UNIVERSITY OF SASKATCHEWAN

PARTICIPANT INFORMATION AND CONSENT FORM

TITLE: Management of Recurrent and Progressive Ligneous Conjunctivitis Due to Plasminogen Deficiency. An N of One Clinical Trial of Topical Administration of Allogenic Plasma to Affected Eye

PROTOCOL: USASK0511ST

SPONSOR: University of Saskatchewan

INVESTIGATOR: Dr. Sarah Tehseen
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(639) 998-3972

24-HOUR CONTACT: After hours, please call 306-655-1000 and ask for the study Doctor (Dr. Sarah Tehseen) or the on-call pediatric hematologist (who will be aware of the details of your case)

If you are the parent or legal guardian of a child who might qualify for this study, permission from you is required. If you are reading and signing the consent form as the parent or legal guardian of a child taking part in this study, the words "you" and "your" always refers to the child, the participant in the study.

INTRODUCTION

You are invited to take part in this research study because you have been diagnosed with congenital plasminogen deficiency, a rare deficiency of a blood clotting (coagulation factor), with recurrent ligneous conjunctivitis.

Your participation is voluntary. It is up to you to decide whether or not you wish to take part. If you decide to participate, you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to participate, your decision will not affect your medical care.

Please take time to read the following information carefully. You can ask the study doctor or staff to explain any information that you do not clearly understand. You may ask as many questions as you need. Please feel free to discuss this with your family, friends or family physician before you decide.

WHO IS CONDUCTING THE STUDY?

The study is being sponsored by the University of Saskatchewan. The study doctor and the University of Saskatchewan are not being paid to conduct this research study.

WHY IS THIS STUDY BEING DONE?

Congenital plasminogen deficiency is an extremely rare genetic disorder caused by alterations in the plasminogen (PLG) gene, which leads to a deficiency of the plasminogen enzyme. Congenital means a condition you were born with. Gene(s) in the cells of your body carry information for certain traits that can be passed on to you from your parents or grandparents (hereditary) and information that is necessary for your body to function.

Plasminogen is a protein in your body that breaks down clots by degrading fibrin, aids in wound healing renovation of tissues. Fibrin is a protein produced by liver which is the main component of blood clots.

When levels of plasminogen enzyme are lower than normal, wound healing gets affected and fibrin rich growths are formed on mucous membranes in various parts of the body, including eyes, ears, nose, gastrointestinal or urogenital tract. Over time these growths can impair the function of the affected body part. The mucous membranes are a moist layer of tissue that lines our eyes, interior of mouth, stomach, colon, etc. The clear mucous membranes most often affected in this disorder are those lining the inside of the eyelids and the front surface of the eye (called the conjunctiva) and the inside of the mouth.

Ligneous conjunctivitis is characterized by the buildup of a protein called fibrin which causes inflammation of the conjunctiva (conjunctivitis) and leads to thick, woody (ligneous), inflamed (irritated lining) growths on the inside of the eyelids, but may also affect other parts of the eye (such as the sclera, cornea and pupil) leading to loss of vision or visual acuity (how well you can see). Without any substitute therapy with plasminogen, the abnormal growths that form on these surfaces can cause significant complications (damage to the eye, eye infection, lazy eye and loss of vision) and they usually recur, even if they are surgically removed (resected). Plasminogen replacement (in the form of eye drops of plasminogen concentrate or donor plasma) has been shown to be the most effective treatment for preventing growth of these lesions.

Plasminogen is an abundant plasma protein that exists in various forms in the blood. Plasma is the liquid component of your blood, which helps your body recover from injury, distribute nutrients, remove waste and prevent infection, while moving throughout your circulatory system. One way to obtain plasminogen, when your body cannot produce its own plasminogen, is to use plasminogen from plasma of healthy donor's blood.

This study will examine the use of small doses of allogenic (the plasma donated from healthy donors) donor plasma as a source of plasminogen for treatment and prevention of these pseudomembranous lesions. These will be applied to the affected eye.

The plasma will be collected from healthy donors by Canadian Blood Services (CBS) under strict regulations of the Food and Drugs Act (October 23, 2014). The plasma will be provided to you in small vials for use as eye drops (ophthalmic application). The plasma vials will then be frozen at a temperature of -18 degrees Celsius or lower for shipment to the local blood bank. It is important that the plasma vial is maintained at or lower than minus 18 degrees Celsius (-18^{o}C) until it can be thawed at the time of dispensing to eyes. You will be able to store these plasma vials at home as long as you have a freezer that maintains temperature <-18 degrees Celsius.

All handling of plasma vials has been carried out in a sterile manner. Plasma collected from the voluntary donors at Canadian Blood Services is tested for microbial agents that can be

transferred through blood or plasma to other people who receive it. Additionally, the plasma is tested for any bacterial contamination that may happen during the processing and division into small amounts (aliquots). The vials are issued for use only once the bacterial cultures have shown no growth of bacteria. While frozen, the product can be used up to 365 days from the date plasma was collected. A patient information leaflet will be provided to you with this consent form from the Canadian Blood Services. You can also refer to the Canadian Blood Services website at https://www.blood.ca/en/plasma to obtain more information about the process of plasma collection and issue. Such information is also published by the Government of Canada with regards to Blood Safety in Canada, and your study doctor will be able to explain or provide more information in this regard.

Health Canada, the regulatory body that oversees the use of drugs in Canada, has not approved the sale or use of plasminogen replacement eye drops to treat ligneous conjunctivitis, although they have allowed its use in this study.

This is a single-site study, meaning no other centres or hospitals are participating in this study across Canada or other countries. You are the only patient being invited to participate in this study.

This study has 2 aims:

1) To determine the safety of the plasma eye drops, and
2) To determine the effectiveness of the plasma eye drops. Effectiveness will be determined by considering the amount of change to the size of the lesions (woody growth in the eye) and the time it takes to reduce the size, as well as changes to eyesight (visual acuity) and whether the lesions reoccur (come back).

WHAT DOES THE STUDY INVOLVE?

If you agree to participate in this study, your study involvement will last approximately 24 months and will include the following study visits:

- **Screening Visit** – During this visit, the study staff will collect your medical history. You will undergo a physical exam. You will have blood drawn for tests (such as performing blood group (ABO, RhD) and an antibody screen) before plasma vials can be issued and used. You will also be asked to go to Saskatoon City Hospital for an eye exam.
- **Daily Visits for first 5 Days** – During the initial 5 days of study treatment, you will come to the study site for study drug administration by the study staff. The study staff will ask you about any potential side effects and will provide training for you to be able to administer the eye drops at home.
- **Weekly Visits for first 6 Weeks** – During the first 6 weeks of study treatment, you will undergo physical examination by the study staff every week at the Jim Pattison Children's hospital. The study staff will review your history to determine if you are having any complications from plasma use and also perform limited eye examination as appropriate. If you experience any side effects or the physical examination reveals any concerns, the plasma administration will be put on hold. The study staff will immediately contact your ophthalmologist and the Canadian Blood services to determine next steps.
- **Follow-up Visits** – Every 3 to 6 months after the end of the Weekly Visits, you will return to the study site. The study staff will collect your medical history. You will undergo a physical exam and a limited eye exam. The detailed eye examination will be

performed by your ophthalmologist based on their assessment. You will have the contact information of the pediatric hematology team to call them 24/7 for any questions, concerns or complications associated with your disease or administration of plasma drops.

The table below provides an overview of the study visits and the tests/procedures conducted in this study for your ease of understanding.

Procedures/Visit	**Screening (Visit 1)**	**Visits 2 to 6**	**Visits 7 to 12**	**Visits 13+**
	Day 1	**Daily for 1st 5 Days of Treatment**	**Weekly for 1st 6 Weeks of Treatment**	**Every 3-6 months following Visit 12**
Consent Discussion	X			
Medical History	X		X	X
Physical Exam	X		X	X
Eye Exam	X			X
Lab Tests	X			
Eye Drop Administration by Study Staff		X		
Training on Home Eye Drop Administration (Handover of Medication/eye drops diary and instruction sheet)		X		
Self-Administration of eye drops			X	X
Monitoring for Side Effects		X	X	X

Study Treatment

You will receive treatment with the plasma eye drops for 3-6 months, depending on your response to the treatment. Treatment will involve administering 1-2 drops of the plasma eye drops to the affected eye every 1-5 hours per day. The administration of the plasma eye drops can change in frequency based on the Ophthalmologist's' assessment of your response to the therapy. You will receive an instruction checklist from the study staff at the time of your first visit, which provides instruction on how to safely administer and store eye drops at home.

The first few administrations will occur under staff and nursing supervision in the outpatient clinic. The remainder of the eye drops will be provided to you for administration at home.

Transportation of study drug (eye drops) from outpatient clinic to home:

Once available in the local blood bank, you can collect the 14 to 30 day supply of plasma vials to store at home. These vials will be frozen to -18 degree Celsius or lower and provided in a validated container from Canadian Blood Services that can keep them frozen for as long as 24 hours.

Storage of study drug (eye drops) at home: As the eye drops must be kept frozen (-18°C) before use, you will be required to have a freezer with appropriate temperature for storage of the eye drops. You will also be required to monitor the freezer temperature twice a day to ensure it is staying at -18ºC or lower. If the temperature of freezer gets higher than -18ºC, contact the study physician immediately.

Home (self)- Administration of eye drops: Your caregiver or parent may administer the eye drops at home. Ensure that the person administering the eye drops has washed their hands thoroughly with soap prior to handling eye drops. Before administering, the eye drops can be warmed to room temperature by rolling the bottle between the palms of your hands for about 5 minutes, or by leaving the bottle at room temperature on a clean surface away from direct sunlight for about 30 minutes prior to use. Do not heat the plasma vial (such as in a microwave or place in sunlight) to accelerating thawing.

Conditions where you must discard the eye drop dispenser/vial and report to the study doctor so a new vial may be dispensed to you:

- If particulate matter (which may appear like small flakes) is present, the bottle should be rolled between palms of one's hands for approximately 5 minutes to dissolve it. If the particulate matter persists, the product must be discarded and must not be used.
- If there is any visible damage to the bottle (e.g. cracked, leaking), the product must be discarded and must not be used.
- Once thawed, the product should be stored at room temperature (15 to 30ºC) and any unused product must be discarded 4 hours after removal from the freezer.
- All used bottles and unused/expired product must be discarded in a waste container which must be provided to the hospital for safe disposal. DO NOT place the bottles in regular trash.
- If at any stage you notice that the eye drops cause discomfort or irritation, STOP using eye drops and contact the study doctor (Dr. Sarah Tehseen, Pediatric Hematology)

WHAT ARE MY RESPONSIBILITIES?

As a study participant, you will be expected to:

- Follow the directions of the Principal Investigator
- Report all medications being taken or that you plan on taking
- Report any changes in your health (or if you experience any side effects) to the Principal Investigator
- Complete the eye drop medication diary and bring it to every visit
- Report any issues with storage and maintenance of eye drops at home to your study doctor

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

If you choose to participate in this study, there may or may not be direct benefits to you. It is hoped the information gained from this study can be used in the future to benefit other people with a similar condition.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

While on the study treatment, you may experience side effects. There may be side effects that are not known at this time.

Serious or severe adverse reactions to the plasma eye drops may include irritation, inflammation (redness, swelling, pain, and/or a feeling of heat in an area of the body) or infection (caused by germs such as bacteria, virus or fungi).

The first few (~3 to 5) eye drop administrations will be closely monitored by the study doctor and study staff in the hospital to assess for any adverse events (side effects). In case you experience any side effects at home, stop the eye drops and contact the study doctor at the earliest. The study doctor will be able to provide appropriate treatment.

Risk of contamination including surface contamination:
The plasma aliquots, when made up, do not contain any preservatives and as such there is a small chance of contamination from microorganisms/germs such as (bacteria, virus or fungi) which may cause irritation, inflammation and rarely infection arising from the use of this product. For this reason, it is extremely important that you follow the procedures outlined in the Important Information for Patients and Instructions for Use document you will receive. It is important to ensure that the person who opens and dispenses the eye drops has thoroughly washed their hands with soap prior to opening and dispensing the eye drop vial. This helps to avoid surface contamination of the eye drops.

Risk of Contaminated Plasma from Donor carried infections:
Careful donor selection and available laboratory tests do not eliminate the hazard of transmitting infectious disease agents for which testing is performed or for pathogens (organisms that can produce disease) that are either not recognized or for which there is no donor screening test. The risk of contracting viral infections from the donated plasma in the eye drops is as follows:

- Human immunodeficiency virus (HIV): 1 in 21.4 million donations
- Hepatitis C virus (HCV): 1 in 12.6 million donations
- Hepatitis B virus (HBV): 1 in 7.5 million donations
- Human T-lymphotropic virus (HTLV): 1 in 619 million donations

Blood Draw Risk:
The possible risks associated with blood drawing are pain, bleeding, fainting, bruising, infection and/or hematoma (blood clot under the skin) at the injection site.

Other Rare Risks:
You may develop a local or generalized allergic reaction with the use of plasma. This can include rash, redness and swelling of face, tongue swelling, difficulty breathing or feeling faint. If you experience any allergic symptoms, stop the use of plasma immediately and call 911.

WHAT ARE THE ALTERNATIVES TO THE STUDY TREATMENT?

You do not have to participate in this study to receive treatment for your condition. If you choose not to participate in this study, other treatment options are available to you, such as heparin (a medication is used to prevent and treat blood clots) or membrane resection (surgical removal of the abnormal growths). Your study doctor will discuss these options with you, including the risks and benefits of each option.

WHAT IF NEW INFORMATION BECOMES AVAILABLE?
During the course of this study, new information that may affect your willingness to continue to participate will be provided to you by the investigator. This includes information about newer, more effective treatments that might become available or any significant change in the risks you are exposed to from your participation in this study.

WHAT HAPPENS IF I DECIDE TO WITHDRAW?
Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. Your future medical care will not be affected.

If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment will be retained for analysis.

CAN I BE ASKED TO LEAVE THE STUDY?
The study doctor may decide to discontinue the study at any time or withdraw you from the study at any time if it is felt to be in your best interest. You may be withdrawn from the study if staying in the study would be harmful, you need treatment not allowed in the study, you fail to follow instructions or the study is cancelled by the sponsor for administrative or other reasons.

WHAT HAPPENS IF SOMETHING GOES WRONG?
In the case of a medical emergency related to the study, you should seek immediate care and, as soon as possible, notify the study doctor. Inform the medical staff you are participating in a clinical study. Necessary medical treatment will be made available at no cost to you. By signing this document, you do not waive any of your legal rights against the sponsor, investigators or anyone else.

WHAT HAPPENS AFTER COMPLETION OF THE STUDY?
You will not be able to receive the study treatment after your participation in the study is completed. If prolongation of the administration of plasma drops is required based on the Ophthalmologist assessment, the study team will determine a plan for future use. The study doctor will discuss all other future treatment options with you at the end of the study.

The results of the study will be shared with you by the study doctor after the study is complete.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT05404932). 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.

WHAT WILL THE STUDY COST ME?
You will not be charged for the study treatment or any research-related procedures. You will not be paid for participating in this study. Reimbursement for study-related expenses (e.g. travel, parking, meals) is not available.

WILL MY PARTICIPATION BE KEPT CONFIDENTIAL?
In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected.

Your study records will be identified by a unique code. They will be kept for 15 years in a secure facility. No information that discloses your identity will be released or published without your specific consent.

Some authorities have a duty to check your study and medical records to make sure all the information is correct. Your study and medical records may be inspected under the authority of the investigator or a qualified designate by representatives of the University of Saskatchewan (the study sponsor), Health Canada and the University of Saskatchewan Biomedical Research Ethics Board.

If you decide to withdraw from this study, your study and medical records will be made available to these agencies. However, they will only look at your records up to the date of your withdrawal, except where the reporting of side effects associated with the study medication is required. Rarely, your study documents may be obtained by courts of law.

You may ask the study doctor to see and copy your personal health information related to the study. You may also ask the study doctor to correct any study related information about you that is wrong.

The results of this study may be presented in a scientific meeting or published, but your identity will not be disclosed.

For your own safety, it is strongly recommended that your family physician be informed of your participation in this study. With your permission, he/she will be informed and may be consulted regarding your health and treatment.

COVID-19 CONSIDERATIONS

The research site is located under the jurisdiction of the Saskatchewan Health Authority. We are taking appropriate safety precautions to reduce the risk of spread of COVID-19 and expect you to do the same.

The researcher will keep you informed and up to date on COVID-related safety requirements and information that may affect your participation (for example, contact information and contact tracing, if applicable).

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

If you have any questions or desire further information about this study before or during participation, you can **contact Dr. Sarah Tehseen at the RUH hospital switchboard (306-655-1000 and ask for Dr. Sarah Tehseen).**

CONSENT TO PARTICIPATE

- I have read (or someone has read to me) the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I have been informed of the other treatments available for my condition.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.
- I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future medical care.
- I agree to follow the study doctor's instructions and will tell the study doctor at once if I feel I have had any unexpected or unusual symptoms.
- I have been informed there is no guarantee that this study will provide any benefits to me.
- I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.
- I understand that by signing this document I do not waive any of my legal rights.
- I will be given a signed and dated copy of this consent form.

My family physician can be informed about my participation in this study, and, if required, consulted regarding my health and treatment.

☐ Yes, you may contact my primary care physician

Physician's Name: _____

☐ No, please do not contact my primary care physician

☐ I do not have a primary care physician.

I agree to participate in this study:

_____
Participant Name (print)

_____ _____
Signature of Parent/Guardian/ Authorized Representative | Date (DD/MMM/YYYY)

_____ _____
Printed Name of Parent/Guardian/ Authorized Representative | Relationship to Participant

ASSENT

Minors who have the capability of understanding their diagnosis and consequences of the diagnosis have had the study and treatment explained to them, in the presence of their parents/legal guardians. Signed consent using this form, was obtained from the parent/legal guardian and verbal assent was obtained from the minor.

_____

Name of person conducting consent discussion (print)

_____ _____

Signature of person conducting consent discussion Date (DD/MMM/YYYY)

STATEMENT OF PERSON OBTAINING CONSENT

I have carefully explained to the participant and their parent/legal guardian the nature and purpose of the above study. The participant and their parent/legal guardian signing this form have been given enough time to review the information. There has been an opportunity to ask questions and receive answers regarding the nature, risks and benefits of participation in this research study. The participant and their parent/legal guardian appear to understand the nature and purpose of the study and the demands required of participation.

_____

Name of person conducting consent discussion (print)

_____ _____

Signature of person conducting consent discussion Date (DD/MMM/YYYY)