

Northwell Health

Feinstein Institute for Medical Research

Cohen Children's Medical Center of New York

Consent for Participation in a Research Study

Title: Phase I/II, Open-Label Study to Determine Safety of Trifluoperazine (TFP) in Adults with Red Blood Cell Transfusion-Dependent Diamond Blackfan Anemia

Principal Investigator: Adrianna Vlachos, MD

Supporter: CAMP4 (previously Marauder Therapeutics), National Institutes of Health National Heart, Lung, and Blood Institute

Introduction

You are being asked to join a research study. The purpose of a research study is to answer specific questions, sometimes about the safety of a drug or device and how well it works. Being in a research study is different from being a patient. When you are a patient, you and your doctor have freedom in making decisions about your healthcare. When you are in a research study, the researcher will follow the rules of the research study as closely as possible, while monitoring your health.

This consent form will explain:

- the purpose of the study
- what you will be asked to do
- the potential risks and benefits

It will also explain that you do not have to be in this study to receive medical care. You should ask questions before you decide if you want to participate. You can also ask questions at any time during the study.

Why is this research study being done?

The purpose of this research study is to determine if the medication trifluoperazine (TFP) is safe in patients with Diamond Blackfan anemia (DBA) who require chronic red blood cell transfusions. You are being asked to participate in this study because you have been diagnosed with Diamond Blackfan anemia and require chronic red blood cell transfusions.

Research has demonstrated that zebrafish with mutations (defects) in the one of the genes known to cause DBA were able to make red blood cells and increase their hemoglobin (Hb) levels when treated with TFP. TFP was also tested in a mouse model of DBA and showed significant increase in both red blood cell counts and Hb levels. TFP was well tolerated and resulted in improved anemia without any gross side effects in the mice.

TFP was also tried in cells from DBA patients and the red blood cell production was increased with improvement of the anemia.

Why is this research?

This is a research study because TFP has never been tested in patients with DBA. TFP is a drug that has been approved by the Food and Drug Administration (FDA) for the treatment of psychiatric disorders. TFP has not been approved by the FDA to be used in patients with DBA. In this research study the safety of TFP is being tested at different dose levels in patients with DBA.

How many people will take part in this study?

This research study may enroll up to 24 participants.

How long will you be in this study?

If you choose to take part in this study, you will take the study drug TFP for 21 days, and you will be monitored for an additional 7 days. If you stop taking TFP before the 21 days are completed, you will still be followed for a total of 29 days from the first day you took TFP. You will be asked to attend 4-5 visits over the period of 4 weeks. The initial screening visit will last approximately 2-3 hours; the other 4 visits will last about 1 hour each. The screening visit may also be considered as the first visit if the patient has previously signed this consent form and the screening has been completed at the time of the visit.

What will happen in this research study?

This is a dose escalation, open-label study testing the safety of TFP in patients with DBA who require chronic red blood cell transfusions.

TFP is a tablet that is taken orally and has been approved by the FDA since 1958 for the short-term treatment of psychotic disorders, anxiety, and nausea.

An Open-Label Study is a study in which all parties (the patient taking part in the study, the doctor and the study coordinator) know the drug and dose being given. In an open-label study, none of the participants are given placebo tablets (a tablet which looks like the study drug but has no real medicine in it).

A Dose Escalation Study is as a study in which the amount of the investigational drug is increased during the study.

If you decide to participate in this study and you sign this informed consent form, a review of your medical records which includes your diagnostic work up, transfusion history, physical examination, and laboratory blood work results, will be performed in order to determine if you are able to participate. A list of all of the procedures that will be performed at the visits during this study follows.

The initial Screening visit is the visit at which the doctor conducting the study will decide if you are able to participate in this study based on the answers to multiple questions, the results of a physical examination, and the results of blood tests.

At the first Treatment study visit you will undergo a history, physical examination and blood tests. You will be asked to take one TFP tablet orally for 21 days. There will be 4 dose levels of TFP (1 mg, 2 mg, 5 mg and 10 mg [taking two 5mg tablets]). You will be assigned to a dose level based on how many patients are on the study before you. You will be asked to take the same dose of TFP for up to 21 days. During these 21 days you will return to the study center once every 7 days (3 times) to complete a study visit, including history, physical examination, and bloodwork. Any and all adverse events will be assessed at each visit. At the end of the 21 days you will discontinue TFP.

Once you have completed the 21 days of TFP, you will return to the study center for one Follow-Up visit 8 days later.

A summary of the plan for your visits follows:

Visits	What Happens	Treatment Plan
Screening (Day -28 to Day -1)	Sign consent; get all prior records for review; physical exam; bloodwork; pregnancy test (if female)	None
Visit 1 Day 1	Physical exam; bloodwork; pregnancy test (if female); assess any adverse events	Receive 21 day supply of study drug; start designated dose on Day 1 then daily
Visit 2 Day 8	Physical exam; bloodwork; assess any adverse events	Continue daily dose of study drug
Visit 3 Day 15	Physical exam; bloodwork; pregnancy test (if female) ; assess any adverse events	Continue daily dose of study drug; will discontinue on day 21
Visit 4 Day 22	Physical exam; bloodwork; assess any adverse events	Return the day after stopping study drug
Visit 5 Day 29	Physical exam; bloodwork; assess any adverse events	Return for one follow-up visit 8 days after stopping study drug

You will be given the 21-day supply of TFP tablets at one time. TFP can be taken in the morning or the evening but should be taken at the same time every day. It can be taken before or after meals.

During the course of this study the following procedures will be performed:

Informed consent: If you choose to participate in the study you will be asked to sign this form before any study procedures are performed.

Medical History: The study doctor will ask you a series of questions about your health in order to determine your medical condition. This may include questions about family members, use of medications, and any surgeries or procedures that you have had. At each study visit, you will also be asked about your transfusion history and any changes in your health or medications while taking the study drug.

Physical examination: This will include height at first visit only, weight, vital signs, blood pressure, and neurological exam.

Bloodwork: You will have blood taken at every visit. Depending on the study visit you will have between 15 to 20 ml of blood drawn (3 to 4 teaspoons).

Pregnancy test (females only): You will have a blood pregnancy test at the screening visit (before any study drug is given) and at visits 1 and 3. You will be withdrawn from the study if it is found that you are pregnant. **You must notify the study doctor immediately if you think you may be pregnant.**

Drug Dispensation: You will be given the 21-day supply of TFP tablets at one time. TFP can be taken in the morning or the evening, but should be taken at the same time every day. It can be taken before or after meals.

Birth Control: The study drug may affect a baby, before or after the baby is born. As a result, women should not be in this study if they are:

- pregnant,
- breast-feeding, or
- trying to become pregnant.

If you are a female who is able to become pregnant while participating in the study, you are to use highly effective methods of birth control for the entire time you are on the study drug and for 1 week after the last dose of TFP, i.e. for a total of 29 days. Hormonal methods (oral birth control pills, etc.), double-barrier methods (condom with spermicidal, sponge with spermicidal or diaphragm with spermicidal), or not having sex may be used. Your doctor will discuss these with you.

If you are a man, you should not have unprotected sex with your partner while on this study. You and your partner should use birth control for the entire time you are on the study drug and for 1 week after the last dose of TFP, i.e. for a total of 29 days. Hormonal methods (oral birth control pills, etc.), double-barrier methods (condom with spermicidal, sponge with spermicidal or diaphragm with spermicidal), or not having sex may be used. Your doctor will discuss these with you.

As noted before, females of child-bearing potential will have a blood pregnancy test at the screening visit (before any study drug is given) and at visits 1 and 3. You will be withdrawn from the study if it is found that you are pregnant. **You should notify the study doctor immediately if you think you may be pregnant.**

What are the risks of the research study? What could go wrong?

Blood Draws: There are no major risks of having blood drawn. It can be uncomfortable and can sometimes cause a bruise. In rare cases, it can cause fainting. Only trained staff will draw your blood.

Trifluoperazine: Common possible side effects of TFP may include:

- agitation
- constipation
- drowsiness

- dizziness
- dry mouth
- jitteriness
- loss of appetite
- nausea
- tiredness
- increased sensitivity to the sun

To reduce the risk of dizziness you should get up slowly when rising from a sitting or lying position. You should not drink alcohol while taking TFP. You should also check with your doctor about taking other medicines that may cause drowsiness while taking TFP. TFP may cause you to become sunburned more easily so you should use sunscreen or wear protective clothing if outside for more than a short period of time.

Unlikely but severe side effects of TFP may include:

- severe allergic reactions (skin reactions, rash, hives, itching, difficulty breathing, swelling of mouth, lips or tongue, wheezing)
- confusion
- decreased coordination
- sleeplessness
- muscular weakness
- muscle spasms of the face, neck or back
- uncontrolled twisting or twitching movements (twitching of face or tongue, loss of balance, uncontrolled movements of arms or legs; trouble speaking or swallowing)
- restlessness
- shuffling walk
- lactation and/or loss of your menstrual cycle
- blurred vision
- difficulty urinating

The muscle/nervous system problems possibly caused by this class of drugs including TFP are also called extrapyramidal symptoms or EPS. Your doctor may prescribe another medication to decrease these side effects. **Stop taking the TFP and tell your doctor right away if you notice any of the following side effects:**

- feelings of anxiety or agitation or jitteriness
- drooling or trouble swallowing

- restlessness or constant need to move
- shaking (tremor)
- shuffling walk
- stiff muscles
- severe muscle spasms or cramping (such as twisting neck, arching back, abnormal eye movements, eyes rolling up, tongue sticking out, lip smacking)
- mask-like expression of the face

Symptoms of motor restlessness and agitation often disappear spontaneously. Symptoms of prolonged abnormal contractions of muscle groups may occur in susceptible individuals during the first few days of treatment. While these symptoms can occur at low doses, they occur more frequently at higher doses. In very rare cases, involuntary (non-purposeful), stiff or jerky movements of the arms or legs can occur. This is called tardive dyskinesia. Sometimes symptoms may persist for months or years and, while they gradually disappear in some patients, they may never go away (be irreversible) in rare patients. The risk appears to be greatest in elderly patients (which are not included in this study) on prolonged, high-dose therapy. There is no known effective treatment for tardive dyskinesia. This is why it is important to call your doctor immediately if you experience any of these rare symptoms.

Rarely, Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, of which TFP is one. Cardinal features of NMS are high fever, stiff muscles, confusion, abnormal thinking, fast or irregular heartbeat and sweating. NMS is potentially fatal and requires symptomatic treatment so you should contact your doctor immediately if you have any of these symptoms.

Collection of Sensitive Information

Some of the questions we will ask you are personal. You may feel embarrassed or stressed. You may ask to see the questions before deciding whether or not to take part in this study.

Unknown Side Effects

As with any drug, there might be side effects that are unknown at this time. You will be closely watched for side effects. You should report any unusual events to the study staff.

Risks to Women of Childbearing Potential and Pregnant Women

We do not know the effects of TFP on fertility or a fetus. For this reason, if you believe you are pregnant or have a chance of becoming pregnant, you should not take part in this study. A blood pregnancy test will be performed prior to the start of study procedures and during the study. If you are pregnant, you will not be allowed to be in the study.

If you become pregnant during the study, you will be immediately withdrawn from the study and closely monitored through your entire pregnancy.

The side effects of TFP on newborns are also not known; therefore, if you are currently breastfeeding you cannot be in this study.

You will be closely watched for side effects. You should report any unusual events to the study staff or Dr. Adrianna Vlachos at (718) 470-3460 or (516) 562-1504 immediately.

What are the benefits of this research study?

The possible benefits you may experience from the drug described in this study include an improvement in the anemia of DBA and a decrease in the amount of transfusions that you may need.

This research may not benefit you directly. However, information we learn about this disease may help patients in the future.

Drug Availability after Completion of Study

There is no plan to continue study drug after the study is complete because of the possible side effects that become more prevalent the longer a patient is on TFP.

If you do not want to take part in this research study, what are your other choices?

If you do not join this study, you will continue to receive red cell transfusions as per your usual schedule.

Are there any costs for being in this research study?

You will not have any added costs from being in this study. All study related visits, procedures and study drug will be given to you at no cost. Neither you nor your insurance company will be billed for your participation in this research. All other routine costs such as transfusions will be billed to you and your insurance company in the usual way, as part of your standard care.

Will you receive any payments for participating in this research study?

You will not receive any payment for participating in this research study.

If the research produces marketable products, will you receive any payment?

If this research produces a marketable product, there are no plans for you to receive any money.

What happens if you are injured while participating in this study?

If you are sick or hurt from being in the study as a direct result of a properly performed study procedure or because you are taking the Study Drug as directed, you will receive medical care and treatment as needed from Northwell Health. The Sponsor will pay for the reasonable and necessary costs associated with this care. No other compensation or payment will be provided to you, including lost wages.

What are your rights as a research participant?

Your participation in this study is voluntary. The quality of your medical care will be the same, whether you join, refuse to join, or decide to leave the study.

If you do not join the study you will not be penalized or lose benefits to which you are entitled. If you join the study you may withdraw at any time without prejudice to your future care at Northwell Health. Follow-up examinations may be needed to assure your well-being.

Could you be taken off the study before it is over?

It is possible that your participation in this study may end without your consent. This decision may be made by a researcher, study sponsor or the Institutional Review Board (IRB; the committee that oversees research at this institution).

Reasons for withdrawal may include:

- failure to follow instructions,
- failure to show up for study visits,
- it is not in your best interest to continue on this study, or
- the study is stopped.

If you withdraw from this study or if you are withdrawn from the study, any data (or samples) already collected will continue to be used. However, no new tests will be performed or data will be collected.

For safety reasons, if you withdraw from the study, you will be urged to return for final safety testing.

What happens if new information is learned?

You will be told of any new findings that may change your decision to continue to participate. Your consent to continue to take part in this study may be obtained again.

What information will be collected and used for this study?

If you agree to be in this study, we will collect health information that identifies you. We will collect the results of your tests. We may also collect information from your medical record. We will only collect information that is needed for the research study. This information has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization. If you do not want to provide authorization, then you cannot participate in this research study.

Who else will see your information?

Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside Northwell Health.

The following reviewers may access your study and medical records to make sure that this study is being done properly:

- Representatives from federal funding agencies such as the National Institutes of Health National Heart, Lung, and Blood Institute,
- Representatives from federal and state government oversight agencies such as the U.S. FDA,
- Representatives from Northwell Health's Human Research Protection Program (the group of people that oversee research at this institution),
- The medical monitor of the study, and

- CAMP4 (the supporter of the study).

We will do our best to protect the privacy of your records but it is possible that once information is shared with people listed on this form, it may be released to others. If this happens, your information may no longer be protected by the federal law.

In the future, we may publish results of this study in scientific journals and may present it at scientific meetings. If we do we will not identify you.

If the researchers learn about potential serious harm to you or someone else or other public health concerns, it will be shared with the appropriate authorities.

Will you be able to access your records?

If your research records are used for decisions related to your clinical care, then you have the right to review this information and request changes. This is limited to information about your treatment, and does not include information related to procedures or tests that are for research purposes only. You may access this information only after the study analysis is complete. You have the right to know who has and who will see your records. To request this information, please call the Institutional Review Board/Human Research Protection Program at 516-465-1910.

How long will your health information be kept?

There is no limit on the length of time we will keep your information for this research study because it may be analyzed for many years. We will keep it as long as it is useful, unless you decide you no longer want to take part or we close the study. You are allowing access to this information indefinitely.

Can you change your mind?

If you change your mind about being in the study, you may withdraw at any time. If you want us to stop collecting your health information, you need to send a letter to the researcher at the following address:

Adrianna Vlachos, MD
The Feinstein Institute for Medical Research
350 Community Drive
Manhasset, NY 11030

Your letter needs to say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.

Will information about this study be available to the public?

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 website will include a summary of the results. You can search this website at any time.

Does the investigator of this study receive money if you take part?

There is funding provided to conduct the study and supply the medication. The investigators do not financially benefit from your participation. Funding for this research study is provided by CAMP4 and the National Institutes of Health National Heart, Lung, and Blood Institute. If your doctor is an investigator for this study s/he is interested in both your healthcare and the conduct of this research. You do not have to take part in a research study conducted by your doctor.

Who can answer your questions about this study?

If you have any questions about the study, you may call Dr. Adrianna Vlachos, MD, at (516) 562-1504. If you have questions about side effects or injury caused by research you should call Dr. Adrianna Vlachos, MD, at (516) 562-1504. If you need emergency care, dial 911 or go to the nearest Emergency Room. If you have questions about your rights as a research participant, or concerns about being in the study, or would like to offer input, you may contact the Office of the Institutional Review Board (the committee that oversees research at this institution) at 516-465-1910. A signed copy of this consent form will be given to you.

[Signature Page Follows]

Summation/Signature

You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. A member of the research team will answer any future questions you may have. You voluntarily agree to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your legal rights.

Signature of Participant

Date

Printed Name of Participant

Signature of Witness

Date

(Note: A witness can be a member of the research team, but cannot be the same person signing consent as the investigator)

Witness's Printed Name

Investigator's Statement

In addition to advising the above participant of other forms of treatment and therapy which are appropriate, I have offered an opportunity for further explanation of the risks and discomforts which are, or may be associated with this study and to answer any further questions relating to it.

Investigator's Signature

Date

Investigator's Printed Name