Official title: Characterization of AmnioExcel Plus in two treatment paradigms

NCT number: NCT04233580

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Form A

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PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

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. The purpose of this study is to evaluate two different application paradigms with AMNIOEXCEL Plus® in Diabetic Foot Ulcer. The study will further characterize AE+ in wound healing outcomes and assess the role of aggressive debridement in wound healing outcomes. Study outcomes include

- Incidence of healing at 12 weeks
- Percent area reduction
- Percent volume reduction
- Level and type of Debridement
- Wound bed perfusion (hyperspectral imaging)

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

The overall objective of this pilot study is to evaluate the use of AMNIOEXCEL Plus® to heal diabetic foot 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, diabetes associated metabolic co-morbidities, 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.

b. Current practice

Human amniotic membrane (AM) has been widely applied in the management of burns, dermatological defects and ocular surface reconstruction. AMNIOEXCEL Plus® is a human placental-based tissue consisting of dehydrated, tri-layer Placental (Amnion/Chorion/Amnion) Allograft Membrane (T-PAM) layers. T-PAM is a minimally manipulated placental membrane product intended for homologous use for the repair, reconstruction and replacement of skin at the direction of a physician. AMNIOEXCEL Plus contains Human Cellular and Tissue Based Products (HCT/P) as defined by US FDA 21 CFR Part 1271. 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.

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3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

We plan to evaluate healing in two cohorts of patients with diabetic foot wounds (n=20) that receive optimal treatment including serial wound debridement and off-loading with a boot or postop shoe and AmnioEXCEL+. In one cohort, AmnioEXCEL+ will be applied weekly at study visits and in the second cohort, AmnioEXCEL+ will be applied maximum every 2 weeks (PRN, in the case that the wound requires debridement at a visit not intended for AE+ application, the wound will be treated as SOC). In addition, we will collect data on other potential confounding factors that could affect healing such as antibiotic, anti-fungal and anti-infective medications, tobacco, comorbidities, diabetes control, infection, perfusion, and activity. Wound healing, including wound size and adverse events will be evaluated.

4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Subjects will be identified by the PI or Sub- from the investigators' clinic schedule. We plan a prospective cohort study of 40 diabetic patients with foot ulcerations treated at Parkland foot wound clinic and UTSW wound clinic.

The PI, Sub-I, or study coordinator will carefully review this research study with the subject in a private area and any family members or caregivers. Any questions will be answered, 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. Subject will be given ample time to consider.

Study Procedures:

Collection of Demographic data, medical/social history

Collection of medications1

Ankle Brachial Index2

Wound debridement3 (standard of care procedure) and tissue collection of normally discarded tissue of up to 3 samples on Baseline visit and weeks 3, 6, and 9.

Imaging with eKare4

Hyperspectral Imaging

Application of study product

1Only collect antibiotics, anti-fungal and anti-infective medications.

2 ABI (with toe pressure) can be done at screening or baseline.

3 Once wound is healed, wound debridement will not be done at weekly visits.

4 Once wound is healed, eKare will not be done at weekly visits.

5 EOS will occur on the date the subject is healed.

*Screening and Visit 1 may be done on the 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):

Visit 1*:
- Demographics (such as age, gender, race or ethnicity)
- Past Medical History, Social History, Medications documented.
- Labs documented as SOC within 6mo of initial visit
- ABI with toe pressures2
- Wound debridement and collection (3 samples) of discarded tissue from debridement
- eKare wound measurement
- Hyperspectral Imaging
- Randomization
- Application of AmnioEXCEL+
- Source documentation
- Stipend disbursement

Visits 2 through 6:
- Wound debridement3 (tissue collection at weeks 3 and 6)
- eKare wound measurement4
- Hyperspectral imaging
- Application of AmnioEXCEL+ per cohort assignment
- Source documentation
- Stipend disbursement

Visit 7:
- Medications documented
- Wound debridement3
- eKare wound measurement4
- Hyperspectral imaging
- Application of AmnioEXCEL+ per cohort assignment
- Source documentation
- Stipend disbursement

Visits 8-11:
- Wound debridement3 (tissue collection at week 9)
- eKare wound measurement4
- Hyperspectral Imaging
- Application of AmnioEXCEL+ per cohort assignment
- Source documentation
- Stipend disbursement

Visit 12:
- Wound debridement3
- eKare wound measurement4
- Source documentation
- Stipend disbursement

End of Study (EOS) Visit 5:

- Medications documented
- Wound debridement3
- eKare wound measurement4
- Source documentation
- Subject exit from study

6. Criteria for Inclusion of Subjects:

- Diagnosis of Diabetes Mellitus
- 21-90 years of age
- Able to provide informed consent
- Chronic foot ulceration below the ankle – persistent for >30 days

7. Criteria for Exclusion of Subjects:

- <21 or >90 years of age
- Unable to provide informed consent
- History of poor compliance in the opinion of the investigator
- Gangrene
- Untreated osteomyelitis
- Widespread malignancy
- Active alcohol or substance abuse such as cocaine, heroin, or methamphetamines that in the opinion of the investigator will impact the subject's participation in the study
- Pregnancy

The eKare and Hyperspectral Imaging cameras are research-only. Everything else is standard of care. The cameras do not touch the patient.

Analysis and Statistical Approaches

As this study is designed as open-label case series to evaluate different treatment protocols using AmnioEXCEL+. Descriptive statistics will be performed there will be no statistical analysis for this study. Wound healing outcomes will be assessed in both treatment cohorts.

The eKare and Hyperspectral Imaging cameras are research-only. Everything else is standard of care. The cameras do not touch the patient. We will collect up to 3 samples of discarded tissue from debridement at Baseline and weeks 3, 6, and 9 if applicable. This is the standard of care debridement and tissue that would have been discarded.

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4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	AmnioEXCEL+ will be applied weekly	☒ UTSW	☒ Yes
		☒ PHHS	☒ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes
2	AmnioEXCEL+ will be applied maximum every 2 weeks (PRN, in the case that the wound requires debridement at a visit not intended for AE+ application, the wound will be treated as SOC).	☒ UTSW	☒ Yes
		☒ PHHS	☒ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

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4.c.
Study Intervention #1
AmnioEXCEL+ will be applied

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All Groups/Subjects will receive the AmnioEXCEL+ product. As with most advanced wound care biologics, AmnioEXCEL+ is expensive. 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. Please see product insert for precautions.	

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

		4.d. List ALL other research procedures or components not listed in table 4.b. ***The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.*** Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)		
		All procedures/components are listed in 4a.		
#	**Research component** • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Eligibility Assessments** **Please complete table**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
2	**Research component**			
	The eKare and Hyperspectral Imaging cameras are research-only. Everything else is standard of care. The cameras do not touch the patient.	Please see 4a.	The eKare and Hyperspectral Imaging cameras are research-only. Everything else is standard of care. The cameras do not touch the patient.	None
	Insert procedure here			
	Insert procedure here			
3	**Insert component 3 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
4	**Insert component 4 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			

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5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Please see attached product preparation insert for precautions.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Describe here

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

If yes, describe here