ApoPharma Inc.

Informed Consent to Take Part in a Clinical Trial, Parent/Guardian Version

Study Title: Safety and efficacy of early-start deferiprone treatment in infants and young children newly diagnosed with transfusion-dependent beta thalassemia

Study Code: LA55-0417

Sponsor: ApoPharma Inc.
200 Barmac Drive, Toronto, Ontario, Canada M9L 2Z7

Investigator: [*insert name*]
[*insert name and address of study site*]
Telephone: [*insert telephone number of investigator***]**

ApoPharma Model ICF Version 3.0, 24 APR 2019

Site-Specific ICF Version [x.x], DD MMM YYYY

Dear Parent or Guardian,

Your child (son, daughter, or ward) is invited to take part in a research study. It is important that you fully understand what this participation will mean before you give your consent, so take your time to review this form, and ask the Investigator (study doctor) or other study staff to explain anything that is not clear. You may wish to discuss things with your child's regular doctor and family members before making your decision.

Having your child take part in this study is up to you. You do not have to say yes, and if you do agree, you may later change your mind at any time. It is important to note that if you say yes but your child is old enough to be asked as well and says no, he/she will not be enrolled.

This study is organized and paid for by the pharmaceutical company ApoPharma Inc. (the "Sponsor"). The Investigator, Dr. [*insert name*], is being paid by the Sponsor to do this research. *If there are any conflicts of interest affecting the investigator, identify them here.*

What is the purpose of this study?

Your child has been diagnosed with **beta thalassemia major**, a genetic blood disorder. People with this disease have an abnormal form of hemoglobin, the protein in red blood cells that carries oxygen throughout the body, and must therefore receive transfusions of healthy red blood cells for their entire lives. These transfusions are life-saving, but since each unit of transfused blood contains iron and the body has no natural way of getting rid of extra iron, over time there is a build-up of iron in blood and organs. While a certain amount of iron is necessary, too much of it

is harmful and can lead to serious medical problems. Patients who need frequent transfusions must therefore take drugs called **iron chelators** to help their bodies get rid of the extra iron.

The iron build-up caused by blood transfusions is gradual, and according to medical guidelines, treatment to remove the extra iron from the body should not be started until a certain iron level is reached. This delay is due to a concern that removing too much iron from the body may interfere with normal development in young children. In fact, with the first iron chelator, deferoxamine, growth delays were often seen in children who were started on this drug while their level of iron overload was still mild, and postponing the start of iron-removal treatment was found to prevent that problem. However, this delay may increase the risk of extra iron building up in glands and organs, which may cause health problems later in life.

Deferiprone (brand name Ferriprox®) is an iron chelator that binds to iron less strongly than deferoxamine does and has a greater ability to redistribute it in the body, which may reduce the risk of reducing iron levels by too much when the build-up is not yet very high. Therefore, it may be safe to start using this drug at a lower level of iron load than usual. The purpose of this study is to give deferiprone to patients who are not yet eligible to start iron-removal treatment according to the guidelines, to see if doing so will postpone the build-up of iron without causing significant side effects.

Deferiprone is produced by ApoPharma, the sponsor of this study, and is licensed for use in thalassemia patients who have a high level of iron overload. It has already been tested in an earlier study in 64 young children whose levels were too low to start iron-removal treatment in the standard way. (Half the children in that study received deferiprone, while the other half did not receive any iron-removal treatment.) The Investigator has received permission to give deferiprone to such children in this study as well.

Where is the study being done, and how many children will take part in it?

This study is expected to be done at treatment centers in North America, Europe, the Middle East, and Asia. A total of 64 patients are expected to take part.

Who can participate?

Patients in this study must be between 6 months and 10 years of age, have a diagnosis of beta thalassemia major, and have started receiving regular red blood cell transfusions, but have an iron level that has not yet reached the point when iron-removal therapy is typically started.

What drugs will be used?

Patients will be assigned randomly (by chance) to receive either deferiprone or placebo, with an equal chance of being in each group. Both these products are provided by ApoPharma.

- The form of deferiprone that is provided in this study is a liquid called **deferiprone oral solution**, which contains 80 milligrams of active medication per milliliter.
- The **placebo solution** looks and tastes the same as deferiprone but does not contain any active medication. By comparing patients who are getting the active medication to those who are getting placebo, we can tell if effects (both positive and negative) are due to the drug itself, and not to other factors.

Both products are taken by mouth, using a syringe if necessary. The total daily dose is divided into three equal amounts to be given in the morning, afternoon, and evening.

What will be done during the study?

If your child takes part in this study, you will both need to come to the treatment center about once a month for up to a year. Counting the screening visit, there will be a maximum of 14 clinic visits. (For your convenience, we will try to schedule each of these visits on the same day on which your child will be coming in anyways for a blood transfusion.) In addition, for as long as your child remains in the study, it will be necessary to have a blood test done once a week for the first 6 months and then once every 2 weeks for the next 6 months, but this can be done at a laboratory that is close to where you live.

Before your child can be enrolled or undergo any procedures, you must sign and date this informed consent form, and if your child is old enough to understand what is happening, he or she will need to sign a separate assent form. The Investigator will then ask you some questions and will carry out some tests to see if it would be appropriate for your child to take part. If anything is found that raises concerns about safety or that might make the study findings harder to understand, your child will not be enrolled.

The details of each study visit are described below. Visits may take up to approximately 2 hours.

Note: At each visit, up to 11 milliliters (about 2 teaspoons) of blood will be taken for testing, so a patient who remains in the study for the full 12 months will be providing a total of about 208 milliliters (about 40 teaspoons) of blood. This total does not include possible unscheduled visits at which there may be a request for additional blood, or the possibility that staff may need to take extra blood samples if any are damaged or handled incorrectly.

<u>Screening visit</u>

- You will be asked questions about your child's medical history, medications, and blood transfusions. Genetic (DNA) proof of a diagnosis of beta thalassemia major is needed, so if this has not been done in the past, a blood sample for genetic testing will be taken at this visit.
- Your child will be given a physical examination, including measurement of vital signs (blood pressure, heart rate, and temperature).

- Blood and urine samples will be taken for safety testing, and additional blood samples will be taken to check the levels of three different markers of iron overload. One of these is called **serum ferritin**. Ferritin is a protein that stores and transports iron in the body, and the amount of ferritin in the blood is used to determine when standard iron-removal therapy should begin. Current guidelines state that treatment is to start when the serum ferritin level reaches 1000 micrograms per liter (µg/L). To be eligible for this study, your child must (among other things) have a serum ferritin level that is between 200 and 600 µg/L at this time.

A child who is found to be eligible once all the laboratory results are available may be enrolled, and the baseline visit will be scheduled.

Baseline Visit

- You will be asked questions about any health issues that have come up, medications taken, and transfusions received by your child since the screening visit.
- Your child will be randomized to receive either deferiprone or placebo. There is an equal chance of receiving either product. Neither you nor any of the study staff will know which one is being given.
- Blood samples will be taken for safety testing, including checking the level of prolactin (a protein in the body that plays an important role in metabolism), and to measure the three markers of iron load.
- Your child's weight, height, and vital signs will be measured.
- The Investigator will calculate the amount of study drug that is to be given each day, based on your child's weight:
    - For the first 2 weeks, the amount will be 25 milligrams of deferiprone per kilogram of body weight (mg/kg) per day. For example, for a child who weighs 10 kg, this works out to a volume of about 3 milliliters (mL) per day. Since the daily dosage is divided into 3 equal parts, each dose would be about 1 mL. For patients who are getting placebo, the volumes will be the same as for the active product.
    - After 2 weeks, if there are no safety concerns, the dosage will be increased to 50 mg/kg per day. (Note that this is still lower than the usually prescribed dose of deferiprone, which is between 75 and 99 mg/kg per day.) For example, a child weighing 10 kg at this time would now be given 6 mL per day, divided into three 2-mL doses. A staff member will tell you exactly how much to give your child at each dose for the first 2 weeks, and how much to give after that.

- Your child will be given the first dose of study drug by a clinic staff member.
- Exactly an hour and a half after the dose is given, a blood sample will be taken for a second measurement of prolactin. (Prolactin will be measured again at the end of the study, to see if its level has changed from baseline.)
- You will be given a quantity of the assigned study drug that will be enough to last until the next scheduled visit, along with instructions on how to administer it. (Remember that the amount of study drug given will change after 2 weeks if there are no safety concerns.) At the next visit, you must bring back all medication containers, whether empty, partly used, or unopened.
- You will be given a diary card in which you must keep track of the amount of study drug you give your child each day, the time at which you give it, any health problems your child experiences, and any medications taken other than the study drug. You must bring back the completed diary card at the next site visit.
- We will give you a card that briefly describes this study and provides an emergency number which you can call at any time. You should carry this card at all times. If at any time during the study your child develops signs of infection, such as fever (a temperature greater than 38°C or 100.4°F), sore throat, or flu-like symptoms, you must stop treatment immediately and call the study center. A thermometer will be provided to you for the measurement of temperature.

From this visit until your child leaves the study, you are to administer the assigned study drug 3 times daily, always at about the same times of day. The only exceptions are that on days of study visits, 1) the evening before, you must give the third dose at least 12 hours before the expected start of the visit, and 2) the morning of the visit, do not give the first dose; it will be given at the site.

Blood Draws

For as long as your child is in the study, blood tests must be done once a week up to Month 6, and then once every 2 weeks until the end of the study. On weeks that include a site visit, this testing will be done as part of the regular study procedures. On other weeks, it may be done either at the site or at a laboratory that is near you. The reason for these blood tests is explained in the section "What are the possible risks of taking part in the study?"

Remaining Visits

The rest of the visits will be scheduled approximately once a month, potentially up to Month 12. At each visit, the Investigator will check your child's level of iron load, based on the now-available results of the blood tests that were done at the last visit. **If the level of serum ferritin is found to be greater than 1000 µg/L at 2 consecutive visits, your child will be immediately**

withdrawn from the study, and arrangements will be made to begin standard iron-removal therapy. This ensures that any patient who was assigned to the placebo group, or who is not responding adequately to the dose of deferiprone being given, will start to receive the necessary treatment at the same point where this would have happened if he or she were not in the study.

For as long as your child remains eligible to remain in the study, the following procedures will be done at each visit:

- You will be asked questions about any health issues, medications taken, and transfusions received since the previous visit.
- You will return all study drug containers that were given to you at the previous visit.
- The diary card that you completed over the past month will be collected and reviewed, and (except at the final visit) you will be given a new one.
- Your child's weight, height, and vital signs will be measured.
- Blood samples will be taken for safety testing and to check levels of iron load.
- Except at the final visit, the Investigator will calculate the next month's dosage, and will provide you with enough study drug to last until the next scheduled visit. The dosage will now be based on two factors:
    - Body weight, as before
    - Level of iron load, based on the now-available results of the blood tests that were done at the previous visit. If certain criteria are met for any of the three markers of iron load, the dosage will be increased to 75 mg/kg per day; otherwise, the dosage will remain at 50 mg/kg per day (and the same volumes for placebo).
- A staff member will give your child the morning dose of study drug. (Remember that on days of study visits, you are not to give this dose yourself before coming to the site.)

The following additional procedures will be done only at some visits. The visits that include more procedures will take a little longer than the others.

- **Months 1, 3, 6, 9, and 12:** Extra blood will be taken for additional safety tests
- **Months 1, 3, 6, 9, and 12**: A physical examination will be performed
- **Month 12:** A urine sample will be collected
- **Month 12:** A blood sample will be taken for measurement of prolactin, before dosing, and an hour and a half after the last dose was given

If at any time before Month 12 your child's serum ferritin level is found to have been greater than 1000 µg/L at 2 consecutive visits, all the procedures scheduled for the Month 12 visit will be done at this visit instead, and participation in the study will be ended.

Are there any medications that are not allowed during the study?

There are some medications that may interact with the study drug. The Investigator will let you know which ones are not permitted.

No iron chelators other than deferiprone, and no increase in the dose of study drug that your child is assigned, are permitted. Patients whose iron load is not being well controlled by the product that they are receiving in the study will be withdrawn so that they can start on standard therapy.

What are the possible benefits of taking part in this study?

Deferiprone may prevent your child's level of iron load from increasing. However, there is no guarantee that this will happen.

Your child's health will be monitored closely during the study, and there will be many chances to speak with the Investigator and other health care workers about any medical concerns that you may want to discuss.

Apart from any direct benefit to your child, the information we get from his/her participation will add to our knowledge about the use of early iron-removal therapy in children with beta thalassemia major, and may help other patients in future.

What are the possible risks of taking part in the study?

Risks of receiving deferiprone

With any medication, there is the possibility of experiencing unwanted side effects. If your child develops health problems at any time during the study or up to 30 days after completing or leaving the study, you should tell the Investigator or nurse about them.

The most serious side effect of deferiprone is a sudden drop in **neutrophils**, a type of white blood cell that is a very important part of the immune system. A very low neutrophil count, which is called **severe neutropenia** or **agranulocytosis**, has occurred in 1 to 2 out of every 100 people who have taken deferiprone in clinical studies. If your child develops agranulocytosis, it may be necessary to have a blood sample taken to be tested for evidence of infection. If he/she is being treated in hospital, there may also be a request to have a bone marrow sample taken for testing. Agranulocytosis can be successfully treated, and all patients who developed it while they were taking part in a clinical study recovered. There have been a few cases however where patients who were not in clinical studies (and therefore were not under such close observation) have died as a result of developing agranulocytosis. We cannot predict who is at risk for

agranulocytosis. There are no symptoms before an infection develops, which is why it is so important to have your child's white blood cell count checked regularly and to stop deferiprone immediately in case of fever, flu-like symptoms, or any other signs of infection. If the results of blood tests show that your child's white blood cell count is too low, the Investigator will make sure that the right treatment is provided. Patients who develop agranulocytosis will be withdrawn from the study, and will come back only for follow-up tests until the agranulocytosis is resolved.

Other side effects that have been seen in patients taking deferiprone are the following:

Very common (more than 1 user in 10):

- Abdominal pain
- Nausea
- Vomiting
- Reddish/brown discoloration of urine (this is due to iron leaving the body, and is harmless)

Common (1 to 10 users in 100):

- Low white blood cell count (agranulocytosis and neutropenia)
- Headache
- Diarrhea
- Increase in liver enzymes
- Fatigue
- Increase in appetite
- Fever

Events of joint pain and swelling (5% to 12% of patients) have ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking deferiprone.

Allergic reactions may occur with any product. Common symptoms may include rash and itching. Rarely, a severe and possibly life-threatening allergic reaction can occur. Symptoms of a severe reaction include swelling of the face, difficulty breathing, and a sudden drop in blood pressure that may cause dizziness. If your child has any of these symptoms, call an emergency service at once, and let Dr. [name of investigator] know as soon as possible, at [telephone number].

It is possible that your child could experience other side effects that have not previously been reported, particularly since he or she has a lower level of iron load than that seen in patients who take this drug under standard conditions. If you notice any side effects not listed here, tell the Investigator or study staff immediately.

Risks of receiving placebo

Patients who are assigned to get placebo will not be receiving any active medication, so if your child happens to be in this group, his/her level of iron load will increase with each blood transfusion received. However, since only patients who are not yet eligible to start on iron-removal therapy according to standard guidelines will be enrolled, this will not put your child at any risk compared to children with the same condition who are not in this trial.

Risks of blood sampling

Having blood taken may cause reactions of pain, swelling, bruising, minor bleeding at the site of the needle entry, redness, and occasionally fainting. In rare cases, an infection or small blood clots may result.

Are there other treatments available?

There are iron chelators other than deferiprone, but at this time your child is not eligible to receive any of them. If you choose not to enroll your child in this study, he or she will be monitored for signs of iron overload until it is determined that it is time for iron-removal therapy to begin, at which point your doctor will suggest which product will be best.

What will happen if new information becomes available?

If any new information is discovered that may affect the risk to your child or may affect your willingness to let him or her stay in the study, you will be told about this as soon as possible. You will be given a new version of this informed consent form that explains the new findings, and you will need to sign the updated form in order for your child to continue in the study.

What will happen if I don't want my child to take part?

Participation in this study is completely voluntary. If you do not wish to enroll your child (or if your child is old enough to express that he or she does not wish to enroll), or if you agree to the enrollment but later change your mind, there will be no penalty or loss of benefits to which your child is entitled.

If you decide to withdraw your child from the study after enrolling, we ask that you let us know, and that your child return to have some final tests done so that we can do some safety checks and collect information that may help increase our understanding of the study product.

If your child withdraws or is withdrawn from the study (see next section), any study information that was collected up to the date of leaving will still be used.

Can my child be taken out of the study even if I don't want that to happen?

The Investigator may withdraw your child from the study at any time without your consent if you are not following instructions or if there are concerns about safety, including the development of other medical problems or of severe side effects from the study drug.

Any patient whose serum ferritin level is found to be greater than 1000 µg/L at 2 visits in a row, or whose neutrophil count is found to be too low, will be automatically withdrawn.

If the study is cancelled for administrative or other reasons, all patients will be withdrawn.

What will happen if my child is harmed by being in this study?

If your child is harmed as a result of being in this study, the Investigator will provide or will refer you for any necessary medical treatment. The Sponsor will pay for necessary medical costs not covered by your health care plan or private medical insurance (if any).

Costs for medical care for injuries or illnesses that are not a direct result of research activities pertaining to this study will not be covered.

Your signing this consent form does not mean that you waive your legal rights or release the Investigator, the institution, the Sponsor, or their representatives from legal responsibility of negligence.

Will there be any costs or payments for being in this study?

There will be no cost to you for any of your child's study visits, examinations, tests, and drug supplies.

Describe any compensation that participants will receive. Sample text: As compensation for your child's participation, at the end of the study, you will receive [*insert amount*] for each visit that you and your child attended. If your child voluntarily withdraws or is withdrawn by the Investigator before the scheduled end of the study, you will be paid for the visits that were completed to date, unless the reason for withdrawal was because you or your child were not following the study instructions. *OR:* For each visit that your child attends, you will receive [*insert amount*] to compensate you for transportation and parking costs.

If there will not be any compensation, include the following: You will not receive any compensation for enrolling your child in this study.

Who has approved the study?

The proposal for this research study was reviewed and approved by the research ethics committee [*insert name of IRB or IEC*] and by [*insert name of regulatory body; e.g., the Food and Drug Administration, Health Canada, European Medicines Agency*]. A research ethics committee is a group that is independent of a study's sponsor and investigators and is responsible for protecting the rights and safety of subjects.

Who will be allowed to see my child's information?

Access to your child's records at the study site will be given only to authorized persons. Members of the research team and representatives of the Sponsor, the research ethics committee, and government agencies may be given access, as permitted by laws and/or regulations, in order, for example, to check that the study information is being collected properly. Any information about your child that they are allowed to see will remain confidential. The findings of this study will be reported to the Sponsor, the [*insert name of regulatory agency*], and possibly other regulatory agencies; however, once information leaves the study site, it will not contain your child's name or other details that could make it possible to identify your child. Only the Investigator will have access to the code numbers that link your child's study information to his/her identity. By signing this consent form, you agree to this disclosure.

If the findings of this study are published or presented, your child's identity will remain private.

Once the trial is completed, the main results will be posted on the web site www.clinicaltrials.gov. *Refer to other registries if applicable.* Only group findings will appear there; no participants will be identified.

Your child's information and results will be kept on file by the Investigator and Sponsor for at least 25 years, as required by local regulations, after which time they may be destroyed following the Sponsor's written authorization.

If you agree, we will tell your child's primary care physician that he/she is taking part in this study.

What will happen to my child's blood samples?

The blood samples that your child provides will be used only for this research study. After the study is completed, any leftover samples will be destroyed within 6 months.

If it is necessary to do genetic testing to confirm that your child has a diagnosis of beta thalassemia major, this test will be performed by a local laboratory, and any leftover blood sample will be destroyed.

There is a rare but dangerous side effect of deferiprone called **agranulocytosis** (described above under "What are the possible risks of taking part in the study?"). We are trying to find a way of predicting which patients are at higher risk for this, and there may possibly be a genetic cause. If your child develops agranulocytosis, and if you (and your child, if applicable) agree, we will take an additional blood sample for genetic testing. You will need to sign a separate consent form for this testing to be done. Your child can still be in the study even if you do not sign that other consent form.

Whom should I contact if I have any questions?

For any questions about this study, or if you need to report a health problem that may be related to your child's participation, you may contact [*name of individual*] at [*phone number*]. If your question is urgent, you may call a 24-hour line at [*phone number*].

For any questions regarding your child's rights as a study subject, you may contact the research ethics committee at [*phone number of IRB/IEC*].

CONSENT

	Please initial below ↓
I confirm that I have read and understood this informed consent form. I have had the opportunity to discuss it with Dr. [*name of Investigator*] and/or *his/her* study staff and to ask questions about it, and have had any questions answered satisfactorily.	—
I confirm that I understand the research study and the nature and extent of participation, including the risks involved.	—
I agree to let my child take part in this study and to follow the instructions I am given.	—
I understand that my child's participation is voluntary, and that he/she is free to leave the study at any time without any medical care or legal rights being affected.	—
I agree that if my child does not have genetic proof of a diagnosis of beta thalassemia major at the time of enrollment, a blood sample will be taken for DNA testing. I understand that the only test that will be done on this sample will be to look for the genes that cause beta thalassemia major, and that no other tests of any kind will be done on it.	—
I understand that information collected about my child during the study may be looked at by representatives of the Sponsor, regulatory authorities, or the research ethics committee. I hereby give permission for these individuals to have access to my child's records.	—
I will contact the Investigator or clinical study staff immediately if my child experiences any unexpected or unusual health problems during the study, including any signs of infection.	—
I understand that I will receive a photocopy of this informed consent form after it is signed and dated.	—

I agree that the study site may inform my child's primary care physician of his/her participation in this study (please check one):

Yes ☐ No ☐

Name of patient *(please print)*

		/ : hr
Name of parent or legal guardian *(please print)*	Signature of parent or legal guardian	Date: (DD MMM YYYY) and time (24-hr clock)

If signed by a legal representative, identify the authority to act on the parent/guardian's behalf.

Individual is: __ Incompetent __Disabled

Authority: __ Power of Attorney Healthcare __Authorized Legal Representative
__Other (specify): _____

Signature of person authorized to obtain consent:

I, the undersigned, acknowledge having provided all the necessary information for comprehension of this research study to the individual identified above.

		/ : hr
Name *(please print)*	Signature	Date: (DD MMM YYYY) and time (24-hr clock)

Signature of Investigator:

I acknowledge my responsibility for the care and well-being of the above patient, to respect the rights and wishes of the patient and his/her parent/guardian, and to conduct the study according to applicable Good Clinical Practice guidelines and regulations.

/ : hr

Name *(please print)*	Signature	Date: (DD MMM YYYY) and time (24-hr clock)