Sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. The study Sponsor contact information is provided in **Section 1, Key Roles**. The study Sponsor is responsible for conducting an evaluation of an UADE and shall report the results of such evaluation to the reviewing IRB and the Investigator within 10 working days after the Sponsor first receives notice of the effect.

7.4.4 REPORTING OF PREGNANCY

If a female patient becomes pregnant during the trial, she must be followed until the outcome of the pregnancy is known.

8 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with Good Clinical Practice (GCP), and with applicable regulatory requirement(s).

A Clinical Monitoring Plan will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL AND ANALYTICAL PLANS

All statistical tests will be conducted using a type 1 error rate of 5%. The analyses will be conducted using a hierarchical testing strategy; provided the primary analysis is significant in favor of the study product, the analysis of the secondary endpoints can be conducted in sequential order using a type 1 error rate of 5%. The testing will continue, provided the prior analysis was significant in favor of the study product.

9.2 STATISTICAL HYPOTHESES

The hypothesis for the primary endpoint (Group 1 vs. Group 3) is as follows:

1. Ho: π (incidence of complete wound closure in Group 1) > π (incidence of complete wound closure in Group 3)
2. Ha: π (incidence of complete wound closure in Group 1) $\leq$ π (incidence of complete wound closure in Group 3)

The hypothesis for the primary endpoint (Group 2 vs. Group 3) is as follows:

1. Ho: π (incidence of complete wound closure in Group 2) > π (incidence of complete wound closure in Group 3)

2. Ha: π (incidence of complete wound closure in Group 2) ≤ π (incidence of complete wound closure in Group 3)

The hypotheses for the secondary endpoints to be run separately for comparisons of Group 1 to Group 3 and Group2 to Group 3 are as follows:

1. Ho: μ (time to complete closure for wounds treated with the test product) < μ (time to complete closure for wounds treated with the control treatment)
2. Ha: μ (time to complete closure for wounds treated with the test product) ≥ μ (time to complete closure for wounds treated with the control treatment)
3. Ho: μ (change from baseline in the area of the wound treated with the test product) > μ (change from baseline in the area of the wound for wounds treated with the control treatment)
4. Ha: μ (change from baseline in the area of the wound treated with the test product) ≤ μ (change from baseline in the area of the wound for wounds treated with the control treatment)

The average measure of patient satisfaction and cost of treatment per patient are the second and third secondary endpoints; the mean values will be tabulated for each endpoint and compared between the treatment groups.

9.3 ANALYSIS DATASETS

The analysis datasets will be prepared in Statistical Analysis System (SAS) and will contain the patient level data. Specific flags will be derived for the intention to treat population and other populations of interest that will be defined in the Statistical Analysis Plan (SAP).

9.4 DESCRIPTION OF STATISTICAL METHODS

9.4.1 GENERAL APPROACH

This parallel design will randomize patients to 3 groups. The primary comparison will be Group 1 (MicroMatrix® with Cytal™ Burn Matrix 2-Layer) vs. Group 3 (NPWT) to determine if Group 1 is superior to Group 3. NPWT as the standard of care for patients with Stage 3 or 4 pressure injuries and is the active control arm for the study.

A secondary comparison will be conducted comparing Group 2 (MicroMatrix® with Cytal™ Burn Matrix 2-Layer plus NPWT) vs. Group 3 (NPWT) to determine if Group 2 is superior to Group 3.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The analysis of the primary endpoint will be based on a generalized linear model specifying the distribution as binomial. If a patient withdraws prior to the 12-week wound evaluation visit and the last recorded observation revealed complete wound closure, the patient will be counted in the primary analysis as having achieved complete wound closure. If a patient withdraws prior to the 12-week wound evaluation visit and the last recorded observation revealed the wound had not closed, the patient will be counted in the primary analysis as not having achieved complete wound closure.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The first secondary endpoint is the time of the initial observation of complete wound closure; the analysis will be predicated on a time-to-event model where the time of the initial observation of complete wound closure will be compared between the randomized treatment groups. If a patient withdraws prior to the target wounds being closed within 12 weeks, the patient will be censored using the time of the last observation. Stratification factors will be added to the model to adjust for the location of the wound, the duration of the wound under observation, and the relative size of the wound as a categorical variable. A Cox proportional hazards regression model will be used to derive the estimates.

The second secondary endpoint is the change from baseline in the area of the wound, reported in square centimeters. A 1-factor (time) repeated measures (time) analysis will be conducted using a generalized linear model. Stratification factors will be added to the model to adjust for the location of the wound, the duration of the wound under observation, and the relative size of the wound.

Patient satisfaction and data from the PUSH Tool will be assessed separately for each endpoint and wound. The results will be tabulated and compared in a 1-factor (treatment) repeated measures (treatment) analysis using a generalized linear model. Stratification factors will be added to the model to adjust for the location of the wound, the duration of the wound under observation, and the relative size of the wound.

Reduction in pain/narcotic cannot be analyzed by treatment given these medications act systemically. The change will be reported using the morphine equivalent units and descriptive statistics will be reported over time.

The cost of treatment per patient for all wounds, and the nursing time will be assessed. A 1-factor (time) repeated measures (time) analysis will be conducted using a generalized linear model. Stratification factors will be added to the model to adjust for the location of the wound, the duration of the wound under observation, and the relative size of the wound.

9.4.4 SAFETY ANALYSES

Safety will be assessed by physical examinations, clinical laboratory tests and collection of AEs as outlined in the Schedule of Events. All summaries of AEs will be based on treatment-emergent AEs and presented using the incidence and a tabulation of the number of events. The number and percentage of subjects experiencing AEs will be summarized by system organ class and description. Summaries by maximum severity and relationship to the study treatment will also be provided. SAEs and AEs leading to discontinuation from the study will be presented by system organ class and preferred term.

9.4.5 ADHERENCE AND RETENTION ANALYSES

The total duration for a subject on-study will be calculated as the difference between the date of initial exposure to the study treatment and the last day of observation plus 1 day. All calculations for defining the duration on-study will follow the algorithm DURATION = [STUDY COMPLETION OR WITHDRAW DATE – INITIAL STUDY TREATMENT DATE + 1].

9.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline demographic factors and patient characteristics will be summarized by randomized treatment group. This summary will include the gender, age in years at the time of entry into the study, race, ethnicity, height (inches), weight (pounds) and BMI. Age, height, weight, and BMI will be summarized using descriptive statistics. The number and percent of each gender, race, and ethnicity category will be presented using counts and percentages.

The medical and surgical history will be coded for each patient and summarized based on the body system description. The patients will be summarized using counts and percentages for those patients who had a pre-study medical history.

9.4.7 PLANNED INTERIM ANALYSES

Given the size of this clinical investigation, there will not be an interim analysis.

9.4.8 ADDITIONAL SUB-GROUP ANALYSES

Sub-groups of clinical interest will be defined in the SAP and are a function of the type of patients and their co-morbidities.

9.4.9 MULTIPLE COMPARISON/MULTIPLICITY

There will not be a correction to the type 1 error rate for the analyses because a hierarchical testing strategy will be used. If the results from the primary analysis are significant ($p<0.05$) in favor of the Group 1 over Group 3, and separately Group 2 over Group 3, a step-down procedure will be followed for the secondary endpoints. Each secondary endpoint will be tested in hierarchical order provided the previous endpoint tested is significant ($p<0.05$) in favor of the test product over control.

There is no crossover of treatment designed in this trial. Subjects who have a wound that has not healed by Visit 13 will be treated as medically appropriate, but considered to be a failure in the treatment arm they were randomized to.

9.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Patient profiles will be generated to facilitate an examination of the individual response data.

9.4.11 EXPLORATORY ANALYSES

Exploratory analyses will be described in SAP and will not be part of the hierarchical testing strategy.

9.5 SAMPLE SIZE

To estimate the sample size for this clinical investigation, the difference in the incidence of patients who achieve complete wound closure (primary endpoint) was used. Estimates were prepared considering complete closure in the NPWT arm of 20% to 40% and a type 1 and 2 error rate of 5% and 20%, respectively. Based on these estimates, if the incidence in Group 1 is 45% greater than the incidence in Group 3, the difference will be significant ($p<0.05$).

Number of Patients in Group 1	Number of Patients in Group 3	Minimum Incidence of Complete Closure in Group 1	Maximum Incidence of Complete Closure in Group 3
20	20	0.6729	0.2000
20	20	0.7324	0.2500
20	20	0.7787	0.3000
20	20	0.8167	0.3500
20	20	0.8512	0.4000

9.6 MEASURES TO MINIMIZE BIAS

The determination of complete closure and the wound measurements are quantitative and there will be photographs taken for substantiation.

9.6.1 ENROLLMENT/ RANDOMIZATION

A central randomization scheme will be prepared using a permuted block scheme to ensure balance after each block has been assigned. ACell will be responsible for maintaining the randomization schedule and issuing the randomization assignment to the requesting clinical site. A separate randomization plan will be prepared that will provide the details around the following 3 steps to randomizing a patient.

Step 1: The clinical site will consent the patient and complete the screening and enrollment evaluation, and information required for randomization. By completing the Request for Randomization form, the clinical site is making a declaration that the patient meets all of the inclusion criteria for the study and none of the exclusion criteria.

Step 2: The clinical site can either fax or scan and e-mail the completed Request for Randomization form to the designated individual at ACell (between normal business hours [M-F 8:30am – 5:30pm]) who will maintain the randomization log.

Step 3: ACell will review the Request for Randomization form and ensure all of the information is complete. If the form has been completed appropriately, ACell will deliver

the next sequential group assignment, then sign, date, and return the completed Request for Randomization form to the clinical site.

10 SOURCE DOCUMENTS AND CASE REPORT FORMS

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

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON ANY ORIGINAL DOCUMENTS.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a SID and initials.

Copies of the eCRF may be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

If a correction is required for an eCRF, the time and date stamp track the person entering or updating eCRF data and creates an electronic audit trail.

11 QUALITY CONTROL AND ASSURANCE

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol and GCP.

The site will provide direct access to all trial related materials, including source data/documents, electronic medical records (if applicable), CRFs, and reports for the purpose of monitoring and auditing by the Sponsor and/or the IRB.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 LAWS AND REGULATIONS

This clinical study will be conducted in compliance with all national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. The trial will be registered on www.clintrials.gov and on other sites, as appropriate.

12.3 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.4 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The Investigator will explain

the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants 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 consent document is revised due to changes in study procedures, subjects who were enrolled prior to the change, but are affected by the change, will be informed of the changes and will sign the amended consent document. If a consent document is revised due to changes in the risks or safety of the study, all active participants must sign the revised consent.

12.5 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating Investigator(s), their staff, the Sponsor and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, and/or representatives of the IRB may inspect all documents and records required to be maintained by the Investigator for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the local IRB and Institutional regulations.

13 DATA HANDLING AND RECORD KEEPING

13.1 STUDY RECORDS RETENTION

All study documents (patient files, signed informed consent forms, Study Regulatory Binder, etc.) must be kept secured for a period of two years following completion of the study. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

13.2 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

All protocol deviations/violations should be documented using the Protocol Deviations/Violations CRF and submitted to the IRB according to their reporting guidelines.

13.3 PUBLICATION AND DATA SHARING POLICY

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

14 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the device industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

15 LITERATURE REFERENCES

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APPENDIX I: SCHEDULE OF EVENTS

PROCEDURES FOR ALL SUBJECTS	SCREENING (-5 TO 0)	TREATMENT (DAY 1)	F/U VISIT 1 (DAY 2 – 7)	F/U VISITS 2-13 (WEEKLY)	FINAL VISIT (24 WEEKS)	UNSCHEDULED VISIT
Informed Consent	X					
Assign SID	X					
Patient Demographics / Social Hx	X					
Height, Weight, and BMI[1]	X		X	X	X	X (weight only)
Medical / Surgical / Medication Hx	X					
Inclusion / Exclusion Criteria	X	X				
Physical Examination	X	X	X	X	X	X
Laboratory Testing of Blood Sample[2]	X		X	X	X	
Employment and Ambulatory Status	X		X	X	X	X
Urine Pregnancy Test[3]		X				
Randomization		X				
SF-20 Health Survey, Visual Pain Scale, and Katz Activities of Daily Living[4]	X		X	X	X	
Photographs of Wound(s)		X	X (if possible)	X (if possible)	X (as applicable)	X (as applicable)
PUSH Tool		X	X	X	X (as applicable)	X (as applicable)
Medication Use[5]		X	X	X	X	X

AE Evaluation		X	X	X	X	X
Nursing Contact Time		X	X	X		X (as applicable)
Confirm Visit Schedule		X	X	X		
Cost of Tx Method / Length of stay in hospital and SNF, as applicable					X	
Wound Evaluation						
Classification	X	X				
Location	X	X				
Length, Width, and Depth	X	X	X	X	X (as applicable)	X (as applicable)
Surface Area / Volume		X	X	X	X	X
ABI Value (as applicable)			X	X	X	X
Wound Appearance / Characteristics		X	X	X	X (as applicable)	X (as applicable)
Change in Wound Area / Volume			X	X	X (as applicable)	X (as applicable)

[1] Height recorded at Screening Visit only. BMI recorded at Screening and Final Study Visits only.
[2]All labs collected at Screening and Final Study Visit. Albumin collected at Visit 3 and Visit 5. Pre-albumin collected at Visit 3, Visit 5, Visit 7, Visit 9, Visit 11, and Visit 13. Hemoglobin collected as required at F/U Visits.
[3] Childbearing females only[4]Questionnaires to be completed at Screening, Follow-Up Visits 1, 5, 13, and Final Study Visit only
[5] Medications to be captured are: Pain medications, antibiotics, anti-hypertensives, and nutritional protein supplement

APPENDIX II: STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812.

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signature of Principal Investigator	**Date (mm/dd/yy)**
Printed Name	
Name of Institution	