RESEARCH SUBJECT CONSENT FORM

TITLE:	The Effect of Voxelotor on Exercise Capacity of Youths with Sickle Cell Anemia
PROTOCOL:	ESR-C006 WIRB® Protocol #20201909
INVESTIGATOR:	Elizabeth Yang, MD, PhD 8081 Innovation, Park Drive, Suite 765 Fairfax, VA 22031 United States
FUNDING:	Global Blood Therapeutics
STUDY-RELATED PHONE NUMBER(S):	571-472-1717 (24 hours)

In this consent form "you" generally refers to the research subject. If you are being asked as the parent or legal guardian to permit the subject to take part in the research, "you" in the rest of this form generally means the research subject.

RESEARCH CONSENT SUMMARY

You are being asked for consent to take part in a research study. This document provides a concise summary of this research. It describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document will provide all relevant details.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

How long will I be in this research?

We expect that your taking part in this research will last 6 months or when you complete both of the exercise tests required by the study.

Why is this research being done?

The purpose of this research is to find out whether the new sickle cell medication Voxelotor improves the exercise capacity of young people with sickle cell anemia.

Sickle cell patients have lower hemoglobin than people without sickle cell anemia. Since hemoglobin carries oxygen that is necessary for exercise, higher hemoglobin usually enables a person to do more physical activity. The medication Voxelotor can increase hemoglobin in patients with sickle cell anemia. Therefore, we wish to know whether sickle cell patients taking Voxelotor can perform more physical exercise than before they took Voxelotor.

What happens to me if I agree to take part in this research?

If you decide to take part in this research study, you will be asked to perform a baseline cardiopulmonary exercise test, called CPET, take Voxelotor for at least 2 months, then perform the CPET again. You will have to consent to starting this new medication. If you are taking Hydroxyurea, you will continue to take Hydroxyurea and take Voxelotor in addition to Hydroxyurea. You will need to come to clinic monthly for approximately 6 months. You will go to the Exercise Lab in Rockville, MD twice to perform CPET at designated times. You will have assistance with transportation to the Exercise Lab. Blood samples will be sent to a research lab for study labs.

Could being in this research hurt me?

The most important risks or discomforts that you may expect from taking part in this research include side effects of the medication Voxelotor and physical exertion during exercise testing. The side effects of Voxelotor are minor and no significant toxicities that require medical treatment have been reported. The exercise test has been done safely in sickle cell patients without causing pain.

Will being in this research benefit me?

The most important benefits that you may expect from taking part in this research include free access to the newly FDA approved medication Voxelotor. You may experience higher hemoglobin levels with improved oxygen carrying capacity. You may also benefit from free exercise testing that will provide information about your personal exercise capacity.

Possible benefits to others include new information about how Voxelotor affects the ability of people with sickle cell anemia to do exercise, which will provide a new reason to take this medication.

What other choices do I have besides taking part in this research?

Instead of being in this research, your choices may include not participating in this study and continuing your current sickle cell therapy. You can receive Voxelotor without participating in this study.

What else should I know about this research?

Other information that may be important for you to consider so you can decide whether to take part in this research include: the participant must be compliant with their medications, show up to clinic visits at scheduled times and do the exercise testing that is required for the study in a timely manner. Also, the exercise testing will be done in Rockville, Maryland, and assistance with transportation will be provided. Participants will also receive monetary compensation for completing the exercise tests. All collected data will be kept confidential per HIPAA regulations.

DETAILED RESEARCH CONSENT

You are being invited to take part in a research study. A person who takes part in a research study is called a research subject, or research participant.

What should I know about this research?

- Someone will explain this research to you.
- This form sums up that explanation.
- Taking part in this research is voluntary. Whether you take part is up to you.
- You can choose not to take part. There will be no penalty or loss of benefits to which you are otherwise entitled.
- You can agree to take part and later change your mind. There will be no penalty or loss of benefits to which you are otherwise entitled.
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

Why is this research being done?

The purpose of this research is to find out whether the new sickle cell medication Voxelotor improves the exercise capacity of young people with sickle cell anemia.

The medication Voxelotor can increase the hemoglobin level in patients with sickle cell anemia. Since more hemoglobin increases the amount of oxygen that can be carried, and higher hemoglobin usually enables a person to do more physical activity, we wish to know whether

sickle cell patients taking Voxelotor can perform more physical exercise than before they took Voxelotor.

About 10 subjects will take part in this research.

How long will I be in this research?

We expect that taking part in this research will last 6 months or when both of the exercise tests required by the study are completed.

What happens to me if I agree to take part in this research?

If you decide to take part in this research study, you will perform this test:

- Cardiopulmonary exercise test, called CPET. You will perform a baseline CPET, take Voxelotor for at least 2 months, then perform a second CPET.
  CPET consists of a participant running on a treadmill while his/her breaths and vital signs are measured. The treadmill will gradually increase in incline to become steeper as the participant is running. An exercise physiologist will guide you through the exercise test. The exercise test lasts 8 to 12 minutes, or when you communicate to the exercise physiologist that you are too tired to continue. CPET is performed under the supervision of a cardiologist.
- Results of your CPET will be provided to you.
- CPET will be done at the Child Cardiology Associates Exercise Lab located at
  9707 Medical Center Dr #100, Rockville, MD 20850

You will take this study drug:

- Voxelotor – This medication was approved by the FDA in November 2019 for patients with sickle cell disease age 12 years or older. For this study, Voxelotor will be supplied by the drug company Global Blood Therapeutics (GBT). You will take 1500mg (3 tablets) once a day.
- If you are taking Hydroxyurea, you will continue to take Hydroxyurea and take Voxelotor in addition to Hydroxyurea.
- You may continue Voxelotor after the study, but it will no longer be supplied by the manufacturer after you have completed the study. Your doctor will help you obtain the medication.

You will come to clinic

- Sickle cell clinic visits will be monthly for 6 months
- Blood will be drawn for study labs during 2 clinic visits
- Clinic visits will be at PSV clinic in the Schar Cancer Institute building across from Inova Fairfax Hospital at
  8081 Innovation Park Dr, Suite 765, Fairfax, VA

The following is the overall timeline of events that will take place during this research study

Enrollment Visit	Informed consent will be discussed and signed. Routine labs will be obtained and compared to labs in prior 3 months. Routine labs: complete blood count, reticulocyte count, metabolic panel, lactat dehydrogenase (LDH) enzyme, haptoglobin, % fetal hemoglobin (Hgb F)
Visit 1 1 month	This visit should be at least 1 month from enrollment visit. Obtain blood sample for baseline routine labs and baseline study labs. Study labs: % F cells, tests of red blood cell sickling and ability to carry oxygen. If routine labs stable, first CPET will be scheduled.
Visit 2 1-2 months	Perform 1st CPET, as soon as can be scheduled after Visit 1
Visit 3 2 months	This visit should be as soon as can be scheduled after the 1st CPET. Obtain routine labs. Initiate treatment with study drug Voxelotor.
Visit 4 3 months	1st follow-up visit, 1 month after initiation of Voxelotor. Obtain routine labs.
Visit 5 4 months	2nd follow-up visit on study drug Voxelotor, no later than 1 month after Visit 4. Obtain routine labs and study labs. Schedule 2nd CPET. Continue Voxelotor treatment until 2nd CPET.
Visit 6 4-5 months	Perform 2nd CPET, as soon as can be scheduled after Visit 5
Visit 7 6 months	Final Assessments Obtain routine labs Fill out CGIC and PGIC questionnaire

What are my responsibilities if I take part in this research

If you take part in this research, you will be responsible to:

- Come to clinic at the scheduled times
- Take the study drug Voxelotor daily as instructed
- If already taking Hydroxyurea, continue to take Hydrxoyurea as prescribed with daily compliance
- Go to the Exercise lab to perform CPET when scheduled (assistance with transportation will be provided)
- Notify the study team about any schedule changes or unexpected events as soon as possible
- Check with the sickle cell doctor before taking any additional medication and refrain from herbal medicines. Some medications will interact with Voxelotor and should be avoided.
- Report any side effects or allergic reactions to the study team (no significant side effects are expected)
- Female participants who are sexually active need to use highly effective contraception during study participation and for an additional 30 days after the end of the study
- Male participants of reproductive potential: use condoms or other methods to ensure effective contraception.

Could being in this research hurt me?

Physical risks

Voxelotor: The side effects that have been reported are minor. No significant toxicities requiring medical intervention have been reported.

The most common adverse reactions reported with incidence greater than 10% are:
headache, diarrhea, abdominal pain, nausea, fatigue, rash, and fever

Rare side effect:
Hypersensitivity reaction to drug (Symptoms can include hives, rash, fever, itching, watery eyes, shortness of breath.)

If you experience side effects that you find intolerable, Voxelotor will be stopped and you can stop the study. Side effects will go away when the drug is discontinued. There is no expected long-term effect.

CPET: Aggravation of sickle cell symptoms during exercise testing is unlikely, because exercise testing will be stopped if you complain of fatigue or discomfort. Exercise testing has been done by some sickle cell patients who were on a previous study testing Voxelotor, and no adverse events, such as pain crisis, occurred.

Venipuncture: The risks of drawing blood from a vein include fainting, local pain, bruising, swelling, or rarely an infection at the needle site. Patients routinely have blood draws as part of regular sickle cell care, and this study will take blood from the same venipuncture as routine care blood draws, and no extra sticks are required. One or two tubes of blood will be drawn for study labs on 2 occasions in the study.

Psychological risk

Voxelotor treatment: Most patients are already taking medication for sickle cell disease, such as Hydroxyurea. Adding another oral medication to be taken at the same time as Hydroxyurea is unlikely to cause you adverse psychological effect.

CPET: You may experience anxiety, stress, or uncomfortable emotions about your CPET performance. However, since we do not know what result to expect for our patients, we will not be placing any expectations on you. To avoid apprehension or anxiety, the exercise physiologist will explain CPET procedure to you before the test, so you will know what will happen when you do the exercise test.

Venipuncture: This study will obtain blood from the same venipuncture stick used for routine blood work and should pose no additional psychological effect.

Economic risk

You will be compensated for participation in this study and the costs of travel to the exercise lab will be covered by the study, therefore there is no economic risk.

Legal risk

There is no legal risk.

Social risk

Privacy will be maintained. There is no foreseeable social risk.

There may be risks from taking Voxelotor that are currently unknown. In addition, it is not known if Voxelotor causes any harm to pregnant women or unborn children, therefore, you should not become pregnant or cause someone to be pregnant while on this study.

Will it cost me money to take part in this research?

Taking part in this research is not expected to cost you any money. The costs of the exercise tests and the study labs are paid by the study. Travel costs to the exercise lab will be covered by the study. If there are problems with coverage of study monitoring labs, please discuss these with the primary investigator.

Will being in this research benefit me?

The direct benefits of participating in this study include free access to the newly FDA approved medication Voxelotor and free exercise testing that will provide you with information about your personal physical abilities and activity guidelines. You may experience higher hemoglobin levels.

Long-term benefits may include fewer sickle cell complications and potentially improved quality of life.

Possible benefits of this study to others include new information about how Voxelotor affects the ability of people with sickle cell anemia to do exercise, which may provide a new reason for people with sickle cell anemia to take this medication.

What other choices do I have besides taking part in this research?

You may choose not to participate in this study and continue your current sickle cell therapy. You can receive Voxelotor without participating in this study.

What happens to the information collected for this research?

Your private information and your medical record will be shared with individuals and organizations that conduct or watch over this research, including:

- The research sponsor
- People at Global Blood Therapeutics who work with the research sponsor and fund the research
- Government agencies, such as the Food and Drug Administration
- The Institutional Review Board (IRB) that reviewed this research

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

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.

Data collected in this research might be de-identified and used for future research or distributed to another investigator for future research without your consent.

Who can answer my questions about this research?

If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at (800) 562-4789, help@wirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

What if I am injured because of taking part in this research?

If you are injured or get sick because of being in this research, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance may be billed for this treatment. No payment for medical care is routinely available from the study doctor or sponsor.

Can I be removed from this research without my approval?

The person in charge of this research can remove you from this research without your approval. Possible reasons for removal include:

- You are unable to keep your scheduled appointments
- You are unable to take Voxelotor consistently
- You have a side effect or an adverse event such as hypersensitivity to Voxelotor that requires stopping the research
- You are unable to perform CPET exercise test
- You become pregnant
- The research is canceled by the FDA or the sponsor or the funding agency
- If you meet an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- If you discontinue Voxelotor before completing the 2nd CPET but are willing to resume the study drug, then you must take the study drug continuously for at least 1 month before performing the 2nd CPET. If you discontinue the study drug and are unwilling to resume, then you will be discontinued from the study.

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

What happens if I agree to be in this research, but I change my mind later?

Participants are free to withdraw from participation in the study at any time upon request.

If you decide to leave this research, contact the research team so that the investigator can document the reason and date of leaving.

Will I be paid for taking part in this research?

For taking part in this research, you may be paid up to a total of $400. Your compensation will be broken down as follows:

- $150 for each CPET you complete
- $50 for meals for you and your parent for each trip to the exercise lab for CPET
- If you drop out of the study before completing any CPET, you will not be paid.
- If you drop out of the study after completing 1 CPET, you will receive payment for the CPET you completed.
- Your travel to the exercise lab will be paid by the study, but you will not be paid in addition to reimbursement. For example, if you take Uber to the exercise lab, the study will reimburse the amount on the Uber receipt. If the study team arranges a driver, the study team will pay the driver. If you choose to drive yourself, the study will reimburse you by mileage according to the IRS standard mileage rate.

Health Insurance Portability and Accountability Act (HIPAA)

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

I agree to permit Pediatric Specialists of Virginia, the Principal Investigator, co-Investigators, the study team, and Global Blood Therapeutics to obtain, use and disclose health information about me as described below. Authorized staff not involved in the study may be aware that I am participating in a research study and may have access to my information. If the study is related to my medical care, any study-related information may be placed in my permanent hospital, clinic or physician's office records.

The health information that may be used or disclosed may include:

- All information collected during the research and procedures described in this Informed Consent.
- Health information in my medical records that is relevant to the Research, includes my medical history and other medical information relating to my participation in the study.

The following information will be obtained from my medical record:

- Information about me, such as age, sex, ethnic group
- Medications, past and current
- Notes written by health care providers
- Medical history and physical examinations
- Laboratory results
- Procedural results, including cardiopulmonary exercise test results
- Heart monitoring results
- Imaging study results (X rays and scans)
- Medication side effects

My health information may be disclosed to:

- The study team
- The sponsor of the research, Global Blood Therapeutics
- The Institutional Review Board (IRB), the agency that oversees this research
- Federal and State agencies that have oversight of the study or whom access is required under the law. These may include FDA, OHRP, NIH and Virginia Department of Health

All reasonable efforts will be used to protect the privacy of your protected health information. Once your health information is shared with the sponsor, federal agencies, and others as described above, they may share your information without your permission.

I understand that:

I do not have to sign this Authorization, but if I do not, I may not participate in the Research. If I do not sign this authorization, my right to other medical treatment will not be affected.

I may change my mind and revoke (take back) this Authorization at any time and for any reason. To revoke this Authorization, I must write to the Principal Investigator, Dr. Elizabeth Yang at 8081 Innovation Park Dr. Suite 765, Fairfax, VA 22031.

How long does my authorization remain in effect?

This authorization expires when the study and all the analyses are complete.

Will I have access to the information in my Research Record?

I have the right to request access to the information in my Research Record from the investigators and study staff.

Statement of Consent:

Your signature documents your permission for you or the individual named below to take part in this research.

You will be given a copy of this consent form.

Printed name of subject	
Signature of subject age 18 or older	Date
Printed name of parent or legal guardian of subject	Relationship
Signature of parent or legal guardian of subject	Date
Printed name of person obtaining consent	Title/position
Signature of person obtaining consent	Date

Assent for subjects age 12-17

- All children are required to assent, unless the investigator determines that the capability of the child is so limited that the child cannot reasonably be consulted
- If assent is obtained, have the child sign the consent form, unless the investigator determines that the child is NOT capable of signing

❑ I have explained the study to the extent compatible with the subject's capability, and the subject has agreed to be in the study.

Signature of subject		Date
Signature of person obtaining assent	Title/position	Date

Witness Signature if short form is used

My signature below documents that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Printed name of witness to consent process	Title/position
Signature of witness to consent process	Date