GrafixPL PRIME Evaluation Case Study

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The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Protocol
Principal Investigator: Lawrence A. Lavery, DPM, MPH

Title: GrafixPL PRIME Evaluation Case Study

1. Introduction and Purpose: There is a worldwide epidemic of diabetes. Foot ulcers are one of the most common complications in diabetic patients leading to amputation and hospitalization. The identification of biomarkers to determine which patients will heal and those that need more extensive intervention is critical to improve healing outcomes.

2. Background: The overall objective of this pilot study is to **evaluate the use of GrafixPL PRIME to heal chronic wounds.** Failure of a wound to heal in an organized and timely fashion is complex and multifactorial. Chronic wounds are characterized by a persistent inflammatory state resulting from local wound factors such as necrotic tissue, high microbial burden, low oxygen, and repetitive injury. Also, systemic disease processes, especially peripheral arterial disease (PAD) and hyperglycemia, contribute to the persistence of chronic wounds. Treatments include re-vascularization, wound debridement, pressure off-loading, glycemic control, and modification of patient behaviors, such as tobacco abuse and compliance with off-loading devices. Human amniotic membrane (AM) has been widely applied in the management of burns, dermatological defects and ocular surface reconstruction. Grafix is a cryopreserved placental membrane. It is comprised of an extracellular matrix (ECM) rich in collagen, growth factors, fibroblasts, mesenchymal stem cells (MSCs), and epithelial cells native to the tissue. This product is currently in use in Parkland and UT Southwestern hospitals. The product that is the subject of this evaluation, GrafixPL PRIME, is biologically equivalent to Grafix with respect to structure and cell viability as shown in benchtop studies. The original Grafix product is cryopreserved while the GrafixPL PRIME is dried. Once reconstituted (thawed for Grafix, and rewetted with saline for GrafixPL PRIME), these two products are indistinguishable. It has been estimated that 15% of diabetics will have a lower extremity ulcer in their lifetime. In the United States there are approximately 120,000 non-traumatic lower extremity amputations performed each year. The direct cost of foot ulcers and amputations has been conservatively estimated to be approximately 1.6 billion dollars a year without consideration for physician fees, prosthetics, or rehabilitation costs.

3. Concise Summary of Project: We plan to evaluate healing in a cohort of patients with chronic wounds (n=40) that receive optimal treatment including serial wound debridement and off-loading with total contact casts or a boot and GrafixPL PRIME. In addition, we will collect data on other potential confounding factors that could affect healing such as medications, tobacco, nutrition, comorbidities, diabetes control, infection, perfusion, and activity. Wound healing, including wound size and adverse events will be evaluated. The objective of this study is to understand the use of this product to evaluate wound healing in 40 patients.

Analysis and Statistical Approaches
As this study is designed as open-label case series to evaluate GrafixPL PRIME, there will be no statistical analysis for this study. Wound healing outcomes and adverse events will be evaluated for each patient treated.

4. Study Procedures:

Schedule of Events															
		Weekly Visits (±4 days)													
		SC	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/EOS[5]**
General	Informed** Consent	X													
	Screening*	X													
	Enrollment*		X												
	Demographics/ Social/Medical/ Surgical History	X													
	Inclusion/** Exclusion Criteria	X													
	Current Antibiotics	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory	Lab Values	X													X[2]
Examination and Assessment	Vascular – ABI	X													
	Neurological evaluation – Monofilament and VPT	X													
	Hyperspectral Imaging	X			X		X								
	Sitting blood pressure & Pulse rate	X													
	Height/Weight and BMI	X													
	Wound[3] debridement	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Application of[6] GrafixPL PRIME		X	X	X	X	X	X	X	X	X	X	X	X	
	Offloading[2]		X	X	X	X	X	X	X	X	X	X	X	X	X
	Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
	eKare Wound[4] imaging/ measurement		X	X	X	X	X	X	X	X	X	X	X	X	X
Data Collection	Source Documentation	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Only collect antibiotics, anti-fungal and anti-infective medications.
[2] Per physician discretion
[3] Once wound is healed, wound debridement will not be performed.
[4] Once wound is healed, eKare will not be performed.
[5] EOS will occur on the date the subject is healed.
[6] If at week 12 wound not healed the treatment is SOC per physician discretion
*Screening and visit 0 may be completed on same day.
**Informed Consent and Inclusion/Exclusion have to be completed before screening and visit 0 if done on same day.

Screening and Enrollment:

- Review and sign the Informed Consent and HIPAA Authorization
- Review the inclusion and exclusion criteria

If the subject qualifies for the study, they will participate in the following procedures (weekly visits, +/-4 days):

- We will collect past and current data from the medical record such as demographics (age, gender, race or ethnicity), medical and surgical history, physical exams, social history, antibiotic and antifungal medications, height, weight, vital signs, wound measurements and images, off-loading and wound healing treatments, procedures and tests. Results of standard-of-care laboratory tests including glycated hemoglobin (HgbA1C) and pregnancy testing if applicable.
- Hyperspectral imaging (HyperMed Imaging, Inc. and/or Kent imaging): the hyperspectral camera will be used to determine levels of oxygen in the foot and lower leg. The camera is about the size of a video camera and will be set up next to the bed. The camera does not touch the subject in any way and will not alter the surgical results. Recorded images will be taken of the area where the subject is having surgery and at no time will the subject's face or any identifying feature be recorded.
- Ankle Brachial Index (ABI): We will record the numbers from this test if the subject has had it recently. If not, the doctor may send the subject for this test. The Ankle Brachial Index (ABI) is the systolic pressure at the ankle, divided by the systolic pressure at the arm. It has been shown to be a specific and sensitive metric for the diagnosis of Peripheral Arterial Disease (PAD).
- Neurological evaluation/Neuropathy testing: We will do various tests and measurements to assess the sensation (feeling) in the feet and lower legs. None of these tests are invasive (using needles), uncomfortable or have risks greater than standard care.
- Standard of care wound debridement (removal of dead or unhealthy tissue).

Visit 0:

- Wound debridement
- eKare – Wound imaging measurement
- Application of GrafixPL PRIME
- Current Antibiotics
- Offloading
- Adverse Events
- Source documentation

Visits 1 - 11:

- Wound debridement
- eKare – Wound imaging measurement
- Application of GrafixPL PRIME
- Hyperspectral imaging measurements will be taken at Visit 2 and 4
- Current Antibiotics
- Offloading
- Adverse Events
- Source documentation

Visit 12/End of Study (EOS) Visit:

- Wound debridement

- eKare – Wound imaging measurement
- Current Antibiotics
- Offloading
- Adverse Events
- Results of standard-of-care laboratory tests that have been performed while subject was enrolled in this study
- Source documentation

(End of Study will occur on the date the subject is healed)

5. Sub-Study Procedures:

N/A

6. Criteria for Inclusion of Subjects:

- Able to provide informed consent
- 18-90 years of age
- Chronic foot ulceration below the ankle – persistent for 30 days or longer
- Ankle Brachial Index (ABI) >0.5 (Bedside ABI is acceptable for screening purposes as the formal imaging ABI may not be resulted prior to surgery)

7. Criteria for Exclusion of Subjects:

- Unable to provide informed consent
- <18 or >90 years of age
- History of poor compliance with follow-up visits
- Gangrene
- Untreated Osteomyelitis
- Widespread malignancy
- Active alcohol or substance abuse such as cocaine, heroin, or methamphetamines
- Currently Pregnant or planning pregnancy during the course of intended participation in the study
- Is nursing or actively lactating

8. Sources of Research Material: The Researchers will collect demographics (age, gender, ethnic origin), surgical history, social history, medical history, history and current on the following: physical examinations; ABI results; neurological evaluations; current antibiotics and antifungal medications; results of laboratory testing including pregnancy testing, operative reports, results of study tests and procedures, vital signs, height and weight, examinations and images and measurements of the wound, off-loading, adverse events and treatment.

9. Recruitment Methods and Consenting Process: Subjects will be identified by the PI or Sub-from the investigators' clinic schedule. We plan a prospective cohort study of 40 patients with chronic foot ulcerations treated at Parkland wound care clinic, UTSW wound care clinic, Podiatry inpatients at Parkland and Clements Hospitals.

The PI, Sub-I, or study coordinator will carefully review this research study with the subject and any family members or caregivers. Any questions will be answered prior to signing Informed Consent and HIPAA authorization, and it will be emphasized that participation in the research is voluntary. When all questions are answered, and the subject has agreed to participation in the research, the subject will sign the Consent and HIPAA Authorization. The subject will receive a copy of the signed documents. Subjects will be enrolled based on basic inclusion/exclusion criteria.

10. Potential Risks: The risks to the subjects are minimal. An additional potential risk includes loss of confidentiality. Tissue will be discarded after debridement. The following complications of tissue transplantation may occur: Transmission of disease of unknown etiology, transmission of known infectious agents including, but not limited to, viruses, bacteria, and fungi, Immune rejection of implanted GrafixPL PRIME and loss of function and/or integrity of GrafixPL PRIME due to reabsorption, fragmentation, and/or disintegration.

11. Withdrawal Criteria and Procedures
Subject participation is voluntary and a subject is free to discontinue his/her participation in the study at any time and without prejudice to his treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn. Withdrawal from the study entails an early discontinuation visit. A subject may withdraw or be withdrawn for the following reasons:

- Death (complete death form).
- AE or SAE (complete AE/SAE form).
- Any other circumstance that makes the Investigator believe that in the subject's own interest he/she should no longer participate in the clinical study.
- Withdrawal of consent.
- Failed to return/Lost to Follow-Up (LTFU).

Subjects who prematurely discontinue their participation to the study should be followed and treated by the Investigator according to the local medical practice in the medical center. Every effort should be made to determine the reason of early discontinuation and record it on the subject's eCRF and on the subject file. If an early discontinuation occurs, due to AE(s), the subject should remain under medical observation and followed until the medical condition(s) returns to baseline or is considered stable. In all cases, an attempt should be made to perform the procedures listed for the End of Study Visit.

12. Subject Safety and Data Monitoring: Subject Safety and Data Monitoring:
The principal investigator will monitor the experience of the subjects at least monthly and the conduct of the protocol, including:

- Study accrual rate
- Experience of study participants
- Study attrition including participant withdrawals/dropouts
- Patterns of AEs, SAEs, and/or unanticipated events
- Patterns of protocol deviations and/or violations
- Changes in risk/benefit

Adverse Events
Definition of an Adverse Event
An AE is any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. This includes any signs, symptoms, or diagnosis, clinically significant deviation from baseline laboratory values or vital signs, or worsening (more severe, more frequent or increased in duration) of a condition present at screening. Stable chronic conditions that are present prior to study entry and do not worsen during the study will not be considered AEs.

Recording and Reporting Adverse Events
All AEs (serious and non-serious) will be collected from the time the ICF was signed until the subject completes the study. The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. AEs may also be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments. The Investigator will treat all AEs as necessary and follow-up until resolution or until an acceptable stable or chronic condition has been reached, as determined by

the Investigator. In the event the subject prematurely withdraws from the study, an end of study visit should be performed if possible. In the event the subject elects not to return to the site, documented attempts to contact the subject for evaluation of AEs should be made.

An Investigator who is a qualified physician should assess all AEs. All AEs must be recorded on the Adverse Events eCRF with the following information:

Event Term: Related signs, symptoms and laboratory changes should be summarized for a specific event, unless important information will be lost.

Severity Grade:

- Mild: Does not interfere with subject's usual function.
- Moderate: Interferes to some extent with subject's usual function.
- Severe: Interferes significantly with subject's usual function.

Relationship to the GrafixPL PRIME: The Investigator will provide an opinion on the relatedness (causality) of each AE/SAE to the GrafixPL PRIME using the following scale:

- Not Related – The event is definitely not associated with the GrafixPL PRIME. Other conditions including concurrent illness, progression, or expression of the disease state, or reaction to a concurrent medication explain the reported AE.
- Probably – The event follows a reasonable temporal sequence from the GrafixPL PRIME, may abate upon discontinuation of the GrafixPL PRIME, and cannot be reasonably explained by known characteristics of the subject's clinical state.
- Definitely – The event follows a reasonable temporal sequence from the GrafixPL PRIME, may abate upon iscontinuation and reappear on re-challenge, or cannot be explained by known characteristics of the subject's clinical state.

For regulatory reporting purposes, the causality of probably, and definitely are regarded as related to GrafixPL PRIME, whereas the causality of not related is considered as non-related.

Duration: Start and end dates or ongoing if continuing at final examination. The start date is the date of onset of signs or symptoms related to the AE.

Action Taken with GrafixPL PRIME

- None
- Permanently discontinued
- Temporarily discontinued

Treatment of AE (more than 1 may apply):

- concomitant medication given
- other therapy/procedure given
- none

Outcome:

- Recovered with no sequelae – The subject has fully recovered from the AE with no residual effects observable.
- Recovered with sequelae – The event resolved but the subject has sequelae, which is a condition following a consequence of a disease, (e.g., if the event is "stroke" the sequelae may be "numbness in right/left arm and leg").
- Ongoing
- Fatal

Serious Adverse Events
Definition of a Serious Adverse Event
An SAE is any AE occurring at any dose regardless of the Investigator or the Sponsor's opinion on the relationship to the GrafixPL PRIME treatment, and that results in any of the following outcomes:

- Death
- Life-threatening event - AE that places the subject, in the view of the Investigator, at immediate risk of death from the event as it occurred, i.e., it does not include an event that, had it occurred in a more severe form, might have caused death.
- Subject hospitalization or prolongation of existing hospitalization – hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation.
- A persistent or significant disability/incapacity.
- A congenital anomaly or birth defect.
- Event is an important medical event, which may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Reporting a Serious Adverse Event
All SAEs will be reported to the Sponsor or its delegate via an SAE form, regardless of causality assessment, within 24 hours of when the study site becomes aware of it, even if only partial information is available. Once an SAE is detected, it should be followed until its resolution or stabilization, and should be reviewed at each visit for any changes in severity, the suspected relationship to the study, the interventions required to treat it, and the outcome. The Investigator is also responsible for informing his EC/IRB of the SAE as per ICH-GCP and local requirements. Whenever new information to a previously reported SAE becomes available, the study site should report this new information within 24 hours of his/her becoming aware of this new information, using the SAE form. The follow-up information should describe the new information, including whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.
Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event. In the event of death, a copy of the autopsy record should be added, if available.

Pregnancy Reporting
To ensure subject safety, each pregnancy occurring while the subject is in the study must be reported to the Sponsor or its delegate on a pregnancy form within 24 hours of learning of its occurrence. If a pregnancy is confirmed, no GrafixPL PRIME treatment should be administered to that subject. The pregnancy should be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications. Pregnancy follow-up should be recorded and should include an assessment of the possible relationship to the GrafixPL PRIME treatment. Any SAE experienced during pregnancy must be reported.

13. Procedures to Maintain Confidentiality: All study visits and procedures will be conducted in the private treatment rooms at the Parkland Foot Wound Clinic, UTSW Wound Clinic, inpatient Parkland Hospital, and inpatient Clements Hospital.

Subjects will be assigned a unique Subject Number upon consent. All study documents and specimens will contain this number and no unique identifying information. The subject number will be used on all data. No personal identifying information will be included.

Hard copy data (source files) will be kept separately in the locked coordinator's office. The link between the subject's name and the subject number will be kept in a password-protected computer file with access limited to members of the research team.

Electronic data will be password protected with access limited to members of the research team in the departmental 'R' drive.

No identified data will leave the campus.

14. International Conference on Harmonisation-Good Clinical Practice Guidelines

This study will be conducted in accordance with the current ICH-GCP guidelines: GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of study subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

All clinical work conducted under this protocol is subject to GCP rules. This includes an inspection by the Sponsor or its designee, health authority or EC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or the Sponsor or its designee. The study will be conducted in accordance with the Sponsor's standards and the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: 1996

15. Potential Benefits: As with most advanced wound care biologics, GrafixPL PRIME is expensive to patients. Participating in this study will allow patients to receive advanced wound care therapy at no cost to them and that they otherwise may not be able to afford.

The University of Texas Southwestern Medical Center
Parkland Health & Hospital System
Children's Medical Center
Retina Foundation of the Southwest
Texas Scottish Rite Hospital for Children
Texas Health Presbyterian Hospital Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	**GrafixPL PRIME Evaluation Case Study**
Funding Agency/Sponsor:	Osiris Therapeutics Inc
Study Doctors:	Lawrence A. Lavery, DPM, MPH Javier LaFontaine, DPM Dane Wukich, MD Katherine Raspovic, DPM Peter Crisologo, DPM David Truong, DPM, MS, AACFAS Matthew Johnson, DPM

You may call these study doctors or research personnel during regular office hours at 214-648-9159. At other times, you may call them at 214-786-5401.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
The study is being done to evaluate the use of GrafixPL PRIME to heal chronic wounds. This product is biologically equivalent to Grafix with respect to structure and cell viability. The original Grafix product is cryopreserved while the GrafixPL PRIME is dried. Once reconstituted (thawed for Grafix and rewetted with saline for GrafixPL PRIME), these two products are indistinguishable. The GrafixPL PRIME has the potential for greater ease of use in that it is shelf stable and it can be more easily be cut/shaped as it is a dry product. The GrafixPL PRIME looks like a dry sheet that soaks up moisture in the wound or is moistened by applying saline.

Why is this considered research?
This is a research study because it is not standard of care treatment.

The following definitions may help you understand this study:

- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center at Dallas and its affiliated hospitals.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you will be having surgery on a chronic wound that needs to have dead tissue removed. After removal of the dead tissue your wound will need additional wound care.

Do I have to take part in this research study?"
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time. If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?
We will enroll approximately 40 subjects from UTSW wound care clinic, Parkland wound care clinic, Podiatry inpatients at Parkland and Clements Hospitals.

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

<u>Procedures and Evaluations during the Research</u>:

Screening and Enrollment:
- Review and sign the Informed Consent and HIPAA Authorization
- The eligibility criteria for the study will be reviewed to determine if you meet the criteria to participate.

- We will collect past and current data from your medical record such as demographics (age, gender, race or ethnicity), medical and surgical history, physical exams, social history, antibiotic and antifungal medications, height, weight, vital

signs, wound measurements and images, off-loading and wound healing treatments, procedures and tests. Results of standard-of-care laboratory tests including glycated hemoglobin (HgbA1C) and pregnancy testing if applicable.

- Hyperspectral imaging (HyperMed Imaging, Inc. and /or Kent Imaging): the hyperspectral camera will be used to determine levels of oxygen in your foot and lower leg. The camera is about the size of a video camera and will be set up next to your bed. The camera does not touch you in any way and will not alter your surgical results. Recorded images will be taken of the area where you are having surgery and at no time will your face or any identifying feature be recorded.
- Ankle Brachial Index (ABI) We will record the numbers from this test if you have had it recently. If not, your doctor may send you for this test. The Ankle Brachial Index (ABI) is the systolic pressure at the ankle, divided by the systolic pressure at the arm. It has been shown to be a specific and sensitive metric for the diagnosis of Peripheral Arterial Disease (PAD).
- Neurological evaluation/Neuropathy testing - we will do various tests and measurements to assess the sensation (feeling) in your feet and lower legs. None of these tests are invasive (using needles), uncomfortable or have risks greater than your standard care.
- Standard of care wound debridement (removal of dead or unhealthy tissue).

Visit 0:

- Wound debridement
- eKare – Wound imaging measurement
- Application of GrafixPL PRIME
- Collect information about any antibiotics you may be currently taking
- Offloading
- Collect information about any adverse events

Visits 1 - 11:

- Wound debridement
- eKare – Wound imaging measurement
- Application of GrafixPL PRIME
- Hyperspectral imaging measurements will be taken at Visit 2 and 4
- Collect information about any antibiotics you may be currently taking
- Offloading
- Collect information about any adverse events

Visit 12/End of Study (EOS) Visit:

- Wound debridement
- eKare – Wound imaging measurement
- Collect information about any antibiotics you may be currently taking
- Offloading
- Collect information about any adverse events
- Collect the results of standard-of-care laboratory tests that have been performed while you were enrolled in this study

End of Study will occur on the date the subject is healed
The first visit will be the longest at approximately 1.5-2 hours. The other visits will likely be no longer than a usual clinic appointment.

The imaging study for hyperspectral imaging performed is designed for research, not for medical purposes. This is not useful for finding problems or diseases. Even though the researchers are not looking at your oxygen to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the hyperspectral imaging measurements done on this study is not for medical purposes, the research results will not be sent to you or to your regular doctor.

How long can I expect to be in this study?
This study is up to approximately 12 weeks long. If your wound heals before the 12 weeks, the study will be completed at that time.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?

Risks to GrafixPL PRIME
Donor screening methods are limited; therefore, certain diseases may not be detected. The following complications of tissue transplantation may occur:
• Transmission of disease of unknown etiology;
• Transmission of known infectious agents including, but not limited to, viruses, bacteria, and fungi;
• Immune rejection of implanted GrafixPL PRIME or
• Loss of function and/or integrity of GrafixPL PRIME due to resorption, fragmentation, and/or disintegration.

Hypersptectral Imaging
Because the camera does not touch you, there are no immediate risks from use of the camera. The images recorded are a series of bright colors and do not look like a regular image. It is not possible to identify a person based on the images. The images will be kept in a secure office with limited access. They will be coded with a subject ID number and will not contain any personal information. The images will be kept until the study is completed.

eKare Device
eKare wound measurement (3D wound measuring camera. The camera does not touch you in any way and at no time will your face or any identifying feature be recorded).

Loss of Confidentiality
Any time information is collected; there is a potential risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to an Embryo, Fetus or Breast-fed Infant

Females: Although there are no risks to a pregnant person in this study, it is an exclusion criteria. We will not include special populations in this research project. If you can become pregnant, a pregnancy test will be done by a urine sample and it must be negative before you can be a part of this study.

If you do become pregnant during this study, you must tell the researchers immediately.

Vascular-Neurological evaluation
We will do various tests and measurements to assess the sensation (feeling) and circulation (blood flow) in your feet and lower legs. None of these tests are invasive (using needles), uncomfortable or have risks greater than your standard care.

Other Risks
There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?
You will be carefully screened to be sure that it is safe and appropriate for you to participate in this research. At each visit, the investigator or nurse will examine your wound site, and ask questions about any symptoms or problems that you may be having, especially any signs of bleeding or infection.

What will my responsibilities be during the study?
While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.

- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Report to the researchers any injury or illness while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?
If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?
As with most advanced wound care biologics, GrafixPL PRIME is expensive to patients. Participating in this study will allow you to receive advanced wound care therapy at no cost to you, however, there are no direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research.

We hope the information learned from this study will benefit others with chronic foot ulceration in the future. Information gained from this research could lead to better treatment.

What options are available if I decide not to take part in this research study?
You do not have to participate in this research to receive care for your medical problem. Instead of being in this study, you have the following options:
- Receive standard of care for your wound which may include wound dressings, wound ointments and other standard care procedures.
- Placement of skin substitutes or skin grafting; or
- Participation in a different research study if there is one available for your

condition.

Please talk to the researchers or your personal doctor about these options.

Will I be paid if I take part in this research study?
No. You will not be paid to take part in this research study. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Application of GrafixPL PRIME, or Monitoring/Follow-up Procedures described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center or Parkland Health & Hospital System.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor is a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?

Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?

Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Osiris Therapeutics, Inc.
- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people; and
- The UT Southwestern Institutional Review Board.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details

about how your information will be used for this research study, and who may see and/or get copies of your information.

Are there procedures I should follow after stopping participation in this research? Yes. If you, the researchers, or the sponsor stops your participation in the research, you may be asked to do the following:

- Let the researchers know immediately that you wish to withdraw from the research.
- Return to the research center for tests that may be needed for your safety.
- Return any unused study materials.
- Discuss your future medical care, if any, with the researchers and/or your personal doctor.

Is there anything else I should know before I decide? Dr. Lawrence Lavery has financial interests in the Osiris Therapeutics, Inc., the company sponsoring this study. You should feel free to ask questions about this.
Dr. Lawrence Lavery has financial interest in the company that manufactures the HyperMed hyperspectral imaging device being used for this study. You should feel free to ask questions about this.

Whom do I call if I have questions or problems?
For questions about the study, contact Dr. Lawrence Lavery at 214-648-9159 during regular business hours and at 214-786-5401 after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to

call if you have any more questions.

- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers, Osiris Therapeutics Inc, and authorized persons including your insurance company.

_____

Name of Participant (Printed)

_____ _____ _____ AM / PM

Signature of Participant Date Time

_____

Name of Person Obtaining Consent (Printed)

_____ _____ _____ AM / PM

Signature of Person Obtaining Consent Date Time