A Six Month Randomized Open-Label Trial of Pressure Ulcer Healing with Microcyn® Skin and Wound Care with Preservatives Versus Sterile Saline in Adult Spinal Cord Injury Subjects

Study Protocol and Statistical Analysis Plan

NCT02001558

July 31, 2018

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STUDY TITLE MIC-UABWC-001 (Protocol Revision 1)

A Six Month Randomized Open-Label Trial of Pressure Ulcer Healing with Microcyn® Skin and Wound Care with Preservatives Versus Sterile Saline in Adult Spinal Cord Injury Subjects

SPONSOR:

Oculus Innovative Sciences, Inc.
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Petaluma, CA 94954
Tel.: 650-269-6287
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DATE OF DRAFT: June 8, 2012

SIGNATURE PAGE

On behalf of Oculus Innovative Sciences, Inc., I confirm that this is the final version of the protocol that has been approved according to company operating procedures.

Clinical Operations Signature
Oculus Innovative Sciences, Inc.

(Printed Name) **Date**

Regulatory Affairs Signature
Oculus Innovative Sciences, Inc.

(Printed Name) **Date**

INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "A Six Month Randomized Open-Label Trial of Pressure Ulcer Healing with Microcyn® Skin and Wound Care with Preservatives Versus Sterile Saline in Adult Spinal Cord Injury Subjects" and,

I agree that the protocol contains the necessary information required to conduct the study. I also agree to conduct this study as outlined in and according to the obligations of Clinical Investigators and all other pertinent requirements in the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline.

I agree to obtain approval of the protocol and informed consent prior to the start of the study by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that is registered with the US Department of Health and Human Services (HHS).

I agree to obtain formal written informed consent in accordance with applicable federal and local regulations and international guidelines from all subjects prior to their entry into the study.

I have received and reviewed the Microcyn® Skin and Wound Care with Preservatives package insert, including the potential risks and side effects of the product, and instructions for use.

I agree to report to Oculus Innovative Sciences, Inc. adverse events that occur during the course of the study in accordance with the ICH GCP guideline and the protocol.

I agree to ensure that all associates, colleagues, and employees assisting me with the conduct of the study are informed of their responsibilities in meeting the above commitments and the commitments set forth in the Investigator's Agreement.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with the ICH GCP guideline, and federal and local requirements.

The Investigator, agreeing to the foregoing, hereby executes this agreement on the date as set forth below.

_____

Investigator Signature

_____ _____

Printed Name **Date**

_____

Address

_____ _____

Phone Number

PROTOCOL SYNOPSIS

Name of Sponsor/Company:	Oculus Innovative Sciences, Inc.
Name of Finished Product:	Microcyn® Skin and Wound Care with preservatives ("Microcyn")
Name of Active Ingredient:	N/A

Title of Study:
A Six Month Randomized Open-Label Trial of Pressure Ulcer Healing with Microcyn® Skin and Wound Care with Preservatives Versus Sterile Saline in Adult Spinal Cord Injury Subjects

Investigators:
Yuying Chen, M.D., PhD, Xiaohua Zhou, M.D.

Study Center:
University of Alabama at Birmingham, Spain Rehabilitation Center
Suite 190 - 1717 6th Ave South, Birmingham, AL 35294-6810

Number of Subjects Planned:
80 subjects

Publication (Reference):
N/A

Study Period:
Enrollment Period: Rolling enrollment to the earliest of 2 years or enrollment of 80 subjects
Treatment Period: Baseline (Week 0) to Final Evaluation (earlier of 6 months = Week 24 or complete wound closure)
Analysis Period: An interim analysis will be conducted when the greater of 20 patients or those enrolled in the two (2) weeks following enrollment of the first participant have completed the Week 12 visit. The full analysis is when all subjects have completed the Final Evaluation.

Phase of Development: Post-marketing

Objective:
A pressure ulcer (wound/sore) is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear and/or friction.
Primary objective: To compare percentage change in ulcer size in patients with at least one Stage III or Stage IV pressure ulcer in subjects treated with Microcyn versus sterile saline.
Secondary objectives: To compare healing progress using the National Pressure Ulcer Advisory Panel's Pressure Ulcer Scale for Healing (PUSH) score, Version 3.0, and other indicators of wound healing such as time to complete wound closure, elimination of signs of wound infection and to investigate the impact of treatment with Microcyn on subject health care resource utilization (wound-related).

Clinical Hypothesis:

Name of Sponsor/Company:	Oculus Innovative Sciences, Inc.
Name of Finished Product:	Microcyn® Skin and Wound Care with preservatives ("Microcyn")
Name of Active Ingredient:	N/A
Treatment of pressure ulcers with Microcyn results in faster healing and better overall outcomes than treatment with sterile saline in spinal cord injured adults.	
Design and Methodology: Design: Six month (24 week), randomized, open-label, comparative study of treatment of pressure ulcers using Microcyn versus sterile saline. Subjects: Adults with spinal cord injuries with at least one Stage III or Stage IV pressure ulcer who meet all eligibility criteria and who have given informed consent. Treatment: Microcyn or sterile saline liberally sprayed on wound and permitted to remain on wound which will then be dressed with gauze that is moistened with Microcyn or sterile saline and covered with dry gauze twice daily for the earlier of total wound closure or Week 24.	

Study Visits:

Overall: Assessments will be made at Week 0 (Baseline) with follow-up visits every 4 weeks thereafter, for a total of up to 7 study related assessments (Week 0 (Baseline), Weeks 4, 8, 12, 16, 20 and Week 24 (Final Evaluation)). Subjects will return to the clinic for all follow-up assessments.

Baseline: Initial demographics and a brief medical history will be collected at Baseline from subjects or via chart abstraction after informed consent and after meeting all inclusion/exclusion criteria. Data on the primary endpoint will be collected: pressure ulcer size (stage, length, width, and depth) via clinician measurement with photographic documentation. Secondary endpoints of infection status of the ulcer including signs/symptoms of infection, amount and type of exudates, color and type of tissue/character of the wound bed and health care resource utilization (wound-related) and adverse events will also be collected at Baseline. The wound surface area (length x width), amount of exudate and tissue type will be recorded using the PUSH Tool 3.0, and a PUSH baseline score will be calculated (PUSH score).

Follow-up visits: Information collected at each follow up visit will include information on the pressure ulcer size (length, width, depth via clinician measurement with photographic documentation), PUSH sub-scores and total score, time to complete closure of wound, infection status of the ulcer including signs/symptoms of infection, health care resource utilization (wound-related) and adverse events. If applicable, reason for early discontinuation will be recorded. Treatment-related adverse events will be collected at all follow-up visits.

Procedures	Baseline	Follow-Ups	Final Evaluation
Study procedures			
Informed Consent and Privacy Authorization	X		
Inclusion/Exclusion Criteria	X		
Demographics			
Age, Race, Gender, Education, Insurance Status (from chart)	X		
Marital, Employment, Insurance Status			
Medical History			
Height, Weight, Smoking/Tobacco Status	X		
Spinal Cord Injury Information (from chart)	X		
Type of Bladder Management	X		
Number of Concomitant Ulcers	X	X	X
Use of Antibiotics	X	X	X
Primary efficacy endpoint			
Ulcer Depth, Length, Width, Stage	X	X	X
Secondary endpoints			
Wound Infection Status	X	X	X
Amount and Type of Exudate	X	X	X
Color/Type of Tissue/Character of Wound Bed	X	X	X
PUSH Scores	X	X	X
Health Care Resource Utilization (Wound-Related)		X	X
Safety			
Reason for Early Discontinuation (if applicable)		X	
Adverse Events	X	X	X

Name of Sponsor/Company:	Oculus Innovative Sciences, Inc.
Name of Finished Product:	Microcyn® Skin and Wound Care with preservatives ("Microcyn")
Name of Active Ingredient:	N/A

Safety Evaluations:
Adverse Events (AEs) will be recorded at Baseline (pre- and post-application) and at each study visit.

Efficacy Evaluations:
Primary Endpoint: The primary endpoint is pressure ulcer size (length, width, depth via clinician measurement with photographic documentation). Secondary Endpoints: Secondary endpoints include healing progress, as measured through the NPUAP PUSH Tool, Version 3.0, time to complete wound closure, infection status of the ulcer including signs/symptoms of infection, amount and type of exudates, color and type of tissue/character of the wound bed, health care resource utilization (wound-related), and adverse events.

Diagnosis and Main Eligibility Criteria:
Inclusion Criteria:
- Written informed consent including authorization to release health information
- Male or female (non-pregnant/nursing) outpatients over the age of 18
- Spinal cord injured
- One or more Stage III or Stage IV pressure wound located anywhere on the body
- Willing and able to fulfill all obligations of the study, including attending all study visits and has the ability him/herself or via a caregiver to apply study product twice daily

Exclusion Criteria:
- Patient has any wound that at enrollment is scheduled for surgical closure within 14 days
- Use of any immunosuppressant medications (for example, cyclosporine, methylprednisolone, prednisone, methotrexate, alefacept, or infliximab) within 30 days of screening
- Is unable to fully comply with the study requirements; for example, if the wound is in a place that the patient cannot reach him/herself and as such requires a caregiver to apply the study product, if the patient does not have consistent twice daily access to a caregiver, this patient would be ineligible for the study
- Any condition or situation which, in the Investigator's opinion, puts the subject at significant risk, could confound the study results, or may interfere significantly with the subject's participation in the study
- Patient is medically unstable or has a life expectancy of less than 12 months
- Patient is pregnant
- Patient is a woman of child-bearing potential and does not consent to or receive a screening urine pregnancy test prior to study enrollment
- Current enrollment in an investigational drug or device study or participation in such a study within the last 30 days prior to Baseline (Week 0)

Name of Sponsor/Company:	Oculus Innovative Sciences, Inc.
Name of Finished Product:	Microcyn® Skin and Wound Care with preservatives ("Microcyn")
Name of Active Ingredient:	N/A

Test Article, Dose, and Mode of Administration:
Microcyn® Skin and Wound Care with preservatives, applied twice daily, topical administration

Statistical Analyses:

Efficacy Analyses:

Efficacy will be tested via T-tests of percent change in wound size using an intention to treat (ITT) approach as well as a per protocol analysis. Secondary analyses will include Kaplan-Meier analysis to estimate time to complete wound closure, and may include linear and logistical regression to estimate the impact of patient characteristics on study endpoints, with special emphasis on variables that affect healing times, such as diabetes and smoking status. The efficacy population will include all patients entered into the study.

Safety Analyses:

Safety analyses will be conducted via Fischer's exact tests, chi-square, and t-tests, as applicable. The safety population will include all subjects exposed to the any study product (Microcyn or saline) who have provided any post-treatment safety information.

Sample Size Justification:

The sample is a convenience sample of 80 patients.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
ASIA	American Spinal Cord Injury Association
CFR	Code of Federal Regulations
CTEP-	Cancer Therapy Evaluation Program – Common Terminology Criteria for
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HHS	Health and Human Services
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention To Treat
MedDRA	Medical Dictionary for Regulatory Activities
NPUAP	National Pressure Ulcer Advisory Panel
PUSH	Pressure Ulcer Scale for Healing
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SOP	Standard Operating Procedure
UPT	Urine Pregnancy Test
US	United States
WOCBP	Woman of Childbearing Potential

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1. INTRODUCTION AND BACKGROUND

A pressure ulcer (also called a wound or sore) is a localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear and/or friction. Pressure ulcers are staged into Stage I, II, III, IV and unstageable. The National Pressure Ulcer Advisory Panel (NPUAP) has published guidelines on the staging of ulcers for clinicians and patients to more consistently describe wounds. The full guidelines for staging are listed in Appendix A. The focus of the present study is Stage III and Stage IV ulcers, which are described in the NPUAP guidelines as:[1]

- A stage III ulcer exhibits full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present, but does not obscure the depth of tissue loss. May include undermining and tunneling.
- A Stage IV ulcer exhibits full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.

Several published guidelines on the treatment (and prevention) of pressure ulcers are available through the Agency for Healthcare Research and Quality (AHRQ) guideline repository.[2] Included in this repository are the 2010 Association for the Advancement of Wound Care, guidelines, which give the following recommendations for treatment:[3]

1. Remove/alleviate all causes of pressure ulcer damage
2. Debride, cleanse, and dress the wound
3. Implement advanced or adjuvant interventions if insufficient response seen
4. Surgical interventions if continued insufficient response
5. Documentation of response

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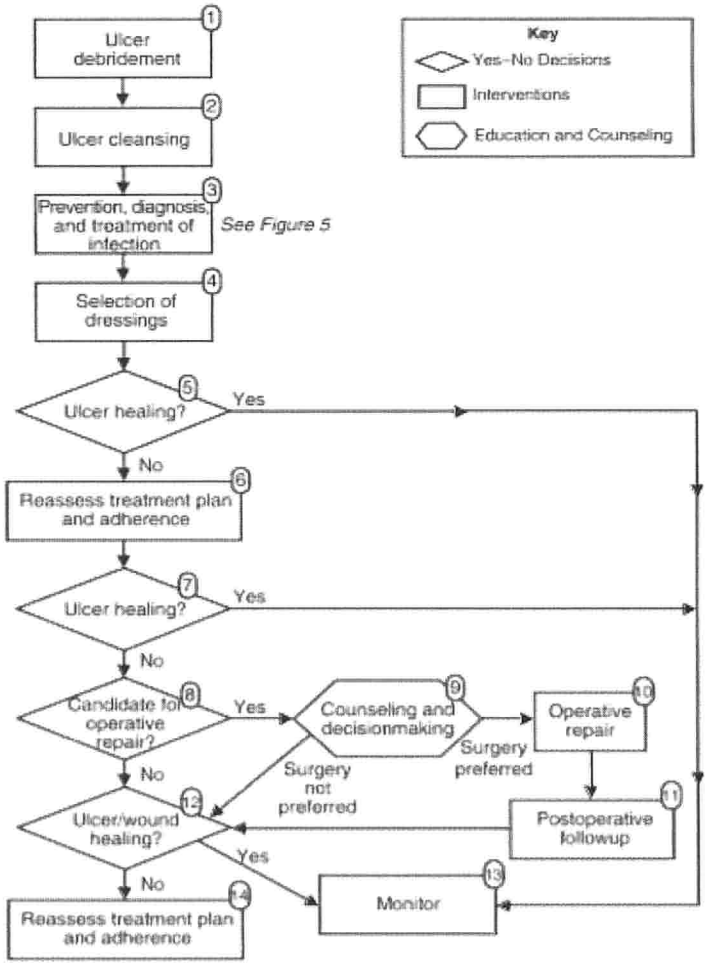
[1] NPUAP, 2007, available at http://www.npuap.org/.

[2] www.guidelines.gov

[3] Association for the Advancement of Wound Care (AAWC). Association for the Advancement of Wound Care Guideline of Pressure Ulcer Guidelines. Malvern (PA): Association for the Advancement of Wound Care (AAWC); 2010. 14 p

6. Palliative care if applicable

While dated, the 1994 Agency for Healthcare Policy Research (AHCPR, now known as AHRQ) guidelines present a heuristic for assessment and treatment of pressure ulcers that still holds today (Figure 1).



The numbers above represent "nodes" of care with nodes 1-4 representing the four basic components of an effective pressure ulcer care plan: (Node 1) necrotic tissue debridement; (Node 2) initial wound cleansing and repeated cleansing with each dressing change; (Node 3), prevention, diagnose and treatment of infection; and (Node 4), using a wet ulcer dressing that keeps surrounding tissue dry. Nodes 5-14 as shown above represent

assessment and reassessment of the healing strategy and its outcome(s) to ensure optimal healing.

Spinal cord injured patients are an especially vulnerable population for pressure ulcers because of both the immobility rendered by resultant paralysis and of impaired sensation. The National Spinal Cord Injury Statistical Center (NSCISC) estimates that between 231,000 and 311,000 Americans are living with a spinal cord injury (SCI), with approximately 12,000 new cases each year.[4] As a result of increased research and interest, remarkable progress has been made in improving the quality of life and life expectancy for SCI patients. Secondary complications, however, continue to challenge individuals living with SCI and their caregivers. Pressure ulcers, in particular, "remain the single most important medical complication in terms of loss of time in educational or vocational pursuits, increased hospital stay and resulting financial expenditures."[5] In patients with paraplegia, pressure ulcers are the leading cause of rehospitalization;[6] across injury levels, sepsis from pressure ulcers and genitourinary tract infections are the leading cause of death in Veterans with SCI.[7]

Recent cost estimates on treating pressure ulcers in SCI patients indicate a range of $2,000 to $70,000 per wound, with an annual aggregate cost of approximately $2.2 to $3.6 billion in the United States alone.[8] In a retrospective study reviewing medical records of veterans with spinal cord injury, it was found that over 50% of pressure ulcers did not fully heal over the three-year study period, with over 70% of Stage IV ulcers remaining unhealed despite surgeries and multiple hospitalizations.[9]

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[4] *Spinal Cord Injury Facts and Figures at a Glance*, National Spinal Cord Injury Statistical Center, Birmingham, Alabama, February 2010, https://www.nscisc.uab.edu.

[5] Jackson, AB., *Secondary Conditions of Spinal Cord Injury*, Spinal Cord Injury Network, http://www.spinalcord.uab.edu/show.asp?durki=32106.

[6] French, DD. et al., *Health Care Costs for Patients with Chronic Spinal Cord Injury in the Veterans Health Administration*, J SPINAL CORD MED., 2007; 30(5): 477-481.

[7] Garber, SL, *Pressure Ulcers in Veterans with Spinal Cord Injury: A Retrospective Study*, J REHAB RES & DEV., 2003; 40(5): 433-442.

[8] Gallagher, SM. *Raising Awareness of Pressure Ulcer Prevention and Treatment.*, ADV SKIN WOUND CARE 2006; 19:398-405.

[9] See Garber, *supra*.

Taken together with the fact that spinal cord injured persons are disproportionately younger males – 81% of new injuries are in males and the average age of injury is 40[10]– pressure ulcers and the resultant disability caused by them points to this population as an important subset of pressure ulcer patients.

1.1. STUDY RATIONALE

Microcyn is developed and manufactured by Oculus Innovative Sciences, Inc. (Oculus), headquartered in Petaluma, California. The Microcyn Technology platform enables the creation of biocompatible solutions containing active oxychlorine compounds, bioactive agents that have been shown to reduce microbial load. Several solutions derived from the shelf-stable Microcyn® Technology platform have demonstrated, in a variety of research and investigational studies, as well as in clinical practice, utility in managing wounds, including wounds infected with a wide range of pathogens (e.g., antibiotic-resistant strains of bacteria (including MRSA and VRE), viruses, fungi and spores). Microcyn products have been used on over 3 million patients in the United States, Europe, and Asia to manage a variety of chronic and acute wounds, including burns, diabetic foot ulcers, pressure ulcers, and other serious wounds without report of an adverse event. Microcyn Skin & Wound Care Solution was first cleared for marketing by the FDA on March 19, 2007 (510(k): K060113), and originally marketed as "Dermacyn." The technology behind the Microcyn portfolio of products involves a unique, patented electrochemical treatment of dilute saltwater through which a pH-neutral solution of hypochlorous acid, and its sodium salt, hypochlorite, is generated.

Hypochlorous acid is a natural product the human body produces to facilitate healing in response to injury. Solutions containing hypochlorous acid have a relatively long history of use in controlling pathogens that can lead to disease in humans and animals, particularly in ensuring food safety during processing. Adoption in wound care has been hampered by both the cytotoxicity of acidic solutions and the lack of stability of pH-neutral solutions. Unlike standard electrochemical processes where the unstable nature of hypochlorous acid solutions makes onsite generation with specialized equipment hypochlorous acid solutions

[10]National Spinal Cord Injury Statistical Center (NSCISC) 2011, available at http://www. fscip.org/facts.htm

makes onsite generation with specialized equipment necessary, Microcyn's stability permits consumers to access a consistent, manufacturer quality-controlled product in a variety of delivery methods (e.g., squeeze and spray bottles). This stability enables Oculus to manufacture Microcyn solution with a free available chlorine (FAC) level at or below 150 parts per million, thus maximizing both safety and shelf life.

1.2. DOSE RATIONALE

N/A

1.3. STUDY OBJECTIVE

The primary objective is to compare percentage change in wound size in patients with at least one Stage III or Stage IV pressure ulcer in subjects treated with Microcyn versus saline.

The secondary objective is to compare other indicators of wound healing such as time to complete wound closure, elimination of signs of wound infection and to investigate the impact of treatment with Microcyn on subject health care resource utilization (wound-related).

1.4. CLINICAL HYPOTHESES

Treatment of pressure ulcers with Microcyn results in faster healing and better overall outcomes than treatment with saline in adult spinal cord injured patients.

2. STUDY DESIGN

2.1. OVERALL DESIGN

2.1.1. STRUCTURE

This study is a randomized, open-label comparative study of Microcyn versus normal saline in the healing of Stage III and Stage IV pressure ulcers in subjects with spinal cord injuries.

2.1.2. DURATION

The study duration is up to 6 months (24 weeks) per subject with an enrollment period of up to two years to enroll a total of 80 subjects.

2.1.3. CONTROLS

Controls will be treated with normal saline.

2.1.4. DOSAGE/DOSE REGIMEN

Treatment with Microcyn or saline will consist as follows, twice daily: Microcyn or sterile saline to be liberally sprayed on wound and permitted to remain on wound, which will then be dressed with gauze moistened with Microcyn or sterile saline and covered with dry gauze twice daily for the earlier of complete wound closure or Week 24.

2.2. TEST ARTICLE

The test article is Microcyn® Skin and Wound Care with Preservatives.

2.3. STUDY POPULATION

The study population is adults, over the age of 18, with spinal cord injury who meet all inclusion/exclusion criteria and who give full informed consent.

2.4. ELIGIBILITY CRITERIA

2.4.1. INFORMED CONSENT AND AUTHORIZATION TO RELEASE HEALTH INFORMATION

Written informed consent will be obtained from all subjects before any study-related procedures (including any pre-treatment screening procedures) are performed. The Investigator may discuss the study and the possibility for entry with a potential subject

without first obtaining consent. However, a subject wishing to participate must give written informed consent prior to any study-related procedures being conducted, including those performed solely for the purpose of determining eligibility for study participation, including withdrawal from current medication (if required prior to study entry). The Investigator has both the ethical and legal responsibility to ensure that each subject being considered for inclusion in this study has been given a full explanation of the procedures and expectations for study participation.

The site-specific informed consent must be forwarded to Oculus for approval prior to submission to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that is registered with the US Department of Health and Human Services (HHS). Each subject will sign the consent form that has been approved by the same IRB/IEC that was responsible for protocol approval. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki[11] and will include the elements required by FDA regulations in 21 CFR Part 50,[12] as well as the elements required by the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline,[13] and applicable federal and local regulatory requirements. The consent form must also include a statement that Oculus, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history.

Once the appropriate essential information has been provided to the subject and fully explained by the Investigator (or a qualified designee) and it is felt that the subject understands the implications and risks of participating in the study, the IRB/IEC-approved consent document shall be signed and dated by both the subject and the person obtaining consent (Investigator or designee), and by any other parties required by the IRB/IEC or other regulatory authorities. The subject will be given a copy of the signed informed

[11] Declaration of Helsinki. World Medical Association. Available from: http://www.wma.net/e/ethicsunit/helsinki.htm.
[12] Title 21 Code of Federal Regulations (CFR) Part 312. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm.
[13] ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance; April 1996.

consent document with the original kept on file by the Investigator. All of the above activities must be completed before any study related procedures are

conducted (including any pre-treatment study procedures).

2.4.2. INCLUSION CRITERIA

All subjects must meet the following inclusion criteria to participate in the study:

1. Written informed consent including authorization to release health information
2. Male or female outpatients age over the age of 18
    a. If a woman of child bearing potential (WOCBP), not pregnant or nursing, and;
    b. If WOCBP, must consent to a screening urine pregnancy test and remain on a reliable birth control method for duration of study
3. Spinal cord injured
4. One or more Stage III or Stage IV pressure wound located anywhere on the body.
5. Willing and able to fulfill all obligations of the study, including attending all study visits
6. Has the ability himself or herself, or via reliable and regular access to a caregiver, to apply study product twice daily.

2.4.3. EXCLUSION CRITERIA

Subjects will not be enrolled if they meet any of the following exclusion criteria:

1. Patient has any wound that at enrollment is scheduled for surgical closure within 14 days;

2. Use of any immunosuppressant medications (for example, cyclosporine, methylprednisolone, prednisone, methotrexate, alefacept, or infliximab) within 30 days of study screening;

3. Is unable to fully comply with the study requirements; for example, if the wound is in a place that the patient cannot reach him/herself and as such requires a caregiver to apply the study product, if the patient does not have consistent twice daily access to a caregiver, this patient would be ineligible for the study;

4. Any condition or situation which, in the Investigator's opinion, puts the subject at significant risk, could confound the study results, or may interfere significantly with the subject's participation in the study;

5. Patient is medically unstable or has a life expectancy of less than 12 months;
6. Patient is pregnant or is a woman of childbearing potential and does not consent to and receive a screening pregnancy test prior to study enrollment;

7. Current enrollment in an investigational drug or device study or participation in such a study within the last 30 days prior to Baseline (Week 0).

3. STUDY PROCEDURES AND METHODS

3.1. SUBJECT ENTRY PROCEDURES

Prospective subjects as defined by the eligibility criteria in Sections 2.4.2 and 2.4.3 (Inclusion/Exclusion Criteria) will be considered for entry into this study. Subject informed consent must be obtained prior to conducting Screening procedures.

After the required procedures are completed and study eligibility is confirmed, study product will be administered at Baseline (Week 0).

3.2. SCHEDULE OF VISITS AND PROCEDURES

A schedule of visits and procedures is provided in Table 1.

Table 1: Schedule of Visits and Procedures

Procedures	Baseline	Follow-Ups	Final Evaluation
Study procedures			
Informed Consent and Privacy Authorization	X		
Inclusion/Exclusion Criteria	X		
Demographics			
Age, Race, Gender, Education Insurance Status (from chart)	X		
Marital, Employment, Insurance Status	X		
Medical History			
Height, Weight, Smoking/Tobacco Status	X		
Spinal Cord Injury Information (from chart)	X		
Type of Bladder Managment	X		
Number of Concomitant Ulcers	X	X	X
Use of Antibiotics	X	X	X
Primary efficacy endpoint			
Ulcer Depth, Length, Width, Stage	X	X	X
Secondary endpoints			
Wound Infection Status	X	X	X
Amount and Type of Exudate	X	X	X
Color/Type of Tissue/Character of Wound Bed	X	X	X
PUSH Scores	X	X	X
Health Care Resource Utilization (Wound-Related)		X	X
Safety			
Reason for Early Discontinuation (if applicable)		X	
Adverse Events	X	X	X

3.2.1. BASELINE VISIT

The following procedures must be performed and recorded at the Baseline (Week 0) visit, gathered from the patient in the clinic unless otherwise specified:

1. Review study procedures and information regarding the study with the subject and obtain written informed consent
2. Review eligibility criteria; inclusion/exclusion (see Section 2.4.2 and Section 2.4.3)
3. For women of childbearing potential, obtain screening urine pregnancy test
4. Obtain demographic information and relevant medical/social history (from chart)
    a. *Demographics*: age, race (Caucasian, African-American, Hispanic, mixed race, other), gender, marital status, employment status, education (≤ high school, some college, ≥ college), insurance status (Medicare, Medicaid, private insurance, other, no insurance) including identification of whether plan is managed care or fee-for-service.
    b. Medical/social
        1. Height (feet/inches), weight (lbs)
        2. Smoking status (current, former, never)
        3. Alcohol (drink every day, a few drinks per week, a few drinks per month, seldom drink, abstain)
        4. Diabetes (yes, no) (from chart)
        5. Injury information (from chart)
            a) Date of injury
            b) Injury level (C1-8, T1-12, L1-5)
            c) American Spinal Cord Injury Impairment Scale (ASIA) score (if known)
                a. ASIA A – complete, no motor or sensory function is preserved in sacral segments S4-S4
                b. ASIA B – incomplete, sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
                c. ASIA C – incomplete, motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

d. ASIA D - Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

e. ASIA E = Normal: motor and sensory functions are normal.

6. Current antibiotic use
7. Results of any potentially relevant clinical laboratory tests, e.g., albumin, hemoglobin, performed at or within 14 days of baseline.

5. Patients will be stratified according to (1) smoking status; and (2) study ulcer Stage. Following stratification, patients will be randomized to study product (Microcyn or sterile saline). Document study pressure ulcer.
   a. *Determination of study ulcer*: if a patient has multiple Stage III or Stage IV ulcers, the ulcer with the highest total NPUAP PUSH score will be considered the study ulcer for the duration of the study. This is the ulcer that will be treated with Microcyn or saline. The patient and investigator should be encouraged to treat the patient's other wounds in accordance with the randomization scheme. However, the other wounds may be treated in whatever manner the Investigator deems most appropriate. If the other wounds are treated differently from the study ulcer, the Investigator needs to emphasize the importance of adhering to the study protocol at all times for the study ulcer.
   b. *Location*: Note anatomical location of study ulcer.
   c. *Debridement*: (yes/no) If in the opinion of the investigator the ulcer requires debridement, Microcyn or saline solution (as per randomization) is to be used during debridement.
   d. *Size*: (volume) This is the primary endpoint. The wound size should be measured <u>after</u> debridement if debridement is performed. Size will be determined through clinician measurement with photographic documentation.
   e. *Description*:

1. % Granulation
2. % Necrosis
3. % Eschar
4. % Slough
5. Purulence
6. Odor
7. Stage
8. NPUAP PUSH 3.0 total and sub-scores

6. Assess for Adverse Events (AEs) before study product application
7. Apply study product to wound, while simultaneously demonstrating to patient and/or caregiver how to apply study product to wound (see Section 3.2.3) subject and provide written instruction for use. For patients receiving home care services, home care nursing staff will be provided written instructions on use of product as well as identification of study ulcer, if multiple ulcers are present.
8. Assess for AEs (post-study product application).
9. Provide study product to the subject to take home in sufficient quantity to last until next clinic visit.
10. Review Subject Instructions and Subject Restrictions with patient. Patient will be given these instructions to take home for their and their caregivers' reference and review.

3.2.2. FOLLOW-UP VISITS (WEEKS 4, 8, 12, 16, 20, 24)

The following procedures and information will be performed and recorded at the Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 visits.

1. Obtain information on current antibiotic use
2. Document study pressure ulcer.
    a. *Debridement*: (yes/no) If in the opinion of the investigator the ulcer requires debridement, Microcyn or saline solution (as per randomization) is to be used during debridement.
    b. *Size*: (volume) This is the primary endpoint. The wound size should be measured after debridement if debridement is performed. Size will be

determined through clinician measurement of length, width, and depth, with photographic documentation.

c. *Description*:
    i. % Granulation
    ii. % Necrosis
    iii. % Eschar
    iv. % Slough
    v. Purulence
    vi. Odor
    vii. Stage
    viii. NPUAP PUSH 3.0 total and sub-scores

3. Apply study product to wound. Review how to use product and dress wound with patient if appropriate.
4. Document wound-related health care resource utilization since previous visit – record number of visits and whether visit was wound-related or not (yes/no):
    a. Home health care orders (yes/no)
    b. Specialized mattress (yes/no)
    c. Medication (yes/no – if yes, what medication(s))
    d. Seating evaluation (yes/wait/no)
5. Assess for AEs (post-study product application) and early discontinuation (if applicable; lost to follow-up, lack of efficacy, adverse event, treatment with prohibited medication, other).
6. Provide study product to the subject to take home in sufficient quantity to last until next clinic visit.
7. Review Subject Instructions and Subject Restrictions with patient. Patient will be given these instructions to take home for their and their caregivers' reference and review.

If the subject withdraws voluntarily at any time, the reason for early discontinuation should be noted at their last (follow-up) visit (if possible; see Section 3.2.4).

3.2.3. SUBJECT APPLICATION INSTRUCTIONS

The subject should be read the following instructions and given a sheet containing these instructions (as well as documentation/identification of study ulcer if multiple pressure ulcers are present) to take home with the study product.

"Microcyn or sterile saline should be generously sprayed on your wound and permitted to remain on wound. Then, dress the wound with gauze that is moistened with Microcyn or sterile saline and cover with dry gauze twice daily until the wound is healed, or until the end of the study."

3.2.4. SUBJECT RESTRICTIONS

Do not use any other topical products (prescription or over the counter, such as Neosporin) on the pressure ulcer.

3.2.5. DISCONTINUATION/WITHDRAWAL PROCEDURES

A subject may voluntarily withdraw from study participation at any time for any reason. If the subject withdraws consent and discontinues from the study, the Investigator will attempt to determine the reason for discontinuation and record the reason in the subject's records. If a subject withdraws consent because of an AE, that AE should be indicated as the reason for withdrawal. In the event of early discontinuation, (i.e., prior to the earlier of complete wound closure or Week 24) and whenever possible, the subject should be asked to return to the study center to complete the final evaluations. Subjects who withdraw from the study will not be replaced.

If at any time during the study, the Investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The Investigator can discontinue a subject at any time if medically necessary. The Investigator may discontinue a subject's participation if the subject has failed to follow study procedures or to keep follow-up appointments. Appropriate documentation in the subject's study record regarding the reason for discontinuation must be completed.

All subjects who fail to return to the study center for follow-up for any visit will be contacted by phone and/or email to determine the reason(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject is unreachable

by telephone after a minimum of two documented attempts (one attempt on two different days), a registered letter (with duplicate sent by first class mail, postage prepaid) will be sent requesting that contact be made with the Investigator. Only after these attempts have failed will a subject be deemed lost to follow-up.

This study may be terminated in accordance with the Clinical Trial Agreement. Should this be necessary, both Oculus and the Investigator will ensure that proper study discontinuation procedures are completed.

3.3. VARIATION FROM SCHEDULED VISIT DAYS

To allow for scheduling flexibility, each visit may be scheduled for up to +/- 3 days from 4 weeks. However, every effort should be made to keep the patient on an every 4 weeks / overall 6 month (24 week) schedule.

3.4. SAFETY ASSESSMENTS

3.4.1. ADVERSE EVENTS

AEs will be evaluated at the Baseline Visit subsequent to the subject signing the informed consent, pre- and post-treatment and at each visit (or early discontinuation). Section 5 outlines all procedures for recording and reporting AEs.

3.5. EFFICACY ASSESSMENTS

The primary endpoint is change in wound size through clinician measurement of length, width and depth, with photographic documentation.

3.5.1. TIME TO WOUND CLOSURE

Time to wound closure will be defined as date from Baseline assessment to the date the patient reports the wound closed or the first time the wound is visually documented to be closed by the investigator at a study visit, whichever comes first. If the patient reports the wound to be closed between study visits, the investigator must confirm closure of the wound at the next study visit and note the exact date of wound closure, as reported by the patient, on the subject's clinic record.

3.6. SCREEN FAILURES

A screen failure subject will be a person from whom informed consent is obtained and is documented in writing (i.e., subject signs an informed consent form) but who does not meet the study eligibility requirements.

3.7. PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact Oculus at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. The Investigator will document this decision).

4. PROHIBITED MEDICATIONS AND TREATMENTS

During the study, patients may not use any of the medications or treatments (prescription or over the counter) listed in Table 2. If the patient begins treatment with any of the listed treatments, the patient will be disenrolled from the study with "treatment with prohibited medication" noted as reason for early discontinuation.

Table 2: Prohibited Medications and Treatments

Type of Medication or Treatment	Not Allowed During the Following Time Period
Moisturizers, creams, lotions, non-study solutions, sunscreen, and make-up on treatment areas	At any time during study
Topical steroid on treatment areas (e.g., hydrocortisone, triamcinolone)	30 days prior to screening and through End of Study – Month 6
Use of medications that suppress the immune system; for example, cyclosporine, methylprednisolone, prednisone, methotrexate, alefacept, or infliximab	30 days prior to screening and through End of Study – Month 6
Any investigational study drugs or devices	30 days prior to screening and through End of Study – Month 6

5. EVALUATION OF ADVERSE EVENTS

All adverse events and Study Device complaints will be reported on an adverse event form at each visit.

5.1. DEFINITIONS

An adverse event is an unfavorable change in health, including abnormal laboratory findings, that occurs in trial participants during the clinical trial or within a specified period following the trial. For purposes of this Protocol, the specified period is Weeks 0-24 (per patient).

An MDR reportable event is one that reasonably suggests that a marketed device has or may have caused or contributed to a death, serious injury, or has malfunctioned, and that the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Serious Adverse Events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned.

Serious injury/(serious illness) is an injury or illness that:

- is life threatening, even if temporary in nature;
- results in permanent impairment of a body function or permanent damage to a body structure; or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

A complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

A malfunction is a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. A reportable malfunction is a malfunction for which:

- the chance of a death or serious injury resulting from a recurrence of the malfunction is **not** remote;
- the consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury;
- the malfunction causes the device to fail to perform its essential function and compromises the device's therapeutic, monitoring or diagnostic effectiveness which could cause or contribute to a death or serious injury, or other significant adverse device experiences; or
- the manufacturer takes or would be required to take action under section 518 or 519(f) of the FD&C Act as a result of the malfunction of the device or other similar devices.

Malfunctions are **not** reportable if they are not likely to result in death, serious injury or other significant adverse event experience.

Permanent impairment means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Reasonably suggests includes any information, such as professional, scientific, or medical facts and observations or opinions, that would reasonably suggest that a device has caused or contributed to a reportable event.

A pre-existing condition is one that is present prior to the start of the study and is to be reported as part of the subject's medical history. It should be reported as an AE only if the frequency, intensity, or the character of the condition worsens during the study.

An unexpected AE is one not identified in nature, severity, or frequency in the current protocol.

Any clinically significant change in the study safety evaluations during treatment must be reported as an AE.

5.1.1. ADVERSE EVENT SEVERITY GRADES

The Investigator is responsible for evaluating all AEs and determining the severity of the event in a manner that enables Sponsor to submit summary AE information in connection with clinicaltrials.gov reporting. Severity will be categorized by toxicity grade according to the CTEP-CTCAE version 4.02, when applicable. AEs not found in the list of AEs described in the CTEP-CTCAE listing will be graded according to the following definitions:

Mild — Grade 1: Event may be noticeable to subject; does not influence daily activities; usually does not require intervention

Moderate — Grade 2: Event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed

Severe — Grade 3: Event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed

Life-Threatening — Grade 4: Event that, in the view of the Investigator, places the subject at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death)

The Investigator will document AEs in all study participants consistent with the adverse events submission requirements for clinical trials registered with clinicaltrials.gov. For any AEs that are caused by or related to Microcyn™ use, and any product complaints (as defined above), the Investigator will inform Sponsor of the AE or complaint and facilitate or conduct the follow-up and information collection necessary for Sponsor to determine

the existence of a reportable MDR, i.e., an instance in which Microcyn™ caused or contributed to a participant's death or serious injury/illness.

5.1.2. STUDY PRODUCT CAUSALITY

The Study Product may have "caused or contributed" to a patient's death or serious injury, if the death or serious injury was or may have been attributed to the device, or the device may have been a factor in the death or serious injury because of:

- device failure;
- device malfunction;
- improper or inadequate device design;
- manufacture;
- labeling; or
- user error.

5.2. REPORTING ADVERSE EVENTS

The Investigator will assess subjects at each scheduled study visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the subject must be recorded on the source documents and the adverse event form.

In addition, Oculus must be notified within 24 hours of the Investigator's first knowledge of any immediately reportable events by telephone or fax by the procedure outlined below. Special attention should be paid to recording hospitalizations and concomitant therapies and medications.

5.3. IMMEDIATELY REPORTABLE EVENTS

Study Product-related deaths and serious injury/illness (reportable MDRs), as well as study participant pregnancy are considered immediately reportable events. If a subject experiences a death, serious injury/illness or pregnancy the Investigator must:

1. Report the death, injury/illness, or pregnancy by telephone (858-335-3115) to Oculus (refer to Appendix C – Study Responsibility List) immediately (within 24 hours) after the Investigator becomes aware of the event.

2. Complete a serious adverse event (SAE) or Pregnancy Notification Form and fax or overnight courier to Oculus within 24 hours of knowledge of the event. Note: The SAE form is NOT the AE report form.
3. Obtain and maintain all pertinent medical records, information and medical judgments of medical personnel who assisted in subject's treatment and follow-up and document on the AE report form as appropriate.
4. Provide a more detailed report to both Oculus and the IRB/IEC no later than seven (7) days after the Investigator discovers the event as further information becomes available, and when necessary update the information with follow-up information including outcomes. This report should include a statement as to whether the event was or was not related to the use of study product.
5. The Investigator will notify the IRB/IEC of the SAE or pregnancy according to specific IRB/IEC requirements.
6. The Investigator will report any device-related deaths using MedWatch Form 3500A to the FDA and the manufacturer within 10 working days, and report any serious injuries to the IRB and Sponsor.

Oculus will submit a written report to the regulatory authorities as soon as possible but no later than 15 calendar days after the initial receipt of the information regarding any serious injury or illness associated with the use of the study product.

5.4. PREGNANCY

WOCBP must consent to and receive a screening urine pregnancy test prior to study enrollment and use an effective method of birth control during the course of the study, such as the oral contraceptive pill, injection, implant, patch, vaginal ring, intrauterine coil, intrauterine device, barrier method used with an additional form of contraception (e.g., sponge, spermicide or condom), abstinence, or has a vasectomized partner. A female is considered to be of childbearing potential UNLESS she is post-menopausal (no menses for 12 consecutive months) or is without a uterus and/or both ovaries.

Before enrolling WOCBP in this clinical trial, Investigators must review guidelines about study participation for WOCBP. The topics should generally include:

Informed consent document

Pregnancy prevention information

Risks to unborn child(ren)

Any drug interactions with hormonal contraceptives

Contraceptives in current use

Guidelines for the follow-up of a reported pregnancy

Prior to study enrollment, WOCBP must undergo a screening urine pregnancy test and be advised of the importance of avoiding pregnancy during participation in this clinical study as well as the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent document stating that the above-mentioned risk factors and the consequences were discussed with her.

During the study, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle). The Investigator must immediately notify Oculus of any female subject who becomes pregnant any time during study participation, record the information on the Pregnancy Notification Form and fax the form to Oculus. Oculus will ask the site to follow-up with the subject periodically during the pregnancy for ongoing health and safety information through term, as applicable. Subjects will remain on the study but will not receive re-treatment. Protocol-required procedures for the final evaluations (Month 6) evaluations must be performed for the subject unless contraindicated by pregnancy.

5.5. FOLLOW-UP OF ADVERSE EVENTS

5.5.1. FOLLOW-UP OF NON-SERIOUS ADVERSE EVENTS

Non-serious AEs that are identified during the last scheduled study visit (Month 6 or early discontinuation) must be recorded on the AE report form as ongoing.

5.5.2. FOLLOW-UP OF POST STUDY SERIOUS ADVERSE EVENTS

In the event of a reportable MDR, the Investigator should continue to report any significant follow-up information to Oculus and the IRB/IEC up to the point the event has been resolved. Resolution means the subject has returned to the Baseline state of health, or the Investigator does not expect any further improvement or worsening of the subject's condition.

Any new SAEs reported by the subject to the Investigator that occur after the last scheduled contact and are determined by the Investigator to be reasonably associated with the application of study product should be reported to Oculus and the IRB/IEC.

6. STATISTICAL ANALYSIS

6.1. GENERAL CONSIDERATIONS

All statistical programming will be performed using SAS version 9.1 or higher, or similar statistical program. Statistical significance will be based on two-sided tests at the 5% level of significance. There are two planned analyses. The first will be conducted when the greater of 20 patients or those enrolled in the two (2) weeks following enrollment of the first participant have completed the Week 12 assessments. The second will be when all 80 patients have completed the Week 24 (Final Evaluation) assessments.

6.2. POPULATIONS

All subjects will be included in the summaries of demographic and other baseline characteristics. The safety population will include all subjects ever exposed to any study product (Microcyn and saline) and have provided any post-treatment safety information. The Efficacy population will include all subjects who complete both a Baseline (Week 0) and at least one follow up visit.

6.3. OVERALL STUDY EVALUATIONS AND MEASUREMENTS

6.3.1. EFFICACY

For the interim analysis, efficacy will be tested via T-tests of percent change in wound size using an intention to treat (ITT) approach as well as a per protocol analysis. For the final analysis, efficacy will be tested via T-tests of percent change in wound size using an intention to treat (ITT) approach as well as a per protocol analysis. Stratification of efficacy results by smoking status and study ulcer Stage will be conducted, although the results are expected to be similar given the stratified randomization.

For the interim analysis and final analyses, secondary analyses will include Kaplan-Meier analysis to estimate time to complete wound closure, and comparisons of infection status of the ulcer. Number and health care resource utilization (wound-related) will be tallied and compared between Microcyn and saline. Other secondary analyses may include linear and logistical regression to estimate the impact of patient characteristics on study endpoints, with special emphasis on variables that affect healing times, such as diabetes. If there are sufficient number of patients with multiple wounds, a mixed effects linear model

will be run, handling the patient as a group that has been randomized to a treatment to determine if there are any spillover effects of treating one wound with Microcyn.

If the interim analysis indicates that the difference in estimated time to complete wound closure between the two populations is 26% or higher at a significance level of $p<0.05$, the study will be halted early for success.

6.3.2. SAFETY

Adverse event analyses will be conducted for the interim and final analyses. Safety analyses will be conducted via Fischer's exact tests, chi-square, and t-tests, as applicable. The safety population will include all subjects exposed to the study product who have provided any post-treatment safety information.

7. STUDY PRODUCT MANAGEMENT

7.1. RECEIPT OF STUDY PRODUCT

Oculus will provide all study product, Microcyn and saline.

7.2. STORAGE AND DISPENSING OF STUDY PRODUCT

Study product maintained at the investigative site will be stored under controlled room temperature conditions until dispensed by the study coordinator to each subject. Subjects will be instructed to keep the study product bottle at room temperature and, if feasible, to return with all assigned study product bottles to the investigative site at each scheduled visit.

The study product will be prescribed and/or dispensed at the discretion and by the direction of the Investigator in accordance with the conditions specified in this protocol.

7.3. STUDY PRODUCT ACCOUNTABILITY

No special records will be kept of the amounts shipped and dispensed due to the FDA-approved/cleared nature of both study products.

7.4. RETURNS AND DESTRUCTION

Because Microcyn and saline are approved or cleared for marketing, the Investigator may dispose of any partially-used study product in the typical manner used in the clinic.

8. RECORDS MANAGEMENT

8.1. DATA COLLECTION

The clinic will use their usual data collection forms for this study with ancillary forms for informed consent, randomization to treatment, identification of the study ulcer and adverse event. The Investigator will enter the data from these forms into a database suitable for analysis (Section 9). It is Oculus's policy that the study database be verifiable with the source data that necessitates access to all original recordings, laboratory reports, and other records for each subject. The Investigator must therefore agree to allow access to subjects' study-related records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document.

The Investigator must keep written or electronic source documents for every subject participating in the clinical study. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

Name
Contact information
Date of birth
Sex
Study visit dates
Performed examinations, evaluations, and clinical findings
Study product administration
AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, must be included in the subject's source document (e.g., laboratory value listings). All these documents must have at least the subject's name and the date of the evaluation.

The data recorded during the course of the study will be documented in the clinic's usual forms and/or the study-specific forms. Before or at study termination, the database will be forwarded to Oculus, with the Investigator keeping the original source forms on site. If reconciliation is needed, Oculus will request photocopies or access to the source data. The

data will be evaluated and stored in anonymous form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study.

Any amendments and corrections necessary will be undertaken in both the source documents and database, stating the date of and reason for the amendment/correction.

Regulatory authorities, the IRB/IEC and/or Oculus Quality Assurance group (or designee) may request access to all source documents, and other study documentation for on-site audit or inspection. The Investigator must guarantee direct access to these documents. The original set of clinic forms, if sent to Oculus, will be kept by Oculus or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by Oculus after descriptive and statistical analyses and reports have been generated and are complete.

8.2. FILE MANAGEMENT AT THE STUDY SITE

It is the responsibility of the Investigator to ensure that the study center file is maintained in accordance with Section 8 – Essential Documents for the Conduct of a Clinical Trial of the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.

8.3. RECORDS RETENTION AT THE STUDY SITE

It is an Oculus requirement that all Investigators participating in clinical studies maintain detailed clinical data for one of the following periods:

- Country-specific requirements, or
- A period of at least 2 years following the last approval of a marketing application approved by a Regulatory Authority in an ICH region or until there are no pending or contemplated marketing applications in an ICH region, or,
- A period of two years after Oculus notifies the Investigator that the data will not be submitted for review by any Regulatory Authority.

For this study, all records related to the study should be maintained for a period of two years after notification that the data will not be submitted for review by any Regulatory Authority.

The Investigator must not dispose of any records or essential documents relevant to this study without either (1) written permission from Oculus, or (2) providing an opportunity for Oculus to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Oculus and relevant regulatory agencies. If the Investigator withdraws from the study (e.g., relocation, retirement), all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to Oculus in writing.

9. MONITORING, COMPLIANCE, AND QUALITY

All aspects of the study will be monitored by Oculus or authorized representatives of Oculus according to Good Clinical Practices (GCP) and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (i.e., Informed Consent Regulations [US 21CFR, Part 50] and Institutional Review Board regulations [US 21CFR, Part 56.103]). Access to all records, both during the trial and after trial completion, should be made available to Oculus at any time for review and audit to ensure the integrity of the data. The Investigator must notify Oculus immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun.

The Investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines; applicable informed consent regulations (US 21CFR, Part 50); and in compliance with the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data is not recorded per protocol, the reasons must be clearly documented on the patient record.

Before study initiation, at a site initiation visit or at a meeting with the Investigator(s), an Oculus representative will review the protocol and study procedures and data collection with the Investigator(s) and their staff.

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables.

The Investigator must ensure all data is recorded and complete after the subject's visit. The Investigator or monitor is responsible for reviewing them and clarifying and resolving any data queries on a regular basis. The completed and corrected clinic form for completed visits will be directly entered into a database by the Investigator or her designee for data processing, as per agreement between Oculus and the Investigator.

The Investigator must provide Oculus and the responsible IRB/IEC with a study summary shortly after the greater of 20 patients or those enrolled in the two (2) weeks following

enrollment of the first participant complete the Week 12 assessment and then again at study completion (all 80 patients), or as designated by Oculus.

9.1. QUALITY ASSURANCE AUDITS AND QUALITY CONTROL

In the event that a regulatory authority requests an inspection, the Investigator must inform Oculus immediately that this request has been made.

Study conduct may be assessed during the course of the study by a Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol and GCP. They will be permitted to inspect the study documents (study protocol, study product, original study-relevant medical records). All subject data will be treated confidentially.

10. ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance and the applicable regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and informed consent form by an HHS-registered IRB/IEC) to Oculus before study product will be shipped for use in the study.

11. CONFIDENTIALITY

Investigator and Sponsor have executed a Clinical Trial Agreement outlining their respective obligations regarding confidential information.

12. AMENDMENT POLICY

Only Oculus may modify the protocol. Protocol amendments will only be made after consultation and agreement between Oculus and the Investigator(s). Amendments may be approved by all applicable national and local committees including, but not limited to, the government regulatory authorities and/or regional IRB/IEC before implementation. The only exception is when an Investigator considers that a subject may be harmed and immediate action is necessary. Under these circumstances, approval of the chairman of the IRB/IEC, or an authorized designee must be sought immediately. The Investigator should inform Oculus, and the full IRB/IEC, no later than five working days after the emergency occurs. Protocol-specified safety reporting requirements must be adhered to independent of any other variables. All amendments that have an impact on subject risk, the study objectives or that require revision of the informed consent document must be approved by the IRB/IEC before implementation. Administrative changes to the protocol and/or changes that do not impact subject safety, risk, or comfort may be implemented prior to IRB/IEC approval if local institutional policy permits. A copy of the written approval of the IRB/IEC, which becomes part of the essential study documents file, must be given to the Study Monitor. Examples of amendments requiring such approval are:

- A significant change in the study design;
- An increase in the number of invasive procedures to which subjects are exposed; and
- An addition or deletion of a test procedure.

The Principal Investigator at each study site must sign the Investigator's Agreement page of the amended protocol.

13. USE OF INFORMATION AND PUBLICATION

It is understood by the Investigator that the information generated in this study will be used by Oculus in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide Oculus with all study data, and access to all study records.

Any results of medical investigations with Oculus products and/or publication/lecture/ manuscripts based thereon, shall be exchanged and discussed by the Investigator and Oculus representative(s) 30 days before submission for publication or presentation. Due regard shall be given to Oculus's legitimate interests for example, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information. Oculus shall be furnished with a copy of any proposed publication. Comments shall be rendered without undue delay.

In cases of publications or presentations of material arising from multi-center clinical investigations, Oculus is to serve as coordinator and referee. Individual Investigators who are part of a multi-center investigation may not publish or present data that are considered common to a multi-center investigation without the consent of the other participating Investigators and the prior review of Oculus.

In case of disagreement amongst the Investigators participating in a multi-center investigation, Oculus will be the final arbiter. Comments shall be given without undue delay. If they are not accepted, the senior author of the manuscript and representatives of Oculus shall promptly meet to discuss further and endeavor to agree mutually on the final wording and/or disposition of the publication. The above procedure also applies to information on prematurely discontinued and other non-completed studies.

APPENDIX A: PRESSURE ULCER STAGING STANDARDS

National Pressure Ulcer Advisory Panel[14]

Press Release
Pressure Ulcer Stages Revised by NPUAP
National Pressure Ulcer Advisory Panel
Washington, DC
February 2007

The National Pressure Ulcer Advisory Panel has redefined the definition of a pressure ulcer and the stages of pressure ulcers, including the original 4 stages and adding 2 stages on deep tissue injury and unstageable pressure ulcers. This work is the culmination of over 5 years of work beginning with the identification of deep tissue injury in 2001.

Pressure Ulcer Definition

A pressure ulcer is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear and/or friction.
A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors is yet to be elucidated.

Pressure Ulcer Stages

Suspected Deep Tissue Injury:

Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue.

Further description:
Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid exposing additional layers of tissue even with optimal treatment.

Stage I:

Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.

Further description:
The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Stage I may be difficult to detect in individuals with dark skin tones. May indicate "at risk" persons (a heralding sign of risk)

Stage II:

Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister.

[14] Source: National Pressure Ulcer Advisory Panel, 2007, http://www.npuap.org/pr2.htm

Further description:
Presents as a shiny or dry shallow ulcer without slough or bruising.* This stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration or excoriation.
*Bruising indicates suspected deep tissue injury

Stage III:
Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.

Further description:
The depth of a stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep stage III pressure ulcers. Bone/tendon is not visible or directly palpable.

Stage IV:
Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.

Further description:
The depth of a stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and these ulcers can be shallow. Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.

Unstageable:
Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown or black) in the wound bed.

Further description:
Until enough slough and/or eschar is removed to expose the base of the wound, the true depth, and therefore stage, cannot be determined. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as "the body's natural (biological) cover" and should not be removed.

The staging system was defined by Shea in 1975 and provides a name to the amount of anatomical tissue loss. The original definitions were confusing to many clinicians and lead to inaccurate staging of ulcers associated or due to perineal dermatitis and those due to deep tissue injury.

The proposed definitions were refined by the NPUAP with input from an on-line evaluation of their face validity, accuracy clarity, succinctness, utility, and discrimination. This process was completed online and provided input to the Panel for continued work. The proposed final definitions were reviewed by a consensus conference and their comments were used to create the final definitions. "NPUAP is pleased to have completed this important task and look forward to the inclusion of these definitions into practice, education and research", said Joyce Black, NPUAP President and Chairperson of the Staging Task Force.

For more information, contact npuap@npuap.org or 202-521-6789

APPENDIX B: NPUAP PUSH3.PDF

APPENDIX C: STUDY RESPONSIBILITY LIST

NOTE: For Serious Adverse Event reporting from a Study Site to Oculus, contact Regulatory Affairs and Device Safety Reporting, or Clinical Leader/Study Director, listed below. During the study, Oculus maintains a master list of Investigator and Clinical Monitor names that may be different than the ones shown below.

Regulatory Affairs and Device Safety Reporting	Name: Antoinette Douglas Fax: Mobile: e-mail:	
Clinical Study Director	Name : Phone: Fax: e-mail:	
Investigator	Name: Phone: Fax: e-mail:	