An Open-label Dose Escalation Study of an Adeno-associated Virus Vector (scAAV2-P1ND4v2) for Gene Therapy of Leber's Hereditary Optic Neuropathy (LHON) caused by the G11778 mutation in mitochondrial DNA.

NCT02161380

Date: September 20, 2020. IRB 20140248

University of Miami - Medical Informed Consent Form
EPROST # 20140248
Version Date 09/02/2020

Title of research study: An Open-label Dose Escalation Study of an Adeno-associated Virus Vector (scAAV2-P1*ND4*v2) for Gene Therapy of Leber's Hereditary Optic Neuropathy (LHON) caused by the G11778A mutation in mitochondrial DNA

Protocol number: 20140248
Clinicaltrials.gov number: NCT02161380

Investigator:
[redacted]

Co-Investigators: [redacted]

24 hour Emergency Number: [redacted]

Note: If you are a parent or legal guardian of a child who will receive the injection, permission from you, and the assent agreement from your child if appropriate, is required. When the words "you" or "your" appear in this consent form, they refer to the patient, whether that is yourself or your child.

Why am I being invited to take part in a research study?
We invite you to take part in a research study because you have Leber's Hereditary Optic Neuropathy (LHON). This condition is a result of chemical changes in your mitochondrial genes called mutations. These mutations cause the genes not to work properly and the result is a loss of vision that occurs in young adults due to a loss of cells in the retina that are needed to send electrical signals to the brain. People who participate in this study will have been shown to have a specific mutation called G11778A that causes the ND4 gene to not work properly. They may have already had a loss of vision, be having a loss of vision, or be genetically prone to a loss of vision.

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What should I know about a research study?
You are being asked to participate in a research study. This consent form provides you with information about the study. The Principal Investigator (the study doctor or person in charge of this research) or his representative will also describe this study to you and answer all of your questions. Listen to the information below and ask questions about anything you don't understand before deciding whether or not to take part. Your participation in a gene transfer study may prevent you from participating in future gene therapy related studies.

Your participation is entirely voluntary and you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

In brief:

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Who can I talk to?
If at any time you have any questions about the study, you may contact [redacted]

In case of study-related injury, please contact [redacted] at the same phone numbers as above.

If you have any questions relating to your rights as a research subject, p[redacted]

Why is this research being done?
This study is a Phase I clinical trial to determine if a new gene therapy called scAAV2-P1*ND4*v2 is safe to use in people with LHON. This information is needed before proceeding to future studies to establish if the study agent will be an effective treatment of Leber's Hereditary Optic Neuropathy. Before describing the study agent, you need to know about

genes and how they might be used to correct diseases (gene therapy). The concept is that diseases that cannot be well treated by present methods might be prevented or corrected by introducing normal genes into diseased cells to replace or correct the defective genes that cause disease. However, such normal genes cannot be introduced into cells without help. In this trial, adeno-associated virus (AAV) will be used to help a gene enter the cells of your retina, a tissue at the back of your eye like film in an old camera that connects to the optic nerve—the nerve that transmits vision from the eye to the brain. Because you have LHON, your optic nerve is not working normally now or may not work normally in the future. AAV does not cause illness in humans. scAAV2-P1*ND4*v2, an AAV that has been modified in a laboratory to contain a properly working copy of human *ND4,* will be injected into the center of your eye, allowing the virus to move to the retina. This procedure is called gene transfer and is the way in which most kinds of gene therapy are currently performed. This study is the first time that scAAV2-P1*ND4*v2, will be given to people.

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.

How long will the research last?
We expect that you will be in this research study for 3 years of study-related evaluations at the Bascom Palmer Eye Institute. After these evaluations, an investigator will continue to contact you by telephone for 7 additional years to ask you questions about your medical and visual history. Other people will also be participating in this study during this time.

How many people will be studied?
We expect about 27 people here will be in this research study. This is the only center recruiting patients for this study.

What happens if I say yes, I want to be in this research?
If you choose to enroll in this study, the first step is to confirm that you have LHON caused by a specific gene mutation—called the G11778A mutation. If you qualify for the screening evaluations you will participate in 3 years of study-related evaluations at the Bascom Palmer Eye Institute. After these evaluations, an investigator will continue to contact you by telephone for 7 additional years to ask you questions about your medical and visual history. Other people will also be participating in this study during this time.

If you agree to participate in this study, you will need to come to the Bascom Palmer Eye Institute for baseline visits, to receive a one-time scAAV2-P1*ND4*v2 injection and for evaluations following scAAV2-P1*ND4*v2 administration.

In the table below, there is a schedule of evaluations that you will need to complete as a participant in this clinical trial. The procedures are also described in detail under the study schedule. On day 0, the day you receive the scAAV2-P1ND4v2 injection, you will stay at the Bascom Palmer Eye Institute / Ann Bates Leach Eye Hospital for several hours after receiving the injection procedure. Combining the second baseline visit with the injection visit and the one day post-injection visit will require that you remain in Miami for 3 consecutive days. However, all the other subsequent visits are expected to take 1 day or less.

Summary table of study procedures (a comprehensive table appears at the end of this document)

Visit (B=baseline, **I=Injection**, D=day, W=week, M=month)

Procedures	B1	B2	**I** D 0	D 1	W 1	M 1	M 2	M 3	M 6	M 9	M 12	M18 to year 3	Years 4-10
Complete Physical Exam	*			*		*		*			*		
Hemat/Chem	*		*	*	*	*		*			*	*	
AAV antibodies / DNA	*				*			*			*		
CXR, EKG	*												
Ocular/Retinal Exam	*	*	*	*	*	*	*	*	*	*	*	*	
Fundus Photography	*			*	*	*	*				*	*	
Visual/Retinal Functio	*	*			*		*				*	*	

NAME: _____

MRN: _____

AGE: _____ DOB: ____/____/_____

Procedures	B1	B2	ID 0	D 1	W 1	M 1	M 2	M 3	M 6	M 9	M 12	M18 to year 3	Years 4-10
Quality of Life	*						*	*			*		
Intravitreal Injection			*										
Longterm follow up													*

Since you will need to return to Bascom Palmer for these evaluations, there will be some flexibility in scheduling your follow-up visits. For example, the visit on Day 7 after the injection could be scheduled 2 days earlier or later, the monthly visits could be 5 days earlier or later, and thereafter the visits could be 30 days earlier or later. Study staff will work with you to schedule your evaluations within these timeframes. It is very important that you understand that when you enroll in this trial, you are also agreeing to maintain the follow-up visit schedule to the best of your ability.

The following is a summary of what will be done each time you are examined:
Baseline 1

After you have signed the informed consent document, you will be interviewed by a member of the research team who will obtain your medical history. You will then undergo the following procedures:

- Neuro-ophthalmic (includes testing of pupil reactions, of eye movement) and Physical examinations
- Electrocardiogram (EKG): This is a standard medical test that records the electrical activity of your heart to assess heart function.
- Chest X-ray
- Blood and urine testing including:
  - Pregnancy testing for females of childbearing capacity.
  - Standard clinical chemistries and hematology
  - Standard urinalysis
  - Blood test to confirm that the G11778A mutation is the cause of your LHON disease (only if you have not had testing from a certified genetics laboratory)
- Testing to establish baseline values for comparison following gene transfer.
  - We will collect blood samples to test for immune response against the adeno-associated virus before and after the injection.

- We will collect blood samples to perform PCR testing before and after the injection to detect leakage of study drug virus from the eye and into the blood.

- Visual function measurement:
  - Ophthalmic (eye history): You will be asked questions about your vision and any condition or treatment of your eyes.
  - Visual function testing: Then you will be asked to read letters from a chart, if possible, as a test of your visual acuity and have a computerized test of your visual field.
  - Ophthalmic examination: Your eyes will be examined using routine eye examination instruments. Your eyes will first be dilated with eyedrops (tropicamide 1% and phenylephrine 2.5%)
  - Pattern Electroretinogram (PERG): The PERG is a test that measures how well your eye makes electricity, which the eye makes normally. It is a routine, safe and noninvasive test to evaluate how well the cells in your eye affected by LHON works. To do this test, skin electrodes will be placed around the front of your eye. An alternating pattern will be flashed on a screen in front of you.

- Fundus photography: Photographs will be taken of your eyes using a special camera.
- Questioning about your quality of life: Because the researchers want to know if your quality of life changes during the course of the study, you will be asked to complete a questionnaire about your life with a member of the research team.
- You will be asked whether you are having any problems related to the study procedures. This is called adverse event recording.

Baseline 2

- Pregnancy testing for women of childbearing age.
- A set of blood tests to check for normal clotting.
- Eye examination
- Visual function measurement
- PERG, OCT
- Adverse event recording

Day 0 – Administration of scAAV2-P1*ND4*v2

Investigators will choose one of your eyes for scAAV2-P1*ND4*v2 administration. If you have loss of vision in both eyes, the eye chosen for injection will be the eye with the worse visual function based on the testing described above. If you have lost vision in only one eye, the unaffected eye will be injected because in almost all patients with LHON, the initially

unaffected eye also loses vision, usually within 6 months. You will receive only a single injection of scAAV2-P1*ND4*v2 and it will only be injected into one eye. No one who participates in this study will have injections into both eyes.

At the time of your injection, you will be taken from the clinic to a procedure room, where a retinal specialist with extensive experience injecting drugs into the eye will inject the study agent into your eye. The procedure is called intravitreal injection, meaning that the injection is into the vitreous compartment of the eye. To prevent an unsafe rise in intraocular pressure from the study drug injection, as part of the injection procedure, a small amount of fluid must be removed from the compartment at the front of your eye called the anterior chamber. This fluid will be stored for later analysis of antibodies against the AAV virus or in case you have an adverse reaction to the injection. Study agent administration will be performed using local anesthesia and standard sterile surgical procedures. Following study agent administration, you may be given antibiotic and steroid eye drops, ointments, or, possibly, minor injections around they eye, and your eye may be covered with a patch. You will then be taken back to the clinic for close monitoring.
The following procedures will be performed:

Day 1

- Physical examination
- Vital signs and monitoring of eye pressure
- Blood and urine testing
- Ophthalmic examination
- Visual function measurement
- Fundus photography
- Adverse event recording
- If you are having any problems, you will need to come back to Bascom Palmer in 1-3 days for a similar evaluation. Otherwise, you will be discharged and asked to return at day 7.

Day 7

- Blood and urine testing
- Ophthalmic examination
- Visual function measurement
- PERG
- Fundus photography and OCT
- Adverse event recording

- If you are having any problems, you will be asked to come back to Bascom Palmer in 4 days for a similar evaluation. Otherwise, you will be discharged and asked to return at day 30.

At Day 30 and below, a Basic examination consists of

- Neuro-ophthalmic examination and brief history
- Visual function measurement
- PERG
- Adverse event recording

Day 30

- Basic examination
- Blood and urine testing
- Ophthalmic examination
- Fundus photography

Day 60

- Basic examination
- Fundus photography and OCT
- Questioning about your quality of life

Day 90

- Basic examination
- Physical examination
- Blood and urine testing

Day 180

- Basic examination
- Questioning about your quality of life

Day 270

- Basic examination

Day 365

- Basic examination

- Physical examination
- Blood and urine testing
- Ophthalmic examination
- Fundus photography and OCT

Year 1.5
- Basic examination

Year 2
- Basic examination
- Blood and urine testing
- Fundus photography and OCT

Year 3
- Basic examination
- Blood and urine testing
- Fundus photography and OCT

After you have been evaluated for 3 years, we will begin yearly telephone calls by an investigator to ask about any problems you are having. Specifically, the investigators will want to know about changes in your vision and medical history since they last talked with you.

Additional Information for Gene Transfer Research

This study involves gene transfer. If you move, you will need to provide your new address and telephone number to your research doctor. You also will need to report any admissions to a hospital or illnesses throughout the study as well as following active participation in the study, indefinitely.

To fully evaluate the effects and safety of gene transfer, it is necessary to obtain as much information as possible. In the unlikely event of your death, regardless of the cause, the evaluation of your organs would be a very valuable method to determine any effects of gene transfer that are not being monitored. By participating in this study, you are granting Dr. Lam and the research team permission to make a request for an autopsy from your next-of-kin in the event of your death from any cause. You are encouraged to discuss this possibility with your family in advance

What are my responsibilities if I take part in this research?
If you take part in this research, you will be responsible to complete all visits, procedures, and follow-up visits as described above.

What happens if I do not want to be in this research?
Participation in this study is entirely voluntary. You are free to decide not to be in the study without any penalty or loss of benefits to which you would otherwise be entitled.
You can leave the research at any time and it will not be held against you.
We are performing this study because at this time, there are no effective treatments for LHON. The alternative to this study is to choose not to participate.

What happens if I say yes, but I change my mind later?
You are free to withdraw your consent and stop participation in this research study at any time without penalty or loss of benefits to which you are otherwise entitled at this institution; however, if you wish to do so, regardless of the reason, you should contact the study doctor ([redacted]). Throughout the study, the researchers may notify you of new information that may become available and that might change your decision to be in the study. We ask that you not enroll in the Study if you may be considering to withdraw after you have received an injection of the Study drug. It is important to note that the study agent cannot be removed from the body after it has been injected into the eye.

If you leave the study before the study visits are complete, you may be asked by the study doctor to have one additional evaluation at the Bascom Palmer Eye Institute. If withdrawing from the study [redacted] will ask you if you wish to provide further data collection from routine medical care.

Will the research team, Universities or regulatory agencies benefit from your participation in this study?
Improved treatment of serious diseases like LHON is a major goal in Medicine and the investigators think that their research study will help in an understanding of LHON and eventually may provide effective treatment.

If the study drug being given to you is eventually sold commercially, the universities that own interest in this agent (University of Florida) may receive money in the form of royalties and stocks from its sale. While there are currently no financial benefits now, it is also possible that in the future the heirs of [redacted] n the patent and one of

the scientists involved in the study, may also receive some money if the study agent is sold commercially. You will not receive any financial compensation if non-identifiable biospecimens collected from you are sold.

Is there any way being in this study could be bad for me?

What are the possible discomforts and risks?
Possible risks relating to your participation in this study include those associated with scAAV2-P1*ND4*v2, administration and with the study procedures. You may experience burning or pain in the injected eye after the anesthesia wears off . This is the first human study of scAAV2-P1*ND4*v2 administration so the risks are not exactly known and could occur years after gene transfer.

Risks associated with scAAV2-P1*ND4*v2 administration

We have injected scAAV2-P1ND4v2 into the eyes of normal rats as well as normal monkeys and have not caused any visual or general problems. Based on these studies, it is likely that intravitreal administration of scAAV2-P1*ND4*v2 at the doses proposed in this study will be safe in you. In addition, similar viral vectors are being injected into the eyes of humans in other scientific studies, and these studies also have reported no major problems.

Nevertheless, anything injected into your eye could damage your retina, and this could result in further damage to your vision. We did not see this potential adverse effect in our monkey studies.

You should also know that there is a small risk that scAAV2-P1*ND4*v2, even though it is injected into your eye, could spread outside of your eye to your blood, to other parts of your body and/or to your sperm or egg cells. It is not known what would happen if that occurs; however, the investigators will check your blood throughout the study to determine if the study agent has spread outside your eye. Once injected into the eye scAAV2-P1*ND4*v2 cannot be removed from the body.

Preclinical studies have shown that injection of scAAV2-P1*ND4*v2 into the eye will cause an immune response primarily consisting of antibodies against AAV2. Some people have natural antibodies against AAV2 levels of these antibodies may rise after injection or if you do not

have antibodies prior to injection you will develop them after injection. The effect of these antibodies on your vision is unknown.

There also is a risk that your eye will become inflamed after the injection, but based on animal studies of the study agent; this risk is believed to be minimal. Nevertheless, the investigators will check your blood and your eyes frequently to see if you have any evidence of inflammation, and if you do, it can be treated with topical or systemic anti-inflammatory or antibiotic medications.

It is possible that scAAV2-P1*ND4*v2 could interact with other viruses with which you have already or may come in contact. This could result in a new virus that could produce unknown side effects. The likelihood that this would occur is thought to be extremely low.

There is a risk of inflammation outside the eye near the administration site. In the animal studies, this inflammation was mild, temporary and controllable using medications (corticosteroids and/or antibiotics) which will also be used during this clinical trial.
Finally, there is the risk that despite or because of the injection, your vision may worsen. Based on animal studies of the study agent, we think the risk that the study agent could damage your vision is low; however, it is possible that the study agent could damage the DNA in your retina. In the unlikely event that this occurred, it could put you at risk for developing retinal tumors in the future. In animal studies to date, there has been no tumor development and the risk of developing tumors is believed to be minimal.
Since we do not know how the study agent will affect a pregnancy or infant, pregnant and breastfeeding women will not be included in the study. If you are female and capable of becoming pregnant, you will be asked to take two pregnancy tests at baseline visits. If either baseline test is positive, you will not be enrolled in the study. It is very important that you understand that for the first year following gene transfer, you should not become pregnant. Both men and woman will be required to use effective contraception for 1 year. Contraception must also include the use of a barrier method for 3 months after the administration of the study agent. If barrier contraception is the only method used, it must be used with a spermicide. Even with these precautions, there is a possibility that the genes in some of your sperm (men) or eggs (women) may be permanently changed. The likelihood is low that such changes would occur based on animal studies of the study agent, and the effects of potential changes are unknown. If you become pregnant, suspect that you are pregnant, or if your sexual partner becomes pregnant while in the study, you should notify

All injections inside the eye carry some risks, including damage to the retina and/or development of a cataract (clouding of the lens of the eye). Both of these complications might require further surgery and could lead to worse vision. Infection is rare but can occur as a result of eye surgery. The majority of these infections can be treated, but despite successful treatment, worse vision could result. Bleeding in the eye is rare in patients without a bleeding tendency, but can happen following an injection. If this bleeding occurs, it usually goes away by itself without any treatment, but it still could make your vision worse, either temporarily or permanently. If there were a lot of bleeding, you might need surgery to remove the blood. Also, an increase in the pressure in your eye could occur for a short time following the injection, but this is usually temporary and is treatable with medications. Risks associated with use of local anesthesia are low. There is a small risk of penetration of the eye or optic nerve from retrobulbar (local) anesthesia injection and also the possibility of bleeding or double vision, which can be treated if necessary.

Risks associated with the study procedures

Rarely people may experience redness, discomfort or allergic reactions to the drops that are used to dilate the pupil prior to the visual function testing. These are generally not serious and can be treated, if necessary. Light sensitivity may be experienced while the pupil is dilated, but this can be helped by wearing sunglasses; light sensitivity decreases in a matter of hours after the drops have been instilled. High blood pressure, heart arrhythmias and some types of glaucoma (i.e. angle closure glaucoma) may be exacerbated by dilating drops in a susceptible individual but these complications can be treated. The investigators will take precautions to remind you not to rub or touch your eyes so as to not scratch the surface of your eyes while they are numb for 20 minutes after anesthetic eyedrops are given.

Possible risks associated with a blood draw are discomfort and/or bruising. Rarely, after blood is drawn, a blood clot may form or you may become faint.
If you take part in this research, you will have a chest x-ray. This procedure involves a small amount of radiation. To give you an idea about how much radiation you will get, we will compare it to the amounts that people encounter in daily life. There is radiation that naturally occurs from space and from rocks in the soil. This natural radiation is greater at higher altitudes. This research gives you about the same amount of radiation as you would get from living in a high altitude city such as Denver for 12 days, or taking 4 airplane flights from

New York to Los Angeles. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests. Although it is not possible to say what health impact such a low exposure might have, current policy dictates that we consider any radiation exposure as resulting in an incremental increase in your likelihood of developing cancer at some time in your life.

You will be monitored for any complications after you receive the study agent. Monitoring will include safety tests, vision measurements, intraocular pressure measurement and physical examinations. In addition, at every visit, an investigator will ask you how you feel and if you are having any health problems.

Will being in this study help me in any way?

What are the possible benefits to you or to others?
No direct benefit to you should be anticipated as a result of your participation in this phase I study. The purpose of this phase I study is to determine the safety of administration of scAAV2- P1*ND4*v2 at various dosages. This is the first time that this study agent has been administered to human subjects and it is not possible to predict how it will affect your vision. The information gained may be useful in the next step of developing the study agent. Although this phase I study is designed to evaluate the safety of scAAV2-P1*ND4*v2, if it is determined to be safe, we may include your information, along with that from additional patients in later studies, to determine the possible benefit of using scAAV2-P1*ND4*v2 as a gene therapy for LHON.

What happens to the information collected for the research?
Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES
Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able

to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.
This study includes a number of researchers, institutions and government agencies. They may use your health information and share it with others. We want you to know who may use this information and how they may use it.

Who may use and give out information about you?
The Investigator (study doctor) and research staff will have information about your health that identifies you. This information may be given to others as described below.

Who may see this information?
The research sponsor and its authorized representatives, business partners, clinical research organizations and affiliates may see your health information and know your identity. This includes the study monitor. They all have the right to see information about you during and after the study.
The following people, agencies and businesses may get information from us that show who you are.

- Doctors and healthcare professionals taking part in the study
- Your primary care physician or specialist
- U.S. Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
- National Eye Institute (NEI)/NIH Data Safety Monitoring Committee (DSMC)
- Recombinant DNA Advisory Committee (RAC) of NIH
- U.S. Department of Health and Human Services (DHHS)
- University of Miami Institutional Review Board
- University of Miami Institutional Biosafety Committee

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented to this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the

research, except 1) if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings; see below); 2) if you have consented to the disclosure, including for your medical treatment and related administrative activities; or 3) if it is used for other scientific research, as allowed by federal regulations protecting research subjects. This information will be available to University of Miami doctors, nurses and other authorized staff who may not be part of the research team but who are involved in providing you medical care and other health care operations. It may also be released to your insurance company in order to receive reimbursement for covered services.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by *The National Institute of Health* or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to any other person not connected with the research, you must provide written consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document, including the inclusion of research data in your medical record at the University of Miami. Any information disclosed pursuant to your authorization may no longer be protected by the Certificate of Confidentiality.

. If you are, or have been, a patient at a University of Miami facility, you will have a University of Miami medical record. We use an electronic medical record system known as UChart, which improves access to information important to your medical care. UChart will show that you are in a research study and a copy of this signed consent form will be included. To provide as complete a record as possible, some or all of your study-related research information may also be placed in UChart. This specifically includes investigational drugs, devices, biologics, or anything else that may, separately or together with other substances or activities, interfere with your clinical treatment or place you at greater risk of harm. Other information from the research study may be included as well.
This information will be available to University of Miami doctors, nurses and other authorized staff who may not be part of the research team but who are involved in providing you medical

care, or who are otherwise allowed to access your information. The confidentiality of the results and other documents in UChart will be governed by laws, such as HIPAA, that concern medical records. We suggest that you tell any non-University of Miami doctors that you are in a research study and that more information may be made available to them at your request. The research team may use your information to notify you of appointments, send you appointment reminders, or schedule additional appointments

What information may be used and shared?
If you decide to be in this study, there will be medical information that identifies you and relates to your participation. This may include the following types of medical information.

- Information obtained from the procedures used to find out whether you are eligible to take part in this study. This may include physical examinations, *mitochondrial DNA* genetic test results, previous eye examinations, blood and urine test results, X-rays and other procedures or tests, and any other information that you may release to us, including information about your health history.

- Information obtained in the course of the study including information about your response to any study treatments you receive, information related to study visits and phone calls, physical examinations, blood, urine, and tear tests, pregnancy tests, X-rays, quality of life questionnaire, and other tests or procedures that may be performed, and other medical information relating to your participation in this study.

Why will this information be used and/or shared?
Information about you and your health that might identify you may be given to others to carry out the research study. The principal investigator and study team will analyze and evaluate the results of the study. In addition, the sponsor or one of his designees will be visiting the research site. The principal investigator, [redacted], or his designee also will follow the study to make sure that it is performed properly and will be reviewing your information for this purpose.
Your information relating to this study may be given to the FDA and NIH. The NEI/NIH DSMC will be receiving and reviewing your information to monitor the safety of the trial.
Because this study involves gene transfer, safety information is required to be reported to the RAC of the NIH. No information by which you can be identified will be reported with the safety information. This safety information is available to the general public. In addition,

the media (i.e. TV, newspaper) may have an interest in the study. [redacted] will make every effort to protect your privacy.
The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

Your health information may be collected, used, and disclosed indefinitely or until your permission to use this information is withdrawn. The data will be maintained in a secure storage facility. The information may be reviewed by University of Miami's Institutional Review Board (IRB). IRB is a group of people who perform independent review of research as required by University of Miami regulations. Identifiers might be removed from your identifiable private information or your identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

What if you decide not to give permission to use and give out your health information?
By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you do not wish to give permission, you will not be able to be in this research.

May you review or copy the information obtained from you or created about you?
You have the right to review and copy your health information. However, if you decide to be in this study and sign this form, you will not have access to your information until after the study is completed, possibly as long as five years.

May you withdraw your permission?
You may withdraw (take away) your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.
After you withdraw your permission, no new health information that might identify you will be gathered. Information that has already been gathered may still be used and given to others if necessary to confirm the validity of the research.

Is your health information protected after it has been given to others?

If you give permission to disclose your identifiable health information to a person or business, the information may no longer be protected.

Can I be removed from the research without my OK?

Your participation in this study may be ended by the study doctor ([redacted] without your consent at any time:

- Because the study doctor thinks it necessary for your health or safety;
- Because you have not followed study instructions;
- Because the study doctor has stopped the study; or
- For administrative reasons.

What else do I need to know?

If you choose to take part in this study, will it cost you anything?

This research is being funded by the National Institutes of Health

Neither you nor your insurance company will be charged for any tests or procedures that are done for the purposes of the research study. Study agent will be provided without charge. You or your insurance company will be responsible for costs of tests or procedures that are part of your routine medical care.

Will you receive payment for your participation in this study?

You will not receive financial compensation for participation in this study. Travel will be provided and arranged by our research staff. In the event that we are unable to provide this service, you will be compensated for your documented travel expenses. This reimbursement for costs will be done in accordance with the travel policies and procedures of Bascom Palmer Eye Institute and the University of Miami School of Medicine. Your name and social security number will be reported to University administrative personnel for purposes of making and recording the payment. The research staff will arrange for payment or reimbursement of procedures associated with the study and performed at non-University locations.

What if you are injured because of the study?

If you have a medical problem at any time during the study, you should contact [redacted] or any member of the study staff listed on the front of this form, even if the problem is not related to your eyes. We are required to report all new medical conditions to the regulatory authorities monitoring the study. You may also contact your doctor, or seek treatment at a local medical facility. The Bascom Palmer Eye Institute maintains a fully staffed eye emergency room 24

hours a day and 7 days a week. Be sure to tell the doctor who treats you that you are in a research study. Ask the doctor to call the telephone numbers on the front of this form for further instructions and information.

In the event of any physical injury resulting from research procedures, only professional medical care that you receive at the Bascom Palmer Eye Institute will be provided without charge. Medical care at other hospitals or centers will not be covered by the study. Since this is a research study, your insurance company may or may not pay for any hospitalizations related to study injuries. No other compensation is offered. If you have an illness or injury during this research trial that is determined by the doctors not to be directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.
If you experience an injury that is directly caused by this study, please contact [redacted] If you have any questions about any discomforts that you experience while participating in this study, please contact the clinical coordinator or [redacted]

In the future, you may have questions about your study participation. You may also have questions about a possible side effect, reaction to study medication, or a possible research-related injury. If you have any questions, contact: [redacted]

In summary, this is a detailed schedule of your study visits and procedures

Detailed schedule of study visits and evaluations table

The injection is performed at day 0 (▼)

Time point	Baseline		Day									Year			
	B1	B2	0 ▼	1	7	30	60	90	180	270	365	1.5	2	3	4 -10
Informed consent/assent	■														
Blood test for G11778A mutation	■														
History and physical exam	■			■		■		■			■				
Electrocardiogram, chest X-ray	■														
Pregnancy test	■	■													
Vital signs monitoring		■	■	■											
Hematology, chemistry, urinalysis	■		■	■	■	■		■			■		■	■	
Coagulation Panel		■													
AAV antibody and specific reactivity (ASR) measurement	■+				■	+		■+			■+				
Peripheral blood PCR	■+			■+	■+										
Visual Acuity	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Perimetry	■	■		■	■	■	■	■	■	■	■	■	■	■	
PERG	■	■		■	■	■	■	■	■	■	■	■	■	■	
Neuro-ophthalmic Exam	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
OCT Imaging	■	■			■		■				■		■	■	
Fundus photography	■			■	■	■	■				■		■	■	
Quality of life questions (NEI VFQ-25)	■						■		■		■				
Adverse event recording	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Long-term follow-up														■	■

Baseline visits are no more than 1 month before day 0, date of vector administration;
+ testing will continue until two consecutive samples test negative

Windows of acceptable timeframes for study related follow-up visits			
	Acceptable timeframes (days)		
Timepoint	+/- 2	+/-5	+/-30
Day 7	■		
Days 30, 60, 90		■	
Days 180, 270, 365			■
Years 1.5, 2-10			■

University of Miami - Medical Informed Consent Form
EPROST # 20140248
Version Date 09/02/2020

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

This section is to be used when reading this form to a subject who is blind.
My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process	Date
Printed name of person witnessing consent process	

University of Miami - Medical Informed Consent Form
EPROST # 20140248
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By signing this form, you are indicating that you have had your questions answered, you agree to take part and to allow your child to take part in this research study, and you are legally authorized to consent to your child's participation.

Consent by Parent or Legal Guardian

Printed name of Parent #1

Signature **Date**

Printed name of Parent #2

Signature **Date**