Study Title	A Randomized, Double-Blinded, Placebo-Controlled Study for the Treatment of Ocular Chronic GVHD with Processed Amniotic Fluid (pAF) Drops (GVHD)
ClinicalTrials.gov ID (NCT Number)	NCT03298815
Principal Investigator (PI)	Catherine Lee, MD
Document (ICF, Protocol, SAP)	ICF
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Consent and Authorization Document

BACKGROUND

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask the research doctor or staff if there is anything that is not clear or if you would like more information. Take time to decide whether or not to volunteer to take part in this research study.

You have a complication from your stem cell transplantation called chronic graft-versus-host disease of the eyes, or chronic GVHD of the eye for short. Chronic GVHD has affected your eyes and caused them to be very dry, sometimes red, itchy or even painful. This eye dryness can cause a great deal of discomfort, it can reduce your vision, and also cause inflammation of the membrane that covers the surface of your eye, named cornea.

The purpose of the study is to find out if amniotic fluid eye drops can improve your chronic GVHD of the eye, decreasing dryness and inflammation. Amniotic fluid is the liquid that surrounds the unborn, growing baby during pregnancy. Amniotic fluid is mainly water, but also has other components like proteins and antibodies that protect the baby from infection and help growth. Some of these components have been shown to have an anti-inflammatory effect. The fluid is obtained during the delivery of the baby and processed so that it is sterile and can be used as eye drops. We hope that the beneficial components of the amniotic fluid will help your chronic GVHD of the eye, decreasing inflammation and dryness. The Amniotic Fluid used in this research study is considered investigational and has not been approved by the FDA.

This study is being conducted by the Cell Therapy and Regenerative Medicine Facility and by the Moran Eye Center, which are part of the University of Utah.

STUDY PROCEDURES

In this study you will be referred from the Blood and Marrow Transplantation (BMT) Program at the Huntsman Cancer Institute and study visits will be performed at the Moran Eye Center, also part of the University of Utah and located on campus.

The first visit is called a screening visit. This visit may be split into two visits if needed. At this visit the research coordinator and your study doctor will perform the following:

- You will be asked to read and sign this consent form before any study procedures can be done. You will receive a copy of this to take home.
- Your medical history and medications will be reviewed
- If you have used or are using medicated eye drops you will need to have a waiting period called a washout for 7 days prior to starting the study medication.
- Your vital signs will be measured including height, weight, blood pressure, pulse and temperature.
- The study doctor will perform a physical exam
- A complete eye exam will be performed including eye dilation

- Blood and urine samples will be collected. These blood and urine samples would be collected even if you were not participating in the study.
- The study team will ask you to complete questionnaires about yourself and the study doctors will ask you questions.
- The study team will give you a pain diary during your participation

Follow Up Visits 2, 3, 4

- Your medical history and medications will be reviewed
- Your vital signs will be measured including height, weight, blood pressure, pulse and temperature.
- The study doctor will perform a physical exam
- Blood and urine samples will be collected. These blood and urine samples would be collected even if you were not participating in the study.
- The study team will ask you to complete questionnaires about yourself and the study doctors will ask you questions.
- The study team will review your pain diary with you
- You will have a follow up eye exam
- Your used and unused eye drop vials will be collected at visit 2 only

Once we have determined you can be part of the study and you have had your eye exam, we will provide you with eye drops for both eyes. The drops for one of your eyes (either right or left) will always be the amniotic fluid, and the drops for the other eye will always be saline solution. The assignment of which eye gets what drop is done randomly, which means by chance. The reason for this is to compare whether one eye benefits from the amniotic fluid compared to the eye that receives the saline solution, which is called placebo and is not supposed to benefit or harm that eye. Neither you nor your doctors will know which eye is receiving amniotic fluid and which eye is receiving placebo. This type of study, called placebo-controlled and blinded (because neither you nor your doctors know what each eye is getting), is the best and most reliable way to determine whether the amniotic fluid drops are truly beneficial.

You will administer these drops twice daily in both eyes, once in the morning and once before you go to bed, for a period of 30 days. You will have to see your doctor in the BMT clinic monthly for three months. You will also have to see the eye doctor at the Moran Eye Center with the same frequency. We will train you on how to administer the drops so you will be able to do this yourself for the rest of the study. After the third visit you will no longer be participating in the study. You will no longer receive eye drops after day 30. After day 30 you are able to resume another form of eye drops at your doctors discretion.

Patient Study Calendar

	Screening/Baseline	Day 30 ±3 days[6]	Day 60 FU ± 3 days[6]	Day 100 ± 3 days[6]	Early Discontinuation of Study Drug
Informed Consent	X				
Eligibility	X				
Medical History	X	X	X	X	X
Concomitant meds	X	X	X	X	X
Randomization	X				
Dispense Drug	X				
Physical Exam	X	X	X	X	X
Drug Compliance		X			
FACT G (QOL)	X	X	X	X	X
DEWS assessment	X	X	X	X	X
NIH CC Response Assessment for Chronic GVHD[1 3]	X	X	X	X	X
Complete Eye [2,3]	X				
Urine Pregnancy Test[4]	X				
FU Eye Exam[2]		X	X	X	X
Adverse Events		X	X	X	X
Review Study Diary[5]		X	X	X	X

[1] Health Care Provider Global Rating, Eye Score, Patient Global Rating

[2] Including DEWS assessment by ophthalmologic assessment and visual acuity

[3] The NIH CC Response Assessment for Chronic GVHD and the Complete Eye exam can be performed within seven days of each other.

[4] Pregnancy test is required if participant is of childbearing potential.

5 The study team may call the participant before the 30-day visit to address diary questions and completion.

6 Follow-up visits may be conducted via phone call if in-person visits cannot be completed.

RISKS

The University of Utah Cell Therapy and Regenerative Medicine (CTRM) screens the amniotic fluid coming from donors for infectious diseases through medical and social history questionnaire, medical record review, and testing of the donor's blood for viruses including HIV, Hepatitis B & C, and others. The CTRM Medical Director reviews the records and test results to determine if the donor meets eligibility requirements. Although the risk of transmitting infectious disease is very minimal, there is a potential for transmission.

Possible risks related to your participation in this study are those related to the tests that will be performed during your study visits to the clinic.

Risks of Eye Exam and Visual Function Tests

Common Risks

- Redness and discomfort from eye drops
- Light sensitivity from dilated pupils
- After images from bright lights
- Discomfort from bright lights

Less Common Risks:

- Allergic to eye drops
- Corneal scratch from rubbing your eyes

Rare Risk:

- High blood pressure
- Irregular heart beat
- Closed angle glaucoma from the dilation drops

We suggest you bring a pair of sunglasses to wear after the exam, as these can help with comfort. If you are injured during the course of your study participation, you should seek medical help immediately, and contact the study doctor or study staff as soon as possible.

Participation in the study may also involve risks that are currently unforeseeable.

BENEFITS

It is unclear whether the product will provide any benefit. The potential benefit from this treatment is improvement of your chronic GVHD of the eye. The information gained in this study will aid in the understanding of chronic graft-versus-host disease of the eyes and help in the development of new approaches to its treatment in the future.

ALTERNATIVE PROCEDURES

You may choose not to be in this study. If you do not want to take part in the study, there are other choices to improve your symptoms of dryness, including:

- Artificial tears, serum tears or topical gels
- Blocking your tear ducts
- Scleral contact lenses
- Eye drops and medications that may increase tear production

You may have received one or more of these treatments, and you may discuss these options with your doctor.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, you can contact Dr. Michael Boyer at 801-662-4700. If you think you may have been injured from being in this study, please call Dr. Michael Boyer at 801-662-4700.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY

If you are injured from being in this study, medical care is available to you at University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION

Research studies include only people who choose to take part. You can tell us that you don't want to be in this study. You can start the study and then choose to stop the study later. We will still give you medical care and answer any questions you have. Your decision will not affect your relationship with your doctor or the study team in any way.

If you want to stop being in this study, please let the research doctor know. That way you can find out what should be done about your normal medical care outside of the study.

RIGHT OF INVESTIGATOR TO WITHDRAW PARTICIPANTS

The investigator can withdraw you without your approval. Possible reasons for withdrawal include:

- Any adverse effect that may affect your eyes significantly, and that in the opinion of the treating doctor justifies withdrawing you from the study.
- Noncompliance with the treatment
- Any other unforeseeable circumstance that in the opinion of the treating doctor justifies withdrawing you from the study.

At the moment, we do not anticipate any adverse effects on your health or welfare. If an adverse effect occurred during the study and you were withdrawn from it, the doctors may have to follow up on the problem until it is resolved.

COSTS AND COMPENSATION TO PARTICIPANTS

The parts of your care that would normally be done as standard treatment such as regular doctor visits and lab work for the follow-up of your chronic GVHD will be billed to you or your insurance company. Anything strictly related to the study, such as the eye drops or exams required by the study outside what is considered standard of care, will not be billed to you or your insurance company. The standard of care exams required by the study include your doctor visits, including eye exams, and your routine blood tests.

You will not be compensated for participating in this study.

NEW INFORMATION

Sometimes during the course of a research project, new information becomes available about the amniotic fluid drops that are being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study.

If you decide to withdraw at that time, your research doctor will make arrangements for your medical care to continue. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your medical care to continue.

NUMBER OF PARTICIPANTS

We expect to enroll 15-20 participants at Huntsman Cancer Institute, University of Utah. This study is not conducted in any other center outside the University of Utah

CONFLICT OF INTEREST DISCLOSURE

The University of Utah has a significant institutional financial interest in intellectual property being used in this study (U-5650 "Amnion/Chorion Membrane as a Wound Cover to Control Adhesions and Heal Wounds, Amniotic Fluid (Supernatant) and Amniotic Fluid (Whole) to Reduce Inflammation, Heal Wounds and Stimulate Bone Growth") and a significant institutional financial interest in Eliksa (a non-publicly traded company which is licensing the technology for commercialization). This is a conflict of

interest as determined by the University of Utah Institutional Conflict of Interest Officer and a management plan has been implemented to ensure transparency, promote data integrity, and to safeguard human subjects in the research.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION

Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study. The FDA may also review research records that are a part of this study.

This is the information we will use and include in our research records:

- Demographic information like name, address, telephone number, and email address
- Related medical information about you like allergies, current and past medications or therapies, and information from physical examinations, such as blood pressure reading, heart rate, temperature, and lab results
- All tests and procedures that will be done in the study

How we will protect and share your information:

- We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

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

- In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:
    - Members of the research team at Huntsman Cancer Institute, and University of Utah Health Sciences Center.
    - The University of Utah Institutional Review Board (IRB), which reviews research involving people to make sure the study protects your rights.
    - Eliksa (a non-publicly traded company which is licensing the technology for commercialization)
    - National Institutes of Health, Food and Drug Administration and National Cancer Institute

- If we share your identifying information with groups outside of Huntsman Cancer Institute, or the University of Utah Health Sciences Center, they may not be required to follow the same federal privacy laws that we follow. They may also share your information again with others not described in this form.

- If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at Huntsman Cancer Institute and University of Utah Health Sciences Center.

What if I decide to Not Participate after I sign the Consent and Authorization Form?
You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.
This authorization does not have an expiration date.
You have a right to information used to make decisions about your health care. However, some information from this study will not be available during the study; it will be available after the study is finished.

CONSENT
I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

INTERPRETER STATEMENT: (For Non-English Speaking Participants Only) I confirm that I was present as an interpreter for the duration of the consent process for this research study. I confirm that I am qualified and have the necessary skills to provide interpretation between the participant's language and English. By signing this form, I confirm that I provided a full and complete interpretation of the exchange between the researcher obtaining consent and the participant, to the best of my ability.

_____
Name of Interpreter

_____ _____
Signature of Interpreter