Mass General Brigham

Research Consent Form
General Consent Form Template
Version Date: February 2021

Subject Identification

Protocol Title: Safety and Feasibility of Cultivated Autologous Limbal Epithelial Cell Transplantation in the Treatment of Limbal Stem Cell Deficiency

Principal Investigator: Ula Jurkunas, MD

Site Principal Investigator:

Description of Subject Population: Adults with Limbal Stem Cell Deficiency in one eye

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Key Information

This consent form is being given to you because you are enrolled in the CALEC study at Mass Eye and Ear, and you now have options regarding the additional corneal surgical treatment you can receive as part of that study. As explained in detail below, you can elect to have a standard transplant known as conjunctival limbal autograft (CLAU), a second CALEC transplant, or you may elect to receive no further procedures. The decision is up to you. You can decide not to have any additional interventions. If you decide to have a CLAU or second CALEC procedure now, you can change your mind and withdraw your consent later. Your decision won't change the medical care you receive within Mass General Brigham now or in the future.

The following key information is to help you decide whether or not to have an additional transplant procedure. We have included more details about the research in the Detailed Information section that follows the key information.

Why is this research study being done?

This research study is being conducted to assess the safety and feasibility of an investigational limbal stem cell transplant for participants with limbal stem cell deficiency (LSCD) in one eye. The investigational transplant is formally referred to as a cultivated autologous limbal epithelial cell (CALEC) graft.

How long will you continue to take part in this research study?

Your current enrollment in the study involves an 18-month follow-up after your initial CALEC surgery. If you elect not to have an additional transplant, your study participation will end with the 18-month follow-up visit. If you decide to have either a CLAU transplant or a second CALEC transplant, your time in the study will continue until the study closes. This will be no more than one year from the time of the second transplant. The follow-up may be longer if Dr. Jurkunas determines that an extension of the follow-up time would be appropriate, but additional visits will be part of usual care outside of the study. After the transplant, you would be asked to return to Mass Eye and Ear for a minimum of four visits.

What will happen if you continue to take part in this research study?

If you decide to have a CLAU transplant, the biopsy and the transplant will occur during the same surgery. If you elect to have a second CALEC transplant, it will be done the same way it was done for your prior transplant: you will have a biopsy and approximately three weeks later you will have the CALEC transplant. The follow-up time for both procedures will be the same, which is no more than one year from the time of the second transplant.

If you elect not to have another procedure, your participation in the study will end at the 18-month follow-up visit after your initial transplant.

Why might you choose to have another transplant procedure?

We cannot promise any benefits to you from taking part in this research study, or from having an additional transplant. However, you should know that CLAU is the current standard of care for your condition, limbal stem cell deficiency, and it is known to provide benefit. However, CLAU involves removing more tissue from the healthy eye than does CALEC. On the other hand, CALEC involves presumably lower risk to the healthy eye because less tissue is removed (compared to CLAU), but we do not know if it has benefit. Before you make your choice about having an additional CALEC procedure or a CLAU procedure, please ask the study doctor if you

have any questions or would like to discuss either procedure and the associated risks and benefits.

Others with limbal stem cell deficiency may benefit in the future from what we learn in this study regarding the outcomes from second CALEC transplants.

Why might you choose NOT to take part in this study?

Electing to have another transplant has some risks and requirements that you should consider carefully.

Important risks and possible discomforts to know about include swelling, irritation, redness, inflammation, or infection in your eyes. You may also experience corneal scarring, thinning or bleeding. A detailed description of side effects, risks, and possible discomforts from having either a CLAU transplant or a second CALEC transplant can be found later in this consent form under the section "What are the risks and possible discomforts from being in this research study?"

What other treatments or procedures are available for your condition?

If you choose not to have another transplant procedure now, you may still receive the standard of care treatment, (CLAU) at MEE or at another institution at another time. In addition, other surgical interventions may be available to you, such as limbal allograft from another person or a cadaveric eye or placement of an artificial cornea (keratoprosthesis). Reconstruction with amniotic membrane also could be determined by your doctor to be a viable treatment option.

If you have questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

The sponsor/investigator, **Dr. Ula Jurkunas** at MEE is the person in charge of this research study. You can call her at 617-573-6897 **Monday to Friday from 8:00 AM to 5:00 PM.**

If you have questions about the scheduling of appointments or study visits, call **Stacey Ellender at 857-231-1593.**

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study

Detailed Information

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

Why is this research study being done?

This research study is being conducted to assess the safety and feasibility of an investigational limbal stem cell transplant for participants with limbal stem cell deficiency (LSCD) in one eye. The investigational transplant is formally referred to as a cultivated autologous limbal epithelial cell (CALEC) graft. This graft has been developed because it may provide therapeutic benefit for people with LSCD.

You already have had a CALEC graft, but we have noted that the cornea in your eye with the graft has a new defect (like a scratch), and that new blood vessels are growing into the cornea, reducing its transparency. This condition may make you eligible to receive a second transplant—either a CALEC graft or another kind of graft, CLAU, that is the standard of care for limbal stem cell deficiency. We can determine your eligibility for a second graft by assessing the size and the persistency of your corneal defect and the extent and location of your new corneal blood vessels.

Limbal stem cells are cells that help maintain the barrier between the cornea (the clear, centrally-located outermost layer of your eye) and the conjunctiva (the white areas on the sides of your eye). When limbal stem cells are absent or not functioning properly, the conjunctiva may grow over the cornea, causing vision loss. The current standard of care for LSCD in one eye is conjunctival limbal autograft (CLAU). The CLAU procedure takes cells from the eye without LSCD and transplants them to the eye with LSCD in the same operation. The investigational CALEC graft is similar to CLAU, but different in some significant ways. During CALEC, a

small amount of cells is taken from the healthy eye and transported to the laboratory where they are grown for a few weeks. After adequate growth, they are grafted into the eye that has LSCD.

CALEC is not approved by the U.S. Food and Drug Administration (FDA). This means that **CALEC** can only be used in research studies. This study is funded by the National Eye Institute.

Who will have the option of having a second transplant procedure?

You are being offered the option of having a second transplant—either a CLAU transplant or a second CALEC transplant—because your eye with the CALEC graft was determined to have a persistent epithelial defect (a scratch of the cornea) and corneal neovascularization (blood vessels growing into the cornea) after the initial CALEC transplant procedure, and the principal investigator on this study, Dr. Ula Jurkunas, has assessed that an additional stem cell transplant might have some therapeutic benefit. The second transplant can only take place after completing 12-months of follow-up after the initial CALEC transplant procedure. We will offer the second transplant option as a limited part of the study to eligible participants up until three participants have selected to have a second transplant. After the third transplant, the second transplant phase will close.

What will happen in this research study?

It may take you an additional four to six months to have a CLAU or CALEC transplant.

If you have the standard of care treatment, a **CLAU** transplant, you will have the following visits, each lasting two to three hours:

- A combined Screening and Baseline visit
- Pre-op visit
- CLAU surgery
- 1-day post-operative visit
- 1-week post-operative visit
- 2-week post-operative visit
- 1 month post-operative visit

You may also have the following visits, which will occur up until the study closeout date (expected March 2023).

- 3 month post-operative visit
- 6 month post-operative visit
- 9 month post-operative visit
- 12 month post-operative visit

If you have a second **CALEC** transplant you will have the following visits, each lasting two to three hours:

- A combined Screening and Baseline visit
- Biopsy
- 1-day post-biopsy visit
- Pre-operative visit
- CALEC surgery
- 1-day post-operative visit
- 1-week post-operative visit
- 2-week post-operative visit
- 1 month post-operative visit

You may also have the following visits, which will occur up until the study closeout date (expected March 2023).

- 3 month post-operative visit
- 6 month post-operative visit
- 9 month post-operative visit
- 12 month post-operative visit

Combined Screening/Baseline Visit

You will undergo a combined screening and baseline visit where we will collect updated information about you to determine your eligibility for a second transplant. The following evaluations and procedures will be performed during the baseline visit on both eyes:

- Pre-operative health screening: You will also be asked to complete some additional health screening that is standard for the MEE. Assessments will include past medical, social, and family history and a review of your general health prior to surgery. If you are age 50 years or older or have a history of diabetes or cardiac problems an Electrocardiogram (EKG) test may be required. The EKG is a noninvasive test that is used to reflect underlying heart conditions by measuring the electrical activity of your heart.
- Blood collection: Your blood will be drawn at screening (and before biopsy if you are to receive the second CALEC transplant) to test for Hepatitis B, Hepatitis C, HIV or AIDS. Your blood draw may be performed for autologous serum eye drops (tears made from your blood) at this visit or any visit prior to surgery. The tears made from your blood have nutrients and growth factors that facilitate tissue healing and will be used after transplants. They will be purified from your own blood in a regulated and sterile process at MEE.
- Slit lamp examination: Both of your eyes will be examined by a physician looking through a magnifying lens with an adjustable light. The physician will determine your corneal opacification, which is how clear or “foggy” your eyes appear. You will receive

fluorescein staining in your eyes, an orange-yellow dye (fluorescein) to look for any defects on the outer surface of your eye.

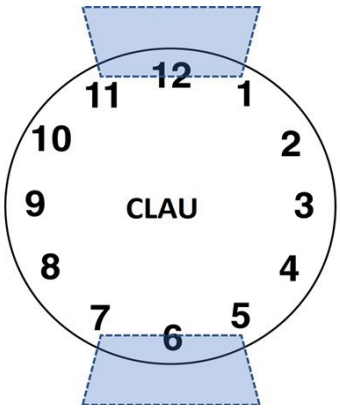
- Visual acuity: Your vision will be assessed by a visual acuity chart with appropriate corrective lenses and you will be asked to read the chart of letters during the exam.
- Conjunctival swab and culture: Cells from the conjunctiva and eye lid will be collected using a moistened swab and then the cells will be grown to determine if any microbes are present.
- Intraocular pressure: The pressure in both of your eyes will be measured with a puff of air, or you will be given eye drops to numb your eyes, and then the study doctor will touch an instrument to each eye. In the week after biopsy (only applies to second CALEC) and in the 13 weeks after transplant, the pressure in your eyes may be estimated by your physician lightly touching your eye lid.
- Slit lamp photographs: Digital photography will be performed using a slit lamp with a digital camera attachment and a flash-through-the-slit illumination system. The entire cornea will be pictured. If your lids are drooping, the photographer will attempt to gently lift them from area of focus with a cotton swab. If you have dark eyes, they may be dilated with a dilating drop to enhance visualization of blood vessels in your eye.
- Anterior Segment-Optical Coherence Tomography: Anterior Segment-Optical Coherence Tomography (AS-OCT) will be performed on both eyes. AS-OCT takes images of the front of your eye and does not touch your eye. If your lids are drooping, the photographer will attempt to gently lift them from area of focus with a cotton swab. Unlike digital photography, these images allow your physician to look at detailed cross-sections of the front of your eye.
- In-Vivo Confocal Microscopy: In-vivo confocal microscopy (IVCM) takes images of the front of your eye and allows the physician to view different cellular layers. IVCM will be performed on both eyes. You will be given eye drops to numb your eyes, and then the photographer will gently touch your eye with the lens of the instrument. If your lids are drooping, the photographer will attempt to gently lift them from area of focus with a cotton swab.
- Symptom assessment: You will complete two surveys to assess the symptoms of your eyes (Ocular Surface Disease Index (OSDI) and Symptom Assessment iN Dry Eye (SANDE) questionnaires).
- Dilated fundoscopy or B-scan ultrasound: The inside and back of both your eyes will be examined using either an ophthalmoscope (a small flashlight) or a B-scan instrument using high frequency sound waves (ultrasound) to visualize anatomic structures in your eyes. To better examine the eyes, your physician may administer pupil-dilating drops.

If you are still eligible after the baseline visit, your surgery will be scheduled.

A summary of each surgical procedure is described below.

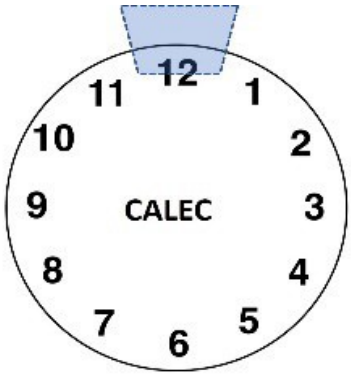
Surgical Procedure:

Conjunctival limbal autograft (CLAU)
The CLAU surgery will involve many steps, including numbing and sterilizing both of your eyes, removing diseased tissue from your affected eye, and taking a biopsy (tissue sample) from your healthy eye. The biopsy (tissue sample) from your healthy eye will include taking two pieces of limbal tissue each measuring approximately 6 mm or 0.23 inches (each piece is about1/6 of the corneal circumference) from the healthy eye and then transplanting them to your affected eye (the eye with LSCD). In the image below, the shaded area represents the approximate size of the material obtained in the CLAU biopsy procedure. Please note that the material removed includes both tissue from the cornea (inside the circle) and the conjunctiva (outside the circle.) The actual location of the tissue removed will be determined by the surgeon. The biopsy and transplantation procedures are performed within the same surgery.



Cultivated Autologous Limbal Epithelial Cell (CALEC)
The CALEC surgery will be performed over two visits to MEE. The first surgery will involve many steps, including numbing and sterilizing your healthy eye. The biopsy (tissue sample) from your healthy eye will include taking one piece of limbal tissue measuring approximately 3 mm or 0.1 inch (about 1/12 of the corneal circumference). In the image below, the shaded area represents the approximate size of the material obtained in the CALEC biopsy procedure. Please note that the material removed includes both tissue from the cornea (inside the circle) and the conjunctiva (outside the circle.) The actual location of the tissue removed will be determined by the surgeon. The biopsy will be transported to the Dana-Farber Cancer Institute for construction of the experimental CALEC graft. The graft will consist of cells taken from your biopsied tissue. Your cells will be grown on an AmnioGraft®, an amniotic membrane (the inner lining of the

placenta) that is used routinely in eye care to promote tissue healing and replacement. The time between biopsy and the follow-up transplant will be approximately 10 to 30 days. The transplantation (second) surgery will involve many steps, including numbing and sterilizing your affected eye, removing scarred tissue, and transplanting the CALEC to your affected eye (the eye with LSCD).



<u>Follow-up Visits and Post-Operative Medications (all participants after corneal reconstruction):</u>

We will perform the same assessments at the follow-up visits after the second transplant that we performed with the initial transplant. Follow-up visits would continue up until the 12 month post-second transplant visit or until the study ends, whichever comes first. We anticipate that the study will end in March 2023.

For a full listing of study procedures and visits, please see the tables below on pages 25 and 26.

<u>Bandage contact lens (BCL):</u> Following surgery, you may be required to wear a contact lens on the eye that receives the transplant. The BCL is a special type of contact lens that will add an extra layer of protection for your eye. These may be applied after the biopsy procedure as well.

You will also be prescribed post-operative medications. These medications will prevent infection, help the eyes to heal, and help keep the eye with the bandage contact lens comfortable.

The medications you may be prescribed include:

- Fluoroquinolone is a class of antibiotic prescribed to prevent infection.
- Vancomycin is another antibiotic prescribed in this study for treatment of MRSA.

- Topical corticosteroids are prescribed to reduce inflammation and relieve swelling, redness, and itching.
- Autologous serum eye drops (tears made from your blood) are made from blood serum and contain diluted concentrations of vitamins and growth factors that are important for corneal epithelial health.
- Artificial tears are specially formulated to moisten the eyes and are used to relieve burning, irritation, and discomfort.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- Your cells do not grow sufficiently to be used in a CALEC graft
- The study doctor thinks it is best for you to stop participating in the study
- You can't make the required study visits
- The sponsor/investigator decides to stop the study
- We stop doing the study for other reasons
- The funder stops funding the research

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit as described above.

Review of Medical Records from Hospital Admissions or Emergency Department Visits

Mass General Brigham has an electronic system that lets your study doctors know if you are admitted to a Mass General Brigham Hospital, or if you visit a Mass General Brigham hospital Emergency Department. We want to make sure the study doctors know about any possible problems or side-effects you experience while you are taking part in the study.

Study Information Included in Your Electronic Medical Record

A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example: list of allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

Sending Study Information to Research Collaborators Outside Mass General Brigham

We will send your study information and specimen to researchers working with us at the Cell Manufacturing Core Facility at Dana Farber. We will label your specimen with your name, date

of birth and medical record number, which will be retained with your specimen while it is at CMCF until it is brought back to MEE for transplant.

How may we use and share your samples and health information for other research?

There are no plans to share your samples and health information for other research.

What are the risks and possible discomforts from being in this research study?

Intraocular Pressure Exam
The intraocular pressure exam may cause irritation to the surface of the eye or blurred vision. Some people report experiencing blurred vision and eye discomfort for up to 24 hours after this exam has been performed.

In-Vivo Confocal Microscopy (IVCM)
There is a risk that your cornea may be scratched or irritated by the IVCM procedure.

Study Dye (Fluorescein Staining)
The dye may make your tears or mucous change color, or they may cause some irritation to your eyes. This effect is usually temporary and disappears within a day.

Numbing Medicine
Numbing medicine may cause a stinging sensation when the drop is first applied to the eye. This sensation usually lasts a few seconds. Depending on the sensitivity of the person, the eye may appear red after the drop is applied. Your study doctor will explain the potential side effects prior to your eyes being numbed.

Conjunctival Swab
There is a risk that you might experience a scratched corneal during the conjunctival swab procedure. This risk is considered to be very rare.

Blood Draws
Blood sampling may result in bruising, pain, or redness of the skin. You may feel lightheaded or faint. Rarely, there may be a small blood clot or infection at the site of the needle puncture.

Fluoroquinolone
Your eye may experience burning, stinging, sensitivity to light, lid crusting/edema/swelling, hyperemia/redness, and tearing. You may also have gastrointestinal disturbance, taste disturbance, neurological disturbance, nausea, or headaches.

Vancomycin
Similar to those of Fluoroquinolone.

Topical steroid
You may experience stinging or burning of the eyes, blurry vision, eye pain, headache, or dizziness.

Autologous Serum Eye Drops (tears made from your blood)
There is the possibility of contamination if not handled properly. Be sure to wash your hands with warm soapy water before handling the bottle and applying to your eye. Store the eye drops as directed.

Artificial Tears
You may experience mild eye burning or irritation, itching or redness of your eyes, watery eyes, blurred vision, or unpleasant taste in your mouth.

Dilation Drops
Your pupils will be dilated for this study. You may expect to experience the following:

- Blurred vision for 4-6 hours
- Sensitivity to bright light until the drops wear off (4-6 hours)

We recommend having someone drive you to and from the study visit. We will give you sunglasses to wear on the way home to reduce discomfort from the bright light.
There is a very rare chance of the eye drops closing off the area of the eye that allows fluid inside the eye to drain (acute angle-closure glaucoma). Acute angle closure would occur within the first 24 hours after we put the eye drops in your eyes. If this happens, you might experience sudden eye pain. It is important to contact your doctor or visit the emergency room if you experience sudden eye pain.

<u>Risks and possible discomforts from having a CLAU Transplant</u>
CLAU transplantation is the standard of care for LSCD in one eye and risks are not specifically related to this study. Potential risks of CLAU are related to the surgical risks and to the inability of the CLAU graft to heal the eye surface and improve your vision. The likelihood that any of these potential complications will occur is approximately 11%. Your treating physician will provide medical care for any events caused by your participation in the study.
Specifically, some of the risks to the eye receiving the transplantation in CLAU include:

- Subconjunctival hemorrhage (transient surface bleeding)
- Chemosis (swelling of conjunctiva)
- Conjunctival inflammation

- Conjunctival epithelial defect (scratch of the conjunctiva)
- Conjunctival hyperemia (redness)
- Pyogenic granuloma (a fleshy bump on the eye surface)
- Suture dehiscence (broken or loose sutures)
- Suture abscess (infected stitches)
- Corneal epithelial defect (scratch of the cornea)
- Punctate epithelial erosion or dry eyes
- Dellen (irregularity of the surface)
- Corneal opacity or corneal scarring (cornea is not clear or hazy)
- Corneal thinning
- Corneal edema (swelling)
- Corneal intrastromal hemorrhage (Bleeding within the cornea)
- Corneal neovascularization (Blood vessels growing into the cornea)
- Filamentary keratitis (fine filaments attached to eye surface)
- Graft edema (swelling)
- Pannus (neovascularization, abnormal peripheral blood vessels)
- Exposure keratopathy (eyelids not closing properly)
- Corneal perforation (hole in the cornea)
- Ocular infection
- Ocular inflammation (Eye redness and swelling)
- Graft detachment (loosening or dislocation of the graft)
- Graft failure

Risks and possible discomforts from having a second CALEC transplant

CALEC transplantation is investigational and all the risks may not be known until the completion of this study. We will continuously evaluate you for both the known risks and for the risks that are currently unknown. Potential risks of the CALEC transplantation are related to the surgical risks and to the inability of the graft to heal the eye surface and improve your vision.

Specifically, some of the risks to the eye receiving the transplantation in CALEC include:

- Subconjunctival hemorrhage (transient surface bleeding)
- Chemosis (swelling of conjunctiva)
- Conjunctival inflammation
- Conjunctival epithelial defect (scratch of the conjunctiva)
- Conjunctival hyperemia (redness)
- Pyogenic granuloma (a fleshy bump on the eye surface)
- Bleeding under amniotic membrane
- Suture dehiscence (broken or loose sutures)

- Suture abscess (infected stitches)
- Corneal epithelial defect (scratch of the cornea)
- Punctate epithelial erosion or dry eyes
- Dellen (irregularity of the surface)
- Corneal opacity or corneal scarring (cornea is not clear or hazy)
- Corneal thinning
- Corneal edema (swelling)
- Corneal intrastromal hemorrhage (Bleeding within the cornea)
- Corneal neovascularization (Blood vessels growing into the cornea)
- Filamentary keratitis (fine filaments attached to eye surface)
- Graft edema (swelling)
- Pannus (neovascularization, abnormal peripheral blood vessels)
- Exposure keratopathy (eyelids not closing properly)
- Corneal perforation (hole in the cornea)
- Ocular infection
- Ocular inflammation (Eye redness and swelling)
- Graft detachment (loosening or dislocation of the graft)
- Graft failure
- Headache
- Increase in intraocular pressure (IOP)

The likelihood of these risks is unknown. An aim of the study is to investigate such likelihood. Some complications may require additional treatment such as eye drops or injection of medication and your treating physician will provide care of such events.

There is a chance that we will be unable to perform the CALEC procedure because we are unable to grow the cells we obtained at the biopsy. In this case, your study participation will end. The likelihood of this occurring is unknown. An aim of the study is to investigate such likelihood. Since your cells successfully grew for your initial CALEC transplant, we have no reason to believe that they will not grow again for a second CALEC transplant.

There is a risk that you will experience an allergic reaction to the ingredients used to create the CALEC graft. The likelihood of this risk is unknown. Your treating physician will provide medical care for any events that occur during your participation.

Biopsy (Tissue Sample) from the Donor Eye
Biopsy requires the removal of healthy limbal tissue and therefore carries a potential risk of causing limbal stem cell deficiency in the donor eye without LSCD. Performing the biopsy may

cause partial limbal stem cell deficiency, presenting as abnormal blood vessel growth and epithelial cell healing. However, the risk of full LSCD in the donor eye from the biopsy is extremely unlikely.

The possible complications from the CALEC biopsy may require additional treatment such as eye drops or injection of medication and your treating physician will provide care of such events.

Potential complications to the donor eye include:

- Subconjunctival hemorrhage (transient surface bleeding)
- Chemosis (swelling of conjunctiva)
- Conjunctival inflammation
- Conjunctival epithelial defect (scratch of the conjunctiva)
- Conjunctival hyperemia (redness)
- Pyogenic granuloma (a fleshy bump on the eye surface)
- Corneal epithelial defect (scratch of the cornea)
- Punctate epithelial erosion or dry eyes
- Dellen (irregularity of the surface)
- Corneal opacity or corneal scaring (cornea is not clear or hazy)
- Corneal thinning
- Corneal intrastromal hemorrhage (Bleeding within the cornea)
- Corneal neovascularization (Blood vessels growing into the cornea)
- Filamentary keratitis (fine filaments attached to eye surface)
- Pannus (neovascularization, abnormal peripheral blood vessels)
- Ocular infection
- Ocular inflammation (Eye redness and swelling)
- Pseudopterygium (abnormal tissue growth from the white part of the eye into the cornea)

The risks and complications of the second CALEC biopsy are the same as the initial CALEC biopsy. However, having a second biopsy may affect your future treatment options. After a second biopsy, the treating doctor may decide not to perform any additional biopsies in your healthy eye due to concerns for inducing LSCD in the healthy eye. This means you may not be eligible for the standard of care CLAU procedure after two failed CALEC biopsies/grafts. If the CALEC procedure fails in the future, you will still be eligible to receive non-biopsy type treatments, such as a cadaveric limbal allograft procedure or placement of an artificial cornea (keratoprosthesis).

Possible Other Risks

There is a risk of breach of confidentiality with your participation in this research study. Study staff members will try to protect your confidentiality by maintaining all study documents on secure computer network drives or locked within staff-only cabinets. Whenever possible, a unique identifier will be used to keep your information anonymous.
It is likely that certain individuals associated with the study, but not medical professionals, such as auditors, safety monitors or funders may need to access your private medical records in the course of reviewing or overseeing the study. While we will limit their access to issues directly related to the study, at this time we cannot predict what information they will need to obtain.

Participation in this study may involve other risks, including those associated with the use of human- derived products, which are currently not known. If significant new findings are developed during the course of the research that relate to your willingness to continue participating, these findings will be shared with you.

What are the possible benefits from being in this research study?

The benefits of the investigational CALEC graft are not yet fully known and are part of the aims of this study. It is possible that you will not receive any benefit from being in this study. In general, the knowledge gained in this study will contribute to the care of future patients, rather than to the study participants.

What other treatments or procedures are available for your condition?

You have the option of not participating further in this research or continuing with follow-up visits without having another stem cell procedure. If you choose not to participate, you may still receive the standard of care treatment (CLAU) at MEE or at another institution. In addition, other surgical interventions may be available to you, such as limbal allograft from another person or a cadaveric eye or placement of an artificial cornea (keratoprosthesis). If you have LSCD, reconstruction with amniotic membrane could be a viable treatment option. We recommend that you speak with your treating physician regarding all treatment options available to you outside of this research.

Can you still get medical care within Mass General Brigham if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Mass General Brigham now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will you be paid to take part in this research study?

No. You will not be paid to participate in this research study. We will reimburse your parking expenses in the hospital lot during study visits.

We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

What will you have to pay for if you take part in this research study?

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs. The CLAU procedure is considered routine care. The CALEC procedure is a study-related procedure.

What happens if you are injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

If you are injured as a direct result of taking part in this research study, we will assist you in obtaining the medical care needed to treat the injury. This means arranging for (but not paying for) transportation to an acute care center for treatment of the injury.

The care provider may bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the beginning of this consent form.

If you take part in this research study, how will we protect your privacy?

Federal law requires Mass General Brigham to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why they may need to do so:

- Mass General Brigham researchers and staff involved in this study

- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Mass General Brigham who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other: None

Some people or groups who get your identifiable information might not have to follow the same privacy rules that we follow and might use or share your identifiable information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your identifiable information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your identifiable information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your identifiable information for any mailing or marketing list. However, once your identifiable information is shared outside Mass General Brigham, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your identifiable information does not expire.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with the law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Please check only one option:

I will remain in the study **without an additional stem cell transplant procedure**

YES _____ **NO** _____

I will remain in the study and **elect to receive a conjunctival limbal autograft (CLAU)** instead of a second CALEC surgery

YES _____ NO _____

If yes, copy each of the below in your own handwriting on the line beneath:

I am aware of the following:

_____

CLAU surgery has a slightly higher chance of harming my good eye than CALEC.

_____

CLAU is a standard procedure for restoring vision in my damaged eye, but

_____

the chance of success with CLAU may be lower because it is a second surgery.

_____

Electing to have CLAU now may mean that I won't be able to have

_____

another CLAU, CALEC, or similar surgery in the future.

_____

I will remain in the study and **elect to receive a second cultivated autologous limbal epithelial cell graft (CALEC)**

YES _____ NO _____

If yes, copy each of the below in your own handwriting on the line beneath:

I am aware of the following:

_____

CALEC surgery has a smaller chance of harming my good eye than CLAU.

_____

CALEC is experimental, so the chance of it restoring vision in my damaged eye

_____

is unknown. A second CALEC surgery may be more or less successful than my first

_____

CALEC surgery. Electing to have a second CALEC surgery now may mean that

I won't be able to have another CALEC, CLAU, or similar surgery in the future.

Signature of Subject:

I give my consent to remain in the study as described above and agree to allow my health information to be used and shared as described above.

Subject (Print Name)

Subject's Signature | Date | Time

Signature of Study Doctor Obtaining Consent:

Statement of Study Doctor Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Signature of Study Doctor | Date | Time

Study Doctor (Print Name)

Study Doctor (must check one of the following):

☐ Study Doctor is obtaining consent for second CALEC transplant—**proceed to** "Optional Research Activities" section.
☐ Subject is not requesting a second CALEC transplant —**skip** "Optional Research Activities" section.

OPTIONAL RESEARCH ACTIVITIES

As stated on pages 4 and 8 above, the cells taken from your biopsied tissue will be grown on an amniotic membrane to create an experimental CALEC graft. It is possible that not all of the graft material developed from your cells will be needed at the time of your transplant.

In this section, we are asking you to allow the researchers to retain the unneeded portion of the graft membrane made from your cells for use in future research. Further study of this graft may help researchers in the future learn more about how to prevent, find, and treat diseases or conditions of the eye.

The leftover graft membrane that you donate will be frozen and stored for an indefinite period of time in an ophthalmology research laboratory at the Massachusetts Eye and Ear Infirmary. Some of your private health information, such as your diagnosis and your treatment outcome, will be linked to your sample, but your name and other information that could be used to identify you will not be linked.

When we store your donated graft material, we will be careful to protect your identity from discovery by others. Strict safeguards are in place to protect your privacy. Staff in the laboratory will assign your donated graft membrane a unique code number and store it in a freezer in a locked room. Only selected research staff will have access to that freezer. They will not keep your name or other information that could identify you with your donated material or on any records in the lab. They will use the code number to connect your material to your health information that is stored in a computer database. The computer database is protected with a password. Only research staff will know the password.

Using your donated graft material for research will probably not help you but we do hope the research results will help people in the future. Your donated material will only be used for research and will not be sold. There is a possibility that this research may lead to development of products that will be commercialized. Although future research that uses your material may lead to the development of new products, you will not receive any payments for these new products.

Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

The choice to donate your unneeded graft material for future research is entirely up to you. You may choose not to let us store and use your material. Your participation in this study and your care will not be affected by this decision. If you decide that your unused graft material can be kept, you may change your mind at any time. Contact the Office of Clinical Research Operations at (617) 573 - 6060 to let them know you do not want your material used any longer. At that time, you can choose to have your material destroyed or made anonymous (the code linking them to your private health information will be destroyed.) You must follow up this request with a written request, mailed to Massachusetts Eye and Ear Infirmary, Office of Ophthalmology Research, 325 Cambridge St., Boston, MA 02114.

I agree to allow my unused graft membrane material and health information to be stored and used for future research as described above:

YES _____ NO _____

_____ _____
Signature of Research Participant Date

_____ _____ _____
Signature of Study Doctor Print name of Study Doctor Date

Consent Form Version: Consent For Second Surgery, V2.0, March 23, 2022

Schedule of Events & Procedures for Participants Having a CLAU Procedure

Visit	1	2	3	4	5	6	7	8	9	10	11
Procedure post-transplant visits timed from transplant date)	**Screening / Baseline**	**Pre-Op**	**Corneal Reconstruction with Conjunctival limbal autograft (CLAU)**	**Day 1 Post-Graft**	**Week 1**	**Week 2**	**Month One 4-wks**	**Month Three 13-wks**	**Month Six 26-wks**	**Month Nine 39-wks**	**Month twelve 52-wks**
Timing Window		1 to 5 days prior to transplant		±0 days	± 3 days	± 3 days	± 3 days	± 1 week	± 1 week	± 1 week	± 1 week
Obtain Informed Consent	X										
Eligibility Assessment	X	X									
Pre-Op Health Screening	X	X									
Slit Lamp Examination	X			X	X	X	X	X	X	X	X
Visual Acuity BCVA	X	X		X	X	X	X	X	X	X	X
Intraocular Pressure	X	X		X	X	X	X	X	X	X	X
Fundus Examination or B-Scan Ultrasound	X	X									
AS-OCT	X	X									X
IVCM	X										X
Slit Lamp Photos	X			X	X	X	X	X	X	X	X
Conjunctival Swab & Culture	X										
Punctal Plugs*				X	X	X	X	X	X	X	X
Bandage Contact Lens				X	X	X	X	X	X	X	X
Antibiotic				X	X	X	X	X	X	X	X
Prednisolone acetate and fluoroquinolone				X	X	X	X	X	X	X	X
Vancomycin		X		X	X	X	X	X	X	X	X
Preserv-Free Artificial Tears				X	X	X	X	X	X	X	X
20% Autologous Serum Drops		X		X	X	X	X	X	X	X	X
Symptom Assessment	X	X						X	X	X	X
Adverse Event Assessment	X	X		X	X	X	X	X	X	X	X

* Punctal plugs will be used as necessary

Schedule of Events & Procedures for Participants Having a Second CALEC Graft

Visit	1	2	3		4	5		6	7	8	9	10	11	12	13	14
Time Period & Procedure (post-transplant visits timed from transplant date)	Screening/ Baseline	Blood draw collected within 1-7 days before or after biopsy	Limbal Biopsy (Within 25 days of Baseline)	Transportation of Tissue to GMP lab and Preparation of Cell Sheets	Day 1 Post-Biopsy	Pre-Op	Transportation of CALEC to Mass. Eye and Ear– Release anticipated 10 to 30 days after biopsy	Corneal Reconstruction with CALEC (Day 0) – Within 24 hours of release	Day 1 Post-Graft	Week 1	Week 2	Month One 4-wks	Month Three 13-wks	Month Six 26-wks	Month Nine 39-wks	Month Twelve 52-wks
Timing Window					1-2 days after biopsy	1 to 5 days prior to trans-plant			±0 days	± 3 days	± 3 days	± 3 days	± 1 week	± 1 week	± 1 week	± 1 week
Obtain Informed Consent	X															
Eligibility Assessment	X				X	X										
Pre-Op Health Screening	X															
Slit Lamp Examination	X				X**	X***			X	X	X	X	X	X	X	X
Visual Acuity BCVA	X				X	X			X	X	X	X	X	X	X	X
Intraocular Pressure	X				X	X			X	X	X	X	X	X	X	X
Fundus Examination or B-Scan Ultrasound	X															
AS-OCT	X															X
IVCM	X															X
Slit Lamp Photos	X				X				X	X	X	X	X	X	X	X
Conjunctival Swab & Culture	X															
Punctal Plugs*					X	X			X	X	X	X	X	X	X	X
Bandage Contact Lens									X	X	X	X	X	X	X	X
Antibiotic					X	X			X	X	X	X	X	X	X	X
Prednisolone acetate and fluoroquinolone					X	X			X	X	X	X	X	X	X	X
Vancomycin					X	X			X	X	X	X	X	X	X	X
Preserv-Free Artificial Tears									X	X	X	X	X	X	X	X
20% Autologous Serum Drops									X	X	X	X	X	X	X	X
Symptom Assessment	X												X	X	X	X
Adverse Event Assessment	X				X	X			X	X	X	X	X	X	X	X

* Punctal plugs will be used as necessary
** X=Donor Eye.
*** X =Recipient Eye. Eye procedures or medications marked with a black **X** will be performed on or given to both the recipient and donor eyes of the participant.