Study Protocol

USASK0511ST

Trial 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

Brief Title: Treatment of Ligneous Conjunctivitis in Children with Plasminogen Deficiency

Version 1 – 20 September 2022

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General Information

Trial 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
Brief Title:	Treatment of Ligneous Conjunctivitis in Children with Plasminogen Deficiency
Target Population:	Minors with Congenital Plasminogen Deficiency
Study Design:	Open-label, N of 1 trial in clinical practice setting
Anticipated Enrolment:	1
Study Duration:	24 months
Study Compound:	Aliquoted allogeneic plasma
Sponsor:	University of Saskatchewan Having a research administration office at: Clinical Trial Support Unit Room 5681, Royal University Hospital 103 Hospital Drive Saskatoon, SK, S7N 0W8
Qualified Investigator:	Sarah Tehseen, MBBS MSc. FRCPC Pediatric Hematology Assistant Professor University of Saskatchewan Telephone: 639-998-3972 Email: sarah.tehseen@saskhealthauthority.ca
Co-Investigator	Shehla Rubab, MBBS Pediatric Ophthalmology Professor University of Saskatchewan Email: rubab.sch@gmail.com
Study Site:	Jim Pattison Children's Hospital 103 Hospital Drive Saskatoon, SK S7N 0W8

Background Information

Study Population

This study will enroll one patient with recurrent ligneous conjunctivitis at University of Saskatchewan, Saskatchewan Health Authority in Saskatoon.

Congenital plasminogen deficiency is an extremely rare autosomal recessive disorder that leads to formation of extravascular fibrin rich pseudomembranes in various organ systems including central nervous system, gastrointestinal, respiratory and otopharyngeal tracts[1, 2, 3]. Conjunctival involvement in the form of recurrent woody growths underneath the eyelid (ligneous conjunctivitis) is the most common manifestation[5, 6]. The symptoms are most severe in infants and children, where it may lead to central nervous system (CNS) hydrocephalus, respiratory failure or blindness, depending on the organ system involved[3,4].

The conjunctival pseudomembranes recur after excision and show a poor response to topical steroids, cyclosporine, or autologous serum administration. These lesions can lead to conjunctival scarring, ptosis, loss of visual acuity and ultimately blindness[5,6].

Investigational Product(s)

This study will examine the use of aliquoted allogenic donor plasma as a source of plasminogen for the treatment and prevention of pseudomembranous lesions.

Plasminogen in the human blood plays a critical role in wound healing and tissue remodeling. Application of plasminogen (from allogenic plasma) at the site of pseudomembranes development will allow for appropriate wound healing, tissue remodeling and hence resolution of pseudomembranes [5, 6].

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 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.

All handling of plasma vials will be out in a sterile manner under a laminar flow biosafety cabinet. Plasma collected from the allogenic voluntary donors at CBS is tested for microbial agents that can be transferred via blood components to other people. The plasma is also tested for bacterial contamination at the time of processing. The vials are issued for use only once the bacterial cultures have shown no growth for 7 days in the BacT/ALERT 3D system and the donor has tested negative for any microbial agents that can be transmitted via blood. Until thawed, the product has an expiration date of 365 days from the date the plasma was collected.

Summary of Past Research

More than 200 cases of plasminogen deficiency have been reported in literature.[14] Plasminogen replacement (in the form of intraocular drops of plasminogen concentrate or donor plasma) has proven to be the most effective modality in preventing growth of these lesions and is required by most patients to prevent end organ damage[7-20].

Plasminogen concentrate is not an option as plasminogen concentrates are not available in Canada. There is one company that produces plasminogen concentrate in North America that is currently not supplying any products on compassionate basis and there are no open clinical trials. Another company (Kedrion) produces it in Italy though it is also not providing on compassionate basis. It is significantly cost prohibitive. Cost: 2800 Euros per ml of concentrate. The product needs to be applied to affected conjunctiva 3-8 times per day for ~3-12 months.

Heparin Therapy alone: Case report data shows utilization of Heparin therapy alone for ligneous conjunctivitis in children which led to orbital inflammation and cellulitis with only partial control of lesion[2].

Sustained control of these lesions has only been achieved with administration of plasminogen (Intravenous [IV]/local) or plasma (as a source of plasminogen) alone or in conjunction with other therapies (such as membrane resection, heparin etc.)[7-13, 15-20].

Risk and Benefits

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.

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. 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

Other Rare Risks:
Participants 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.

Potential for efficacy in the patient considered (analogous human data):
Multiple reports in literature indicate the efficacy of plasma application to affected conjunctiva in preventing recurrence of these lesions. Discussions with experts has also indicated the same.

Study Drug Administration

Drug Formulation/Special instructions for use:
Allogenic plasma will be collected from ABO (blood type) compatible, cytomegalovirus (CMV) compatible, volunteer donors at Canadian Blood Services collecting facilities. Standard transfusion-based investigations (including infectious disease testing for transmissible microbes) will be conducted per collection facility protocols. Bacterial culture will be performed on collected plasma specimen at the time of bottling. The plasma will only be issued once the culture has been confirmed negative, after an incubation time of 7 days in the BacT/ALERT 3D system. It will then be aliquoted into 3 ml aliquots and placed in 7 ml vials/bottles. The vials will be frozen at -18 degree Celsius or lower temperature. These frozen components will be supplied to the administration facility transfusion medicine laboratory.

To administer, the vial/bottle should be warmed to room temperature (15-30 degree Celsius) by rolling vial or bottle between the palms of one's hands for approximately 5 minutes. Alternately, the bottle may be thawed by leaving it at room temperature for approximately 30 minutes with inversion (tipping up and down) of the bottle periodically. Any bottles/vials that are damaged must be discarded[13].

The first few administrations will occur under staff and nursing supervision in the outpatient clinic. The remainder of frozen aliquots will be provided to the patient/family, who will be advised to store at appropriate environment conditions and taught the process for thawing and administration. The patient/family will thaw and administer it.

Frozen allogenic plasma aliquots can be used for 365 days from the time of collection of plasma. After thawing, the bottles/vials can be used for up to four hours and then must be discarded to reduce the risk of infection.

The plasma aliquots, when made up, do not contain any preservatives and as such there is a small chance of bacterial contamination which may cause irritation, inflammation and rarely infection arising from the use of this product. For this reason, it is extremely important that the patient follows the procedures outlined in the Important Information for Patients and Instructions for Use document they will receive with the plasma aliquots[13].

Dose
1-2 drops (0.5-2.5 mL) of aliquoted donor plasma will be applied to the affected eye every 1-5 hours per day daily at maximum. The administration of plasma drops can change in frequency based on the clinical assessment of ligneous conjunctivitis and response to therapy.

Administration period
Two to Six months. The treatment may be repeated based on clinical assessment and response.

Compliance Statement
This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

Trial Objectives and Purpose

This study has 2 aims:

1. Determine safety of topical administration of aliquoted allogeneic plasma to the affected eye.
2. Determine efficacy of topical administration of aliquoted allogenic plasma.

Trial Design

Study Endpoints

1. Safety will be assessed by direct clinical monitoring of patient during initial 5 intra-ocular plasma administrations and communicating with the patient and family at least on a weekly basis while receiving intra-ocular plasma.
2. Efficacy will be assessed by clinical ophthalmologic examination of patient on a frequent basis to determine:
    a. Degree of change in size of pseudomembranous lesions
    b. Time (time required as no. of days) to change in size of pseudomembranous lesions by 50%.
    c. Assessment of visual acuity, strabismus and other defects in the affected eye
    d. Development of recurrence of pseudomembranous lesions after surgical excision and intra-ocular plasma administration

Design of Trial

This is an open-label, N of 1 trial in a clinical practice setting. The study involves the following visits:

Screening Visit

1. Medical History
2. Physical Examination including Ophthalmologic examination
3. Laboratory evaluation (blood group [ABO, RhD] and an antibody screen)

Study Visits

1. Daily for first five days of plasma drops administration for:
    a. Administration by study nurse
    b. Monitoring for adverse events
    c. Teaching family/patient to administer drops
2. Every week for first 6 weeks for eye examination for:
    a. Physical Examination including limited Ophthalmologic examination
    b. Monitoring for adverse events
3. This will be followed by visits every 3-6 months and will include:
    a. History
    b. Physical Examination
    c. Monitoring for adverse events
    d. Ophthalmologic examination

Primary Outcome Measures

1. Mean difference in the size of pseudomembranous conjunctival lesion after 2 months of local administration of aliquoted plasma (reported as mean difference and percent difference from pre-administration size of pseudomembranous lesions)
    a. The size of pseudomembranous lesions will be measured before intervention and after 4 weeks of topical administration of aliquoted plasma in patient's conjunctiva (with/without surgical excision) 8 weeks of topical administration of plasma (with/without surgical excision). This size will be compared to the size of pseudomembranes prior to intervention. The results will be reported as mean difference and percent.
2. Time to change in the size of pseudomembranous lesions by 50% or greater with topical administration of aliquoted allogenic plasma in the affected conjunctiva.
    a. The presence and size of pseudomembranous lesions on the patient's conjunctiva will be assessed via ophthalmologic examination every 2-7 days for first 2 months of topical application of aliquoted plasma in affected conjunctiva. The ophthalmologic assessment will then occur at increasing intervals based on the response of patient's ligneous conjunctivitis (pseudomembranous lesions) to this therapy.
    b. Time interval to the outcome measure (change in size of pseudomembranes) will be reported as number of days from the start of administration of aliquoted plasma.
3. Difference in the visual acuity of affected eye after topical administration of aliquoted allogenic plasma into affected conjunctiva.
    a. The visual acuity in the affected eye will be assessed via ophthalmologic assessment using age-appropriate measures before intervention and on a periodic basis after the start of intervention. The difference in visual acuity before and after intervention will be reported as percent difference.
4. Number of participants with development of strabismus or other visual defects in affected eye.
    a. Assessed via clinical ophthalmologic assessment on a periodic basis after start of administration of aliquoted plasma in patient's conjunctiva.

Secondary Outcome Measures

1. Number of participants with recurrence of pseudomembranous lesions.
2. Time to development of recurrence of pseudomembranous lesions in the eye undergoing intervention.
    a. The time interval to development of recurrence of pseudomembranous lesions will be measured after complete resolution of pseudomembranes in affected eye.
    b. Time interval will be reported as number of days since complete resolution of pseudomembranes

Measures Taken to Minimize/Avoid Bias

Not applicable. Randomization and blinding are not applicable to an n of 1 trial.

Trial Treatments

The allogenic plasma will be aliquoted into 3 ml aliquots and placed in 7 ml vials/bottles. The vials will be frozen at -18 degree Celsius or lower temperature. To administer, the vial/bottle will be warmed to room temperature (15-30 degree Celsius). 1-2 drops of aliquoted donor plasma will be administered to

the affected eye every 1-5 hours per day daily at maximum. The administration of plasma drops can change in frequency based on the clinical assessment of ligneous conjunctivitis and response to therapy.

The vial label will include the following details:

Plasma-3 ml Aliquot
Batch: XXXXXXX
Expiration Date: XXXX-XX-XX
Keep frozen until use. Once removed from freezer keep for a maximum of 4 hrs at room temperature.
Canadian Blood Services

Duration of Study Participation

The treatment administration period will be 2 to 6 months. The duration of study participation, including follow-up, will be approximately 24 months.

Stopping Rules and Discontinuation Criteria

Criteria for discontinuation

- Patient does not want to continue the study
- Patient has a significant adverse reaction to plasma drops
- Patient has no response to therapy after 6 months of intervention. This is defined as:
  - No change in the size of pseudomembranes after 6 months of topical allogenic plasma administration performed according to recommendations (with/without surgical excision)
  - Increase in the size of pseudomembranous lesions despite recommended use of aliquoted allogenic plasma
  - Development of new pseudomembranous lesions in the eye receiving topical allogenic plasma
- More effective therapies (liquid plasminogen concentrate IV/Intra-ocular) become available in Canada
- Plasma drops can no longer be provided

Investigational Product Accountability

The dose and amount of investigational product (IP) dispensed, as well as the date and time, will be recorded on a drug accountability log. When the participant returns for their subsequent visit, they will return all empty vials of IP, as well as any unused IP. The amount of IP returned, as well as the date and time, will be recorded on the drug accountability log.

Trial Treatment Randomization Codes

Not applicable. As this is an n of 1 study, randomization will not occur.

Source Data

The following data will be collected for this study:

- Size of pseudomembranous conjunctival lesion
- Visual acuity of the affected eye
- Development of strabismus or other visual defects in affected eye

- Medical history
- Physical exam
- Blood group (ABO, RhD) and antibody screen results
- Details of any adverse events

All data will be collected on the data collection form. The participant's medical record will be considered to be a source document for the medical history. The lab report will be considered the source document for the lab tests.

Selection and Withdrawal of Participants

Inclusion Criteria

- Patients under the age of 18 years
- Diagnosis of plasminogen deficiency (Definition: clinical presence of pseudomembranous lesions and serum plasminogen level < 50%)
- Ocular involvement (Ligneous Conjunctivitis) due to plasminogen deficiency

Exclusion Criteria

- Patient is 18 years or older
- Patients with no plasminogen deficiency
- Patients with no ocular manifestations of plasminogen deficiency

Withdrawal Criteria

The Investigator may choose to discontinue the study at any time or withdraw a participant from the study at any time if it is felt to be in the participant's best interest. A participant may be withdrawn from the study if the participant develops a serious adverse event, needs treatment not allowed in the study or fails to follow instructions.

Participants who withdraw, or who are withdrawn, during treatment will be asked to return for an end of study visit, for their safety.

If a participant chooses to enter the study and decides to withdraw at a later time, all the data collected about the participant during his/her enrollment will be retained for analysis.

Participants withdrawn from the study will not be replaced and will be included in the total of 1 participant.

Treatment of Participants

Treatment Administration

The allogenic plasma will be aliquoted into 3 ml aliquots and placed in 7 ml vials/bottles. The vials will be frozen at -18 degree Celsius or lower temperature. To administer, the vial/bottle will be warmed to room temperature (15-30 degree Celsius). 1-2 drops of aliquoted donor plasma will be administered to the affected eye every 1-5 hours per day daily at maximum. The administration of plasma drops can change in frequency based on the clinical assessment of ligneous conjunctivitis and response to therapy.

The participant will undergo daily study visits for the first 5 days, weekly study visits for the first 6 weeks and then study visits every 3-6 months until the end of 24 months.

Other Medications/Treatments

Medication(s)/treatment(s) permitted (including rescue medication) before and/or during the trial:

- Surgical excision of the pseudomembranes per ophthalmology discretion with plasma administration is permitted.
- Use of other topical/ocular therapies such as topical heparin, steroids, cyclosporine etc. will be permitted.

Medication(s)/treatment(s) NOT permitted before and/or during the trial:

- N/A

Monitoring of Participant Compliance

Participant compliance will be assessed by maintaining adequate drug dispensing logs and return records. Participants will be asked to return all unused study drug in the provided container at each visit as a measure of drug accountability and patient compliance.

Assessment of Efficacy

Efficacy parameters include:

- Mean difference in the size of pseudomembranous conjunctival lesion after 2 months of local administration of aliquoted plasma (reported as mean difference and percent difference from pre-administration size of pseudomembranous lesions)
- Time to change in the size of pseudomembranous lesions by 50% or greater with topical administration of aliquoted allogenic plasma in the affected conjunctiva.
- Difference in the visual acuity of affected eye after topical administration of aliquoted allogenic plasma into affected conjunctiva.
- Number of participants with development of strabismus or other visual defects in affected eye
- Number of participants with recurrence of pseudomembranous lesions
- Time to development of recurrence of pseudomembranous lesions in the eye undergoing intervention.

Assessment of Safety

Safety Parameters

Safety Parameters include:

- Direct clinical monitoring of patient during initial 5 intra-ocular plasma administrations
- Communication with the patient and family at least on a weekly basis while receiving intra-ocular plasma.
- Source plasma collected from donors who are negative for transfusion transmissible infections
- Source plasma cultured before release to facility to ensure no bacterial contamination
- Clear guidance to parents about situations where plasma administration should be stopped, and clinical care accessed.

- Communication to the pediatric hematology service available 24/7 in case of any issues with plasma administration
- Close liaison with pediatric ophthalmologist who will also monitor response and potential complications

Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Events

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form, or was allowed to continue, might have caused death
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The investigator will seek information on adverse events at each participant contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded.

During and following a patient's participation in a trial, the investigator will ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator will inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

Adverse events will be reported to Health Canada as per Health Canada regulations, and to the Research Ethics Board (REB) as per local REB requirements.

Anticipated adverse events and Risk mitigation:

1. Loss of patient privacy and confidentiality:
    a. All patient information will be recorded in hospital electronic medical record systems which have adequate protections in place to prevent unauthorized spread of patient information.
    b. The data collected for clinical trial will be maintained in University Operated Redcap which will be password protected and have access limited to the study personnel.
2. Serious or severe adverse reaction to topical applications of aliquoted plasma (irritation, inflammation, infection etc.)

a. Initial few (~3-5) topical administrations will be closely monitored in the hospital to assess for any adverse events with nursing and physician oversight.
b. Patient/Family will be permitted to use the topical plasma independently at home only after 3-5 administrations have been monitored in hospital, parents are comfortable with storage and administration process and adverse events have been managed appropriately.
c. In case of any adverse event such as irritation or inflammation etc. patient/family will be able to contact the responsible physician or their service at any time. Appropriate treatment strategies will be undertaken immediately for such events. Processes will be developed to prevent the adverse event from occurring in future if therapy can be continued and the event is non-fatal and non-life/limb threatening. All adverse events will be reported to the manufacturer (Canadian Blood Services).

Statistics

Statistical Methods

Descriptive statistics for categorical and continuous variables will be used based on data points obtained and their distribution. Paired T test (or equivalent non-parametric test) will be used to determine difference in baseline and post intervention plasminogen levels at 4 weeks, 2 months, 3 months, 6 months till 24 months. A p-value of 0.05 will be considered significant. All data analyses will be conducted in Statistical software SAS version 9.4.

Planned Participant Enrollment

One patient and 3 family members will be enrolled in this study currently. The rationale is that this is an extremely rare disorder with less than 5 patients in entire Canada and only one known patient in Saskatchewan.

Trial Termination

The principal investigator reserves the right to terminate the study at any time. The principal investigator also reserves the right to terminate the entire study or temporarily interrupt enrolment and/or treatment of already enrolled patients.

It is not expected that the trial will be terminated prematurely; however, this could happen due to safety reasons or at the request of a regulatory agency. Otherwise, the trial will be complete once data has been collected on the expected study participant.

Should a termination of the whole study become necessary, then adequate procedures will be arranged after careful consideration and communicated to all involved parties. In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the patient's interests. The REB and Health Canada will be notified of premature termination in accordance with applicable regulatory requirements.

Data Accountability

Missing values will not be substituted by estimated values but will be treated as missing in the statistical evaluation. All data from patients randomised in the study will be included in all listings, plots, summary tables, and statistical analyses.

Direct Access to Source Data/Documents

The Investigator acknowledges that some authorities have a duty to monitor the study records to make sure all the information is correct. The study records may be inspected under the authority of the investigator or a qualified designate by representatives of Health Canada or the Research Ethics Board (REB), as necessary.

Quality Control and Quality Assurance Procedures

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 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.

All handling of plasma vials will be out in a sterile manner under a laminar flow biosafety cabinet. Plasma collected from the allogenic voluntary donors at CBS is tested for microbial agents that can be transferred via blood components to other people. The plasma is also tested for bacterial contamination at the time of processing. The vials are issued for use only once the bacterial cultures have shown no growth for 7 days in the BacT/ALERT 3D system and the donor has tested negative for any microbial agents that can be transmitted via blood. Until thawed, the product has an expiration date of 365 days from the date the plasma was collected.

The Investigator is responsible for ensuring participant data relating to the study is recorded on the data collection tool, and for verifying that the data entries are accurate and correct. The Investigator is also responsible for maintaining accurate source documentation that supports the information entered on the data collection tool. Lastly, the Investigator is responsible for permitting study-related monitoring, REB review and regulatory inspections by providing direct access to source data and other relevant study documents.

Ethics

The Investigator will ensure that this study is conducted in full compliance with the principles of the Declaration of Helsinki and with the laws and regulations in Canada. This clinical study will be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice.

This study was submitted to the local REB and an approval exemption was subsequently received.

Data Handling and Record Keeping

All information collected on the data collection form will be identified by a unique study number and the participant's initials. No other personal identifiers will be recorded. All measures will be taken to maintain confidentiality on collected data, however there is a chance of unintentional release of information connecting the participant with the study. A list connecting the participant's name to the participant study number listed on the data collection form will be stored on a password protected computer and access to this list will be limited to study staff.

Data will be stored for 15 years, as per the Health Canada requirements. The Investigator is responsible to archive the documents/data for the required period of time.

Financing and Insurance

This study is currently unfunded.

The liability insurance policies maintained by the University of Saskatchewan, through the Canadian Universities Reciprocal Insurance Exchange (CURIE) include a General Liability Policy and an Educational Institutions Errors and Omissions Liability Policy (both are subject to numerous conditions, exclusions and terms). Physicians have insurance coverage through their CMPA (Canadian Medical Protective Association).

Publication Policy

The key design elements of this protocol will be posted on clinicaltrials.gov. Upon study completion, the results of this trial will be submitted for publication and/or posted on clinicaltrials.gov (NCT05404932). The results of this study may be presented in a scientific meeting or published, but the identities of the participants will not be disclosed.

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Appendix 1 – Schedule of Events

Procedures/Visit	Screening (Visit 1) Day 1	Visits 2 to 6 Daily for 1st 5 Days of Treatment	Visits 7 to 12 Weekly for 1st 6 Weeks of Treatment	Visits 13+ 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