ApoPharma Inc.

Informed Consent to Take Part in a Clinical Trial

Study Title: A dose-ranging study of the efficacy, safety, and pharmacokinetics of deferiprone delayed release tablets in patients with Parkinson's disease

Study Code: LA48-0215

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 4.0, 07 APR 2017
Site-Specific ICF Version [*x.x*], *DD MMM YYYY*

Dear Sir or Madam,

You are invited to take part in a research study. It is important that you fully understand what your participation would 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 regular doctor and family members before making your decision.

Taking part in this study is completely up to you. You do not have to say yes, and if you do agree to take part, you may later change your mind at any time.

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

What is the purpose of this study?

This study is looking at a drug called **deferiprone** for the treatment of Parkinson's disease. While the exact cause of Parkinson's disease is unknown, it is possible that its symptoms are due to a build-up of extra iron in certain brain regions. Therefore, getting rid of some of this extra iron might lead to improvement in Parkinson's symptoms. Deferiprone is an **iron chelator**, a drug that attaches itself to free molecules of iron in the body and causes them to be flushed out or redistributed. There are several different iron chelators available, but deferiprone is better able than the others to cross the blood-brain barrier and remove iron from the brain. Some small pilot studies that have looked at the effect of deferiprone in Parkinson's patients have found evidence that it may improve the symptoms of this disease.

Deferiprone comes in several forms, including tablets and liquid. Some of the forms are licensed to be given to patients with thalassemia, a type of blood disorder, who have too much iron in their bodies due to receiving frequent blood transfusions. However, none are licensed for the treatment of Parkinson's disease. The form of deferiprone that will be given in this study, **deferiprone delayed release**, is not licensed for any type of use, and so far has been tested only in healthy people. The Investigator has received permission from [*regulatory authority*] to give deferiprone delayed release tablets to patients with Parkinson's disease in this research study.

The purpose of this study is to see what effects, both positive and negative, deferiprone delayed release tablets have on patients with Parkinson's disease, and to find the highest dose that can be given without causing severe side effects.

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

This study is expected to be done at sites in North America and Europe. It is planned that a total of 140 patients will take part.

Who can participate?

People who are at least 18 years old but less than 80 years old, who have been given a diagnosis of Parkinson's disease within the last three years, and who have been on a stable dose of certain types of antiparkinsonian medication for at least the last three months, may be eligible to take part in this study. Your doctor will review and discuss the medications with you to confirm eligibility.

What drugs will be used?

Patients in this study will continue to take the medication they are already being prescribed for the treatment of Parkinson's disease, and will additionally receive either **deferiprone delayed release tablets** or **placebo**. Both these products are provided by ApoPharma Inc., the company that is paying for the study.

- Each tablet of deferiprone delayed release contains 600 milligrams (mg) of the drug. Four different dosages (strengths) are being tested: 300 mg (one half-tablet), 600 mg (one tablet), 900 mg (one and a half tablets), and 1200 mg (two tablets). The medication will be taken orally (by mouth) twice a day, for a total daily dosage of 600 mg, 1200 mg, 1800 mg, and 2400 mg, respectively.

- The placebo tablets look exactly the same as the deferiprone tablets but do not contain any active ingredient. The reason for including a placebo group in a drug study is because sometimes patients may either start to feel better or develop new symptoms simply because they are on a new medication. By comparing people who are getting the active drug to those who are getting placebo, we can tell if effects, both positive and negative, are due to the drug itself, and not just due to being in a study.

If you enroll in this study, you will be **randomized** (assigned by chance, like the flip of a coin) to receive one of the above treatments. The chance of being assigned to any of the groups is one out of five. Thus, of the 140 patients, a total of 112 will get deferiprone (28 in each of the four dosage groups), and 28 will get placebo. Neither you nor the Investigator or other study staff will know which product you received until the study is over.

What will be done during the study?

If you decide to take part in this study, you will continue to take your present antiparkinsonian medication at exactly the same dose you are on now. In addition, you will take two doses of the assigned study medication (either deferiprone or placebo) every day for 9 months, one in the morning and the other in the evening, and will need to come to the treatment center nine times over about ten months. In addition, you will need to have your blood checked once a week for safety reasons, but that can be done at a local laboratory. (In some cases, having this done at your home by a visiting nurse may be an option.) A final telephone call will be made one month after your final site visit.

Before you start the study or undergo any procedures, you must sign and date this informed consent form. The Investigator will then ask you questions and carry out a number of tests to see if it would be appropriate for you to take part. If anything is found that raises concerns about your safety or that might make the study findings harder to understand, you will not be enrolled.

Note the following:

- You will need to provide a total of about 60 teaspoons (300 mL) of blood over the ten months of the study (plus an additional 0.75 teaspoon/3.5 mL for pregnancy testing if you are a woman who is able to get pregnant). This total does not include possible unscheduled visits at which you may be asked to provide additional samples, or the possibility that staff may need to take extra samples if any are damaged or handled incorrectly.
- One of the lab tests at each visit is for fasting glucose. Therefore, you will need to fast (water only) for at least 8 hours before each visit. All visits will be scheduled in the morning, and you will be able to eat as soon as the blood sample has been taken. At the baseline and Month 3 visits, and optionally at the Month 1 visit, there are additional blood tests that require a longer fasting period. On those days, you will need to fast for at least 10 hours before coming to the site, and will be allowed to eat about one and a half hours after you arrive.
- The following samples are **optional**, and you may still be in the study if you do not wish to provide them:
    - At one visit, some extra blood samples (a total of 18 samples taken over 12 hours)
    - At one visit, a single sample of cerebrospinal fluid, collected by doing a spinal tap

If you are willing to provide either or both of these types of samples, you will need to read and sign a separate consent form.

- Because of the possible danger of the study drugs to an unborn child, if you are a woman who is able to get pregnant, you must have a negative result on a pregnancy test and must agree to do what you can to prevent pregnancy until 30 days after your last dose of study medication. If you are a sexually active heterosexual man, you must agree that you and/or your partner will do what you can to prevent pregnancy for this same period of time. The study staff will provide counseling on what types of birth control methods are acceptable.

The details of the study visits are described below.

Screening Visit *(about [xx] hours)*

This visit will take place up to 30 days before the first dose is given. The following will be done:

- The Investigator or another staff member will explain the study to you, and you will need to sign this informed consent form if you wish to continue.
- You will be asked questions about your health and your medical history, including what medications you are now taking.
- You will provide a blood sample (approximately 12 mL / 2.5 teaspoons) and a urine sample for safety lab tests, which includes pregnancy testing if you are a woman who is able to get pregnant.
- You will undergo a physical examination, and your vital signs (heart rate, blood pressure, and body temperature), height, and weight will be measured.
- You will undergo an electrocardiogram (ECG), a test that checks heart function. This test does not hurt.
- If applicable, the study staff will provide counseling on birth control methods.

If you are found to be eligible after the results of all tests are in, you will be scheduled to start the study soon afterwards.

Baseline Visit *(about [xx] hours)*

- You will be asked questions about any health problems you have experienced and what medications you are taking.
- Your vital signs will be checked.
- If applicable, a study staff person will provide counseling on birth control methods.

- You will undergo a physical examination
- You will provide baseline (pre-dose) blood samples (approximately 40 mL / 8 teaspoons) and a urine sample for the following tests:
    - **Pharmacokinetics** testing, which will look at how long it takes the drug to enter the bloodstream, to be metabolized (broken down), and to be excreted (leave the body)
    - **Biomarkers** testing, which will look at the effect of the drug on certain substances produced by the body
    - **Genetic** testing, which will look at possible genetic differences in how patients respond to deferiprone
- If you are a female who is able to get pregnant, you will provide both a blood sample and a urine sample for pregnancy testing.
- The Investigator will ask you questions about whether you are having any suicidal thoughts or have carried out any self-harming behaviors. This type of assessment is now a standard requirement for many drug trials that are looking at medications that may affect the brain.
- You will complete two tests that are used to assess the symptoms of Parkinson's disease: the **Movement Disorder Society - Unified Parkinson's Disease Rating Scale** and the **Montreal Cognitive Assessment** test. Your scores on these tests will be your baseline results, and will be compared against your scores at later time points in the study.
- You will be randomized to one of the four dosage groups (one half-tablet, one tablet, one and a half tablets, or two tablets), and then further randomized within that group to receive either deferiprone tablets or a matching number of placebo tablets.
- You will take your first dose of study medication.
- You will provide two more blood samples for pharmacokinetics testing (approximately 5 mL / 1 teaspoon each): the first one about two hours after you took the dose, and the second one about four hours after.
- You will be given a two-month supply of the assigned study medication (either deferiprone or placebo), along with instructions on how to take it.
- You will be given a diary card in which you must record the amount of study medication you take each day for the next month; the times at which you take it; any other medications that you take; and any health problems you experience. You must bring this card, as well as all bottles of study medication, whether empty, partly empty, or unopened, back with you at the next visit.
- You will be given a card with an emergency number to call in case you experience certain symptoms. It is important that you carry this card with you at all times.

Later this day, you will take your second dose of study medication. For the next nine months, you will take two doses every day, at least eight hours apart.

Each remaining visit -- Months 1, 2, 3, 4, 5, 6, and 9 *(amount of time per visit will vary)*

At each of these visits, the following will be done:

- Your vital signs will be checked, blood samples will be taken for lab safety tests and for pregnancy testing if applicable, and a staff member will provide birth control counseling if applicable.
- The Investigator or other study staff member will review the information in your diary card, and will check your bottles of medication to see how many tablets you have taken and how many remain.
- You will be asked about any suicidal thoughts or behaviors.
- You will be given a new diary card (except at Month 9).

In addition, the following procedures will be done at only some visits:

- Months 2, 4, and 6 only: Another supply of study medication will be given to you; a two-month supply at Months 2 and 4, and a three-month supply at Month 6
- Months 2, 4, 6, and 9 only: Physical examination
- Month 3 only: Blood for pharmacokinetics testing (three samples over about four hours). At this visit, you will need to wait until you arrive at the study site before taking your regular morning dose, since the first sample must be taken pre-dose. In addition, you must fast for at least 10 hours before the visit.
- Month 9 only: Electrocardiogram and measurement of weight
- Months 3, 6, and 9 only:
  - Urine sample for safety testing and biomarkers testing
  - Blood samples for biomarkers testing
  - Completion of the Unified Parkinson's Disease Rating Scale and the Montreal Cognitive Assessment test

In addition, the following procedures will be done on only those patients who volunteer for them:

- Month 1: If you agree, you will give extra blood for pharmacokinetics testing (18 blood samples over 12 hours, so this visit will last until the evening).

- Month 3: If you agree, a sample of fluid will be taken by spinal tap at one of three possible times: either just before you take your morning dose, about two hours after you take it, or about four hours after you take it

Details of these optional procedures are provided in a separate consent form.

Weekly blood testing *(about 15 minutes)*

On each week up to Month 9 that does not have a scheduled site visit, you will need to provide a blood sample (about 0.6 teaspoon / 3 mL) for checking your white blood cell count, for safety reasons. This can be done either at the study site or at a local laboratory if that is more convenient to you (or in some cases, at your own home by a visiting nurse). If you show any signs of infection (for example, fever, sore throat, or flu-like symptoms) or if your last white blood cell count was low, you may need to have this testing done more often than once a week. The reason for this is explained under the heading "What are the possible risks of taking part in the study?"

Final telephone call

About four weeks after your last visit, you will receive a telephone call from a study staff member to ask about your health.

After this call, your participation in the study is complete.

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

During the study, you must keep taking the same type and dosage of antiparkinsonian medication you were on when you enrolled. If the Investigator decides that you need to change anything about your medication, you will be withdrawn from the study.

In addition, there are some medications that may interact with the study drug. The Investigator will let you know which ones are not permitted. You should check before starting any new medications while you are in this study.

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

Deferiprone may act to improve your symptoms of Parkinson's disease. However, there is no guarantee that this will happen.

Your health will be monitored very closely during the study, and you will have many chances to speak with the Investigator and other health care workers about any medical concerns that you would like to discuss.

Apart from any direct benefit to you, the information we get from your participation will add to our knowledge about Parkinson's disease, and may help other patients in future.

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

Risks of receiving deferiprone

Like all medications, deferiprone can have side effects, although not everyone gets them. Most of the safety information about deferiprone comes from patients with a blood disorder called thalassemia, who must receive life-long treatment with iron chelators to treat iron overload caused by frequent blood transfusions. (In this study, the maximum dosage of deferiprone will be lower than what is normally given to thalassemia patients.) From the information we have so far, the safety profile of deferiprone in patients with Parkinson's disease and other diseases that may be caused by extra iron in certain brain regions is similar that that seen in iron-overloaded patients.

The most serious side effect of deferiprone that has been seen in thalassemia patients is a sudden sharp drop in neutrophils, a type of white blood cell that is an important part of the immune system. A very low neutrophil count, called **severe neutropenia** or **agranulocytosis**, has been seen in about 2% percent of people who have taken deferiprone in clinical studies. 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. We cannot predict who is at risk for agranulocytosis, and people may not realize that they have it until they develop an infection, which is why it is so important to have your white blood cell count checked weekly. If you ever develop flu-like symptoms such as fever, sore throat, or any other signs of infection, you must stop taking deferiprone immediately and check with the Investigator. Any patient who develops agranulocytosis will be immediately withdrawn from the study and given treatment, and will come back only for follow-up tests.

Other side effects that have been seen in thalassemia 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

Events of joint pain and swelling (seen in 5% to 12% of patients) have ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared after the patients had been taking deferiprone for some time.

Since deferiprone acts to rid the body of iron, patients who do not suffer from general iron overload may experience a drop in their blood iron to a level that is too low. If that happens to you, you may be given iron supplements.

In animal studies, no harmful effects have been seen when deferiprone was given at the doses that are permitted for humans, with the exception of birth defects in some species, which is why deferiprone is not given to pregnant women.

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 you ever get any of these symptoms, call an emergency service at once, and let Dr. [*name of investigator*] know as soon as possible, at [*telephone number*].

With any drug, there is always a chance that an unexpected or serious side effect that has not previously been reported may happen. If you experience any side effects not listed here, please tell the Investigator.

Risks of receiving placebo

If you are assigned to the group that gets placebo, you will not be receiving any active medication other than the antiparkinsonian drugs you are presently taking to treat your symptoms.

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.

Risks of having a spinal tap

This procedure is optional. While it is generally safe, there are some risks associated with it. These are described in a separate consent form titled "Informed Consent for Providing Additional Samples for Pharmacokinetics Testing".

Risks to an unborn child

Since it is possible that deferiprone could harm a fetus, it is very important to not become pregnant or father a child while on this study. Therefore, patients must abide by the following:

Women: If you are pregnant or nursing, you will not be enrolled. If you are capable of becoming pregnant, you will need to have a negative pregnancy test within 24 hours before receiving the first dose of study drug. Following enrollment, you must use birth control during the entire study and for at least 30 days after it has ended. If you do become pregnant during the study, you must immediately stop taking the drug and must inform Dr. [*name*] at [*phone number*]. You will be monitored until delivery, and your baby will be examined and monitored for any medical problems.

Men: If you are heterosexual and fertile, you must confirm that you and/or your partner will use an effective method of birth control during the entire study and for at least 30 days after it has ended. If your partner does become pregnant during this study, you must immediately call Dr. [*name*] at [*phone number*]. It would be desirable for your partner to agree to be monitored until delivery, and for the baby to be examined and monitored for any medical problems. The Sponsor may ask to collect confidential information about the health of the baby.

The following are common methods of contraception (patients must check with the Investigator to make sure that the method they are using is acceptable):

- Birth control pills and other hormonal devices
- Intrauterine device (IUD) in place for at least 3 months before the first dose of study drug
- Condom or diaphragm, provided it is used with spermicidal cream
- Tubal ligation (women) or vasectomy (men)
- Abstinence

To be considered to be of non-childbearing potential, a woman must be defined as surgically sterile (complete hysterectomy or removal of both ovaries) or must be in a menopausal state (being 50 years of age or older and at least 1 year without menses).

Are there other treatments available?

A number of other medications are available to treat the symptoms of Parkinson's disease, and all patients in this study must in fact already be receiving such treatment. However, once the study begins, patients will need to stay on the exact same regimen they were on at the start, so anyone who is likely to be changing regimens soon will not be enrolled, You should discuss the options with the Investigator and/or your regular doctor, to decide which treatment might be the most suitable for you.

What will happen if new information becomes available?

If any new information is discovered that may affect the risk to you or may affect your willingness to 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 to continue in the study.

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

Participation in this study is completely voluntary. If you do not wish to enroll, or if you agree to enroll but then change your mind, there will be no penalty or loss of benefits to which you are entitled.

If you decide to leave the study after enrolling, we ask that you let us know, and that you return to have some final tests so that we can check on your safety and collect more information that will help our understanding of the study product.

If you withdraw, any study information that was collected up to the date you leave will still be used.

Can I be taken out of the study even if I want to stay in it?

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

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

What will happen if I am harmed by being in this study?

If you are 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 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 to me for being in this study?

There will be no cost to you for any of the study visits, examinations, tests, and drug supplies.

For each visit that you attend, you will receive [*insert amount*] to compensate you for transportation and parking costs.

If you agree to provide the extra blood samples at Month 1 and/or the sample of cerebrospinal fluid at Month 3, additional compensation will be provided. Details are provided in a separate consent form.

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 information?

Access to your 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 to check that the study information is being collected properly. Any information about you 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 name. Only the Investigator will have access to the code numbers that link your study information to your identity. By signing this consent form, you agree to this inspection and disclosure.

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

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, it will include a summary of the results. You can search this web site at any time. Similar study information may be posted on other government web sites as required by local law.

Your information and results will be kept on file by the Investigator and Sponsor for at least [*xx*] 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 primary care physician that you are taking part in this study.

What will happen to my blood samples?

The blood samples that you provide for safety assessments will be analyzed at a local laboratory and destroyed after they have been analyzed.

The samples that you provide for pharmacokinetic and biomarker analyses will be shipped to one of several central laboratories for analysis. Portions of these samples will be stored for possible additional analyses, and will be destroyed after the report on this study has been produced, which will be a maximum of 1 year after the end of the study.

The analyses include tests to see if certain genetic differences affect how individual patients respond to deferiprone. We will not look for any genetic information other than this, and we will not share any genetic information with your insurance company or anyone else. We would like to

keep these samples stored in case other genes associated with Parkinson's disease are discovered in future and we would want to do some further analyses. If you do not agree to this, any leftover blood will be discarded after the study is completed. If you do agree and then later change your mind, your stored sample will be destroyed.

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 participation in the study, 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 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 take part in this study and to follow the instructions I am given.	_____
I understand that my participation is voluntary, and that I am free to leave the study at any time without my medical care or legal rights being affected.	_____
I understand that information collected about me during the study may be looked at by representatives of the Sponsor, regulatory authorities, or the research ethics committee. I give permission for these individuals to have access to my records.	_____
I will contact the Investigator immediately if I experience any unexpected or unusual health problems during the study.	_____
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 primary care physician of my participation in this study (please check one):

Yes ☐ No ☐

Consent for additional analyses:

☐ I consent to my blood sample being saved and stored for possible analyses of different genes that may be discovered in future

☐ I do **not** consent to my blood sample being saved and stored for possible analyses of different genes that may be discovered in future

Name of patient *(please print)*

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

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

Individual is: __ Incompetent __ Disabled

Authority: __ Power of Attorney Healthcare
__ Authorized Legal Representative
__ Other (specify): _____

Name of impartial witness, if required *(please print)*	Signature of impartial witness	Date: (DD MMM YYYY) and time (24-hr clock)
		/ : hr

Signature of person authorized to obtain consent:

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

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

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 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)