OREGON HEALTH & SCIENCE UNIVERSITY
Main Study Gene Transfer Consent Form

TITLE: A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected UshStat, Administered to Patients with Retinitis Pigmentosa Associated with Usher Syndrome Type 1B

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SPONSOR: Oxford BioMedica (UK) Ltd.

PURPOSE:

"You" means you or your child in this consent form.

You have been invited to be in this research study because you have Usher Syndrome and a change in a gene called MYO7A. Because of this, your vision is not normal.

The purpose of this study is to learn about a new therapy that may help patients with Usher Syndrome who have the same change in the MYO7A gene.

This study is experimental. It is meant to investigate the safety, possible harms, and side effects of an experimental gene transfer agent called UshStat (called the "study treatment"). This is the first time this study treatment will be used in humans.

The goal of this study is to find out the highest dose of the study treatment that is safe. This is the first step in studying whether it can be used to treat others with your disease in the future.

In order to understand the study, you need to know something about genes. Genes are the units of deoxyribonucleic acid (DNA), the chemical structure carrying your genetic information. Genes determine many human characteristics such as the color of your eyes, your height, and whether you are male or female.

You have changes in one of your genes called MYO7A. The MYO7A gene makes a protein called myosin 7A that is needed for your retina to work normally. The retina is the lining at the back of your eye that detects light. The changes cause your MYO7A gene to not work normally in your retina. Because of this, your vision is not normal. The study treatment tries to provide a normal copy of the MYO7A gene into one of your eyes.

The gene we are trying to replace in this study cannot get into the cells of your retina by itself. It needs a "vehicle" to deliver it into your cells. In gene transfer studies, this vehicle is referred to as a "vector." A common vector used in gene transfer agents is viruses. In this consent form, the vector is referred to as the "study treatment."

The study treatment to be used in this study consists of:

- A virus called Equine Infectious Anemia Virus (EIAV), which has been changed in the laboratory so that it is not likely to reproduce or cause an infection once it is in your body. EIAV is a virus that infects horses and is not known to cause illness in humans. The EIAV virus belongs to a family of viruses called lentiviruses. When lentiviral vectors enter a normal cell in the body, the DNA of the vector inserts itself into the DNA of the cell in a process called DNA integration.

- Pieces of DNA containing normal copies of the MYO7A gene.

This study requires 11 visits to the clinic and will take 48 weeks to complete.

At the end of the 48 weeks, you will have the option to enroll in a long-term follow-up study. Long-term follow-up in gene transfer research allows for the collection of important information on the long-term safety and effects of the gene transfer agent used in this study. The long-term follow-up planned for this study will occur twice a year for 5 years. It will include an eye exam at the clinic, blood draws, and questions about any changes in your health.

At the end of the 5 years, we will continue to follow you for an additional 10 years. The investigators will contact you once a year to find out if you have had any changes in your health and if possible take a blood sample. If you saw your eye care provider or other health care provider, we may request copies of those records.

A total of 18 subjects will be enrolled in the study at OHSU.

PROCEDURES:

We do not know the highest dose of the study treatment that is safe. To find out, we will give the study treatment to three (3) subjects at one dose level. If that is safe we will raise the dose given to the next group of three subjects. The dose you will get will depend on how many subjects get the agent before you and how they react. The investigator will tell you this information. This will help you think about possible harms and benefits. Since the study treatment is experimental, we don't know what will happen at any dose level.

This is an open-label study, which means you and the investigators will know the dose level that you receive and which eye will receive the studytreatment.

You will be asked to come to a hospital or clinic for your visits. If your home is not close to the hospital, you may stay at nearby hotel. At your first 2 visits, you will have tests done to see if you are eligible to continue in this study. Because of the amount of tests required at screening, the visit may be split into 2-3 days. If you are eligible to continue in the study, you will receive the study treatment at your third visit. An eye surgeon will inject the study treatment under the retina in one of your eyes and you will be in the hospital for about half of the day.

After you receive the studytreatment, we will examine you at several visits for the first year of the study. The types of tests that will be done at the visits are shown in a table below. More information about the tests is provided after the table.

			Day		Week						
	Screening	Baseline	0	1	1	2	4	12	24	36	48
Visit Number	1	2	3	4	5	6	7	8	9	10	11
Medical History	X										
Physical Exam	X										X
Pregnancy test	X	X					X	X	X	X	X
Blood Draw	X	X	X	X	X	X	X	X	X	X	X
Urine sample	X	X	X	X	X	X	X	X	X	X	X
ECG	X										
Chest X-ray	X										
Study treatment administration			X								
Vision tests	X	X		X	X	X	X	X	X	X	X
Visual field	X	X				X	X	X	X	X	X
Eye Exam	X	X		X	X	X	X	X	X	X	X
OCT	X	X		X	X	X	X	X	X	X	X
AF	X						X	X	X		X
Fundus photos	X		X	X		X	X		X	X	X
ERG	X								X		X
Quality-of-life questionnaire		X									X

Study Visit Tests
At each visit a member of the research team will ask about changes in your health and take your blood pressure, temperature, and heart rate. Each visit will take between 4-8 hours. We describe the different tests you will receive in the study below:

Pregnancy test: If you are a female who is able to get pregnant, we will give you a test to see if you are pregnant.

Blood tests: We will collect about 1 tablespoon of your blood to test your blood cell counts and how your liver and kidneys are working.

Chest X-ray: A chest X-ray is a picture of the chest that shows your heart, lungs, airway, ribs, and the upper part of the spine. If you are a female who is able to get pregnant, you must have a negative test before you receive the chest X-ray.

Electrocardiogram (ECG): An ECG is a test that measures the electrical activity of your heart.

Vision test: You will be asked to read letters on a chart, if possible.

Visual field: – You will be asked to look at a light in the center of a screen and given a button to press. A computer then shines lights on other parts of the screen and you will click the button whenever you see a light. This test lasts about 2-3 hours.

Quality of life questionnaire: You will be asked a series of questions about how your vision affects your life.

Eye exam: You will be asked questions about your vision and the investigator will use instruments to look through the front of your eye to see your retina (the back of the eye) and other parts of your eye. We will give you eye drops that dilate your eyes for each eye exam.

Optical Coherence Tomography (OCT): The OCT test uses a very thin laser beam to measure the thickness of different layers of cells in your retina. This test takes just a few minutes.

AF (Autofluorescence) & Fundus photos: Photographs will be taken of the back of your eye.

Electroretinogram (ERG): The ERG is a test that measures the electrical activity of your eye. To do this, drops will be placed in your eye and a special contact lens will be placed on your eye. Lights of different colors and strengths will then be flashed on a screen in front of you.

Blood and Urine Collection for other research testing

We will collect an additional blood (about 2 teaspoons) and urine sample to test whether some of the study treatment enters the rest of your body. These samples will be sent to the sponsor. Your blood and urine samples will be coded with your unique study number and not your name.

The sponsor will test your blood sample for antibodies (an immune response) to the study treatment. An immune response is your body's reaction to a foreign substance. Antibodies are proteins made by the immune system that are found in the blood and are part of your body's natural defense against infection and foreign substances. We will be measuring antibodies before and after you receive the treatment to determine if you develop antibodies against the study treatment.

The sponsor expects that the entire sample obtained will be used during the test. However, if any sample remains after completing the tests, the sponsor may use your blood and urine samples for an additional 10 years for general research or quality purposes, such as re-testing for antibodies to the study treatment.

We may ask you to provide a second sample if the sponsor needs to do the tests more than one time. The test might need to be performed again in the event of human or machine error, problems with shipping the sample, or in case a second test is needed to confirm the results of the first test.

Because gene transfer research is relatively new, it is important to collect safety and other useful scientific information about the effects of getting a gene transfer study treatment whenever possible.

In the event of your death at any time during or after the study, your family will be asked if an autopsy and/or tissue sampling from some of your major organs can be done (even if the cause of death is believed not to be related to the study treatment). By signing this consent form you are not consenting to have an autopsy. You do not need to make a decision about this request for an autopsy prior to your participation in this research study. You are just being asked to advise your family of your wishes on this regard.

Study Treatment Administration

The investigator will choose one of your eyes to be given the study treatment. The eye chosen will be the eye with worse vision based on testing at the screening and baseline visits. You will be taken to an operating room where a retinal surgeon will inject the study treatment under the retina in one eye using standard surgical methods.

The surgical procedure you will have is called a "vitrectomy." This procedure is done routinely to treat many different types of eye conditions. A retinal surgeon will make tiny incisions in the sclera (the white part of your eye). He will then remove the vitreous (the jelly-like fluid that fills the eye) and replace it with a salt solution. Using a very tiny needle, the surgeon will inject the study treatment underneath the retina. He will then remove the needle and close the incisions with stitches (the stitches are finer than human hair). The stitches will dissolve on their own after several weeks. Your eye will be patched, and you must wear the patch overnight until your next visit the day after surgery.

Before and during the surgery, you will be given medications (anesthesia) to prevent you from having any pain. Depending on your age and the advice of the surgeon, you will have either

monitored or general anesthesia. With general anesthesia, you are completely asleep. With monitored anesthesia (also called a "twilight sleep") you are typically awake, but you will feel very groggy during the surgery. You may discuss with the surgeon if you prefer one type of anesthesia over the other.

After the study agent is injected, you will be given other medications (antibiotics and steroids) by eye drops, ointments, or small injections around the eye to prevent infection or inflammation. You will be examined several times over the next several hours to check your vital signs (heart rate, breathing rate, blood pressure and temperature) before you are allowed to go home.

You will use eye drops for several weeks after surgery to allow the surface of the eye to heal. The surgeon will decide which eye drops you will need depending on how your eye is healing.

If you have any questions regarding this study now or in the future, contact Dr. Richard Weleber at (503) 494-8386 or other members of the study team at (503) 494-3795. If you need immediate assistance, please call (503) 494-7891 and ask for the ophthalmologist on call. This number is available 24 hours a day.

RISKS AND DISCOMFORTS:

Possible risks related to your being in this study are those risks related to the study treatment, to the surgical procedure, and to other study procedures.

There is a risk that your vision will get worse after you are given the study treatment. This could be due to effects of the study treatment or to effects of the surgical procedure.

You may have some side effects we don't expect because we are still learning about the study treatment.

This is the first time the study treatment will be tested in humans. Humans and animals may respond to the study treatment very differently. Side effects that occurred in animals may or may not occur in humans.

The chance that you will experience any of the side effects listed is uncertain at this early stage of the research.

Risk related to the study treatment

The study treatment has been tested in the eyes of mice, rabbits, and monkeys. In these animal studies, there were reports of mild inflammation of the eye that cleared within two weeks. No other complications were seen.

There is a chance that inflammation in the eye can lead to cataracts (clouding of the lens), clouding of the cornea, glaucoma (increased pressure in the eye), and inflammation of the retina that could lead to a decrease or loss of vision.

Steroids given by eye drops, mouth or injection into the eye are treatments for prolonged inflammation of the eye. You and your study doctor will determine the most appropriate treatment should you need it.

There is a chance that when lentiviral vectors like the study treatment enter a normal cell in the body, the DNA of the vector may insert itself into the DNA of the cell in a place that may cause the abnormal activity of other genes. This has caused harm in some other studies in rare genetic diseases that can affect the immune system.

After getting the gene transfer, some of the subjects developed leukemia or myelodysplasia (types of blood cell cancers) years after receiving the gene transfer. At least one child died from the cancer. A group of experts studied all of the results from tests performed, and they found that the gene transfer caused the cancers by making some cells grow out of control. They also recognized that these cancers were also caused by the effect of the diseases themselves on the normal function of the immune system. The majority of subjects in those studies have not developed blood cancers.

We do not know if the retroviral vector used in this study might cause a new cancer. However, you should be aware that the DNA contained in retroviral vectors will integrate into (join) your DNA. The study treatment uses a vector that has a different pattern of DNA integration than that used in the trials mentioned above. treatmentThe investigators will check your medical history and blood tests before you receive the study treatment to make sure you do not have a problem with your immune system. To date no animals treated with the study treatment or patients treated with the vector in other clinical studies have developed cancer.

It is possible that the viral vector used to transport the gene into your retinal cells, could interact with other viruses you come into contact with. This could result in a new virus that could produce unknown side effects. However, the likelihood of this occurring is thought to be very low.

The levels of the study treatment outside the eye in animal testing have been very low. However, it is possible that small amounts of the study treatment may be introduced in cells outside the eye.

***For pregnancy/risk to fetus (For Women*)**: The study treatment might have harmful effects on a current pregnancy or future pregnancies. We do not know if the gene transfer you will get can become part of normal reproductive cells. If it can, it could cause harm to fetuses conceived after the gene transfer. If you can get pregnant, you and your male partner(s) must use two methods of birth control that work well, like birth control pills, depo-provera, an IUD, a diaphragm or condom with spermicide, or abstinence. You will have to do this for the whole 48 weeks of the study. The risk of harm on future pregnancies is unknown at this time. For concerns about future pregnancies, OHSU offers a variety of options for fertility preservation such as egg or sperm cryopreservation (freezing). If you are interested in this option you should discuss it with the investigator.

If you become pregnant during the research study, please tell the investigator and your doctor immediately. You also should not breastfeed during the study.

Also, we do not know if the study treatment may be present in body fluids. If it is, it could be transmitted to sexual partners. Condoms are essential for preventing transmission to a sexual partner for at least three months following administration of the study treatment.

For pregnancy/risk to fetus (For Men): The study treatment might have harmful effects on sperm. You should not father a child during the study or for three months after you receive the study treatment. We do not know if the gene transfer you will get can become part of normal reproductive cells. If it can, it could cause harm to fetuses conceived after the gene transfer.

For concerns about future pregnancies, OHSU offers a variety of options for fertility preservation such as egg or sperm cryopreservation (freezing). If you are interested in this option you should discuss it with the investigator.

The risk of harm on future pregnancies is unknown at this time. If you may want to have children in the future, we recommend that you bank sperm before beginning the study, so that you have sperm available that has no DNA from the vector and gene. The investigators will provide you with information on sperm banking. In addition to sperm banking, fertile men are encouraged to use barrier birth control devices such as condoms with spermicide during sexual intercourse. You must do this the whole time you are in this study and for three months after you receive the study treatment. The investigators will notify you when it is safe to stop barrier methods of birth control. If you have had a vasectomy, this is an acceptable method of birth control. If a sexual partner becomes pregnant during the research study, please tell the investigator and have your partner tell her doctor immediately.

We do not know if the study treatment may be present in body fluids. If it is, it could be transmitted to sexual partners. Condoms are essential for preventing transmission to a sexual partner.

In studies done on mice and monkeys, no study treatment was found in the reproductive cells.

Risks related to the surgical procedure

You may have inflammation (redness, pain, and swelling), bleeding, or infection around your eye after surgery. You will be given antibiotics and steroids by eye drops, ointments, or small injections around the eye to try to control any inflammation or infection. Most infections can be treated but vision may get worse even with treatment.

Your vision may be blurry for several days after surgery. There is also a risk of retinal tears, retinal detachments or cataracts (clouding of the lens in your eye) that could require additional eye surgery. Symptoms of these problems include blurry vision, flashes of light, sudden onset of floaters (spots or debris floating around in the eye than can be seen), or pain in one or both eyes. You will be treated if you experience any of these problems.

Bleeding in the eye is rare in people without a bleeding tendency. Small amounts of bleeding could occur in different parts of the eye and this usually gets better without treatment. Large amounts of bleeding may require surgery.

Your cornea (the clear covering on the front of your eye) could be scratched during the surgery. Scratches on the cornea usually get better without treatment but may require patching or a bandage contact lens.

An increase in the pressure inside your eye could occur for a short time after surgery but this can be treated with medications.

All of these risks related to the surgical procedure could result in the worsening of vision.

There is also a low risk of complications from anesthesia. There is a small risk of the needle entering the eye or the major nerve in the eye during injection of local anesthesia. General anesthesia may also be associated with nausea or low blood pressure. Rare complications from general anesthesia include prolonged unconsciousness, drowsiness or disorientation, fast heart beat, pneumonia or death.

Risks related to the eye exam
For the eye exams, your pupils will be dilated. Your pupils will remain dilated 4 to 6 hours. This may cause your vision to be blurry, and you may be more sensitive to bright lights. Sunglasses with UV protection should be worn.

Risks related to Optical Coherence Tomography (OCT)
OCT takes about 10 minutes to perform. It is non-invasive and is not painful. You will sit at a machine and look straight ahead while the machine takes pictures of the back of your eyes. No side effects from this test have been reported.

Risks related to AF & Fundus Photography
There are no known risks associated with these procedures. The bright light flashes used to take the photos may cause momentary discomfort, but they will not harm your eyes.

Risks related to other study procedures
Rarely people may have redness, discomfort or allergic reactions to the drops used to dilate the pupil during eye tests. This is usually not serious and can be treated if necessary. Bright lights may be uncomfortable while the pupil is dilated, but this can be relieved by wearing sunglasses. The drops may also make high blood pressure, abnormal heart beating, or some types of glaucoma worse, but these can be treated.

During the ERG test, a special contact lens is placed over your eye after drops are given that numb the eye. Scratches on the cornea might be caused by the contact lens or by rubbing your eye while it is still numb. The investigators will remind you not to rub or touch your eyes after the ERG.

During the Visual Field test, you will have to sit still and look straight ahead at one spot for several minutes at a time. You may feel some fatigue or discomfort during the test, but the test is non-invasive and will not harm your eyes.

We will draw blood from your arm. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, or an infection.

In this study, you will be exposed to radiation during the Chest X-ray. While we cannot be sure any dose of radiation is entirely safe, the amount you will be exposed to in this study is not known to cause health problems.

BENEFITS:

You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

ALTERNATIVES:

You may choose not to be in this study. At this time, there is no treatment or cure for Usher's Syndrome. Since participation in this study is voluntary, your alternative is not to be in this study.

CONFIDENTIALITY:

We will not use your name or your identity for publication or publicity purposes.

This study may attract media attention.

Research records may be reviewed and copied by the sponsor, the OHSU Institutional Review Board, the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), and the National Institutes of Health (NIH) which reviews all gene therapy studies.

COSTS:

There will be no cost to you or your insurance company to participate in this study.

LIABILITY

If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact the study team at 503-494-3795. If you need immediate assistance for an eye-related problem, please call 503-494-7891 and ask for the ophthalmologist on call. This number is available 24 hours a day.

You, or your medical insurance, will be billed for expenses resulting from your condition. However, if you are harmed by the study treatment or study procedures, you will be treated. This treatment will be provided at no cost to you or your insurance company if the harm is

caused by the study treatment or study procedures and would not have been expected from the standard treatment for your condition.

You have not waived your legal rights by signing this form. Any claim you make against Oregon Health & Science University may be limited by the Oregon Tort Claims Act (ORS 30.260 through 30.300). If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

PARTICIPATION:

If you have any questions regarding your rights as a research subject, you may contact the OHSU Research Integrity Office at (503) 494-7887.

You do not have to join this or any research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join or withdraw early from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled.

Your health care provider may be one of the investigators of this research study, and as an investigator is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way involved in this project. You do not have to be in any research study offered by your physician.

You may be removed from the study if:

- the sponsor stops the study
- the investigator stops the study
- you become pregnant
- you develop serious side effects
- your disease gets worse
- you do not follow study instructions

You will be informed of new findings that may affect your wish to continue participation.

If you withdraw from the study early, we will ask you to participate in the long-term follow-up study. We may ask you to provide additional blood or urine samples or have other tests performed, if the investigator thinks this would be in your best interest, such as to evaluate a side effect that has not yet resolved. Participation in the long-term follow-up study is optional.

We will give you a copy of this form.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study.

OREGON HEALTH & SCIENCE UNIVERSITY
INSTITUTIONAL REVIEW BOARD
PHONE NUMBER (503) 494-7887

CONSENT/AUTHORIZATION FORM APPROVAL DATE

Jan. 12, 2012

Do not sign this form after the Expiration date of: 12-07-2013

_____ _____

Signature of Subject Date

_____ _____

Signature of Investigator Obtaining Consent Date