

A Phase I Study of Intravenous (Emulsion) Fenretinide (4-HPR, NSC 374551) in Children with Recurrent or Resistant Neuroblastoma (IND #70,058)

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

FINANCIAL DISCLOSURE

Childrens Hospital Los Angeles (CHLA) holds patents and/or patent applications on anti-cancer therapies using Fenretinide (the study drug). This drug has been licensed to the company CerRx, Inc. founded by the two inventors, Drs. Barry Maurer, and C. Patrick Reynolds (Texas Tech University Health Sciences Center, Lubbock, Texas). CHLA may benefit financially from the future use of the study drug. If you have any questions regarding this disclosure, please contact the Conflict of Interest in Research Committee (COIRC) at CHLA (323-361-8368).

The word “you” used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?

This study is a clinical trial (a type of research study using human patients). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

You are being asked to participate in this study because you have been diagnosed with neuroblastoma, a type of solid cancer that usually affects children. Either your cancer has relapsed or you have persistent tumor after having gotten standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest dose of emulsion fenretinide that can be given intravenously for 5 days, every three weeks, without causing severe side effects.
- To find out the side effects seen by giving intravenous emulsion fenretinide on this schedule at different dose levels.
- To measure blood levels of fenretinide during treatment.
- To measure levels of fenretinide in normal white blood cells during treatment.
- To determine if your tumor gets smaller after treatment with intravenous emulsion fenretinide.

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

Fenretinide is an anticancer agent that may work differently than standard chemotherapy medicines. It may cause the build up of a wax-like substance in neuroblastoma cancer cells, called "ceramide". In laboratory studies it was found that if too much ceramide builds up in neuroblastoma cells, they die.

Fenretinide has been given by mouth as a capsule to many people, including children. When Fenretinide is given in capsules, very little of the drug is absorbed through the intestines into the body. That meant that patients had to take many capsules of Fenretinide by mouth several times a day. In this study, an intravenous preparation of fenretinide (called an "emulsion") is being tested to see if more fenretinide can be delivered into the body by giving it into the veins rather than by mouth using capsules. This is the first study of intravenous emulsion fenretinide in children.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 18 to 30 pediatric patients will take part in this study.

WHAT WILL HAPPEN TO ME ON THIS STUDY AND WHAT IS INVOLVED?

If you agree to be on this study, we will ask you to do the following things.

Intravenous (IV) emulsion fenretinide will be given intravenously (into the veins) continuously for five days every three weeks. You will need to be in the hospital for these five days to receive the drug. If you have bad side effects, you can continue treatment with a lower dose of IV emulsion Fenretinide, provided your side effects have gone away and your tumor is not getting worse.

You will be assigned to get a certain dose of IV emulsion Fenretinide. Each dose will be given to a group of 3 to 6 patients. The first group of patients will get the lowest dose of IV emulsion Fenretinide. (This dose is about 20% lower than what is currently being given to adult patients without bad side effects.) The IV emulsion Fenretinide dose will then be increased ("dose escalation") in each of the patient groups. Every 3 to 6 patients will get an increased dose of IV emulsion Fenretinide until the highest dose is reached or serious side effects are seen. Your doctor will tell you what dose you will get. Once your dose of IV emulsion Fenretinide is decided, it will not be increased with later courses of treatment.

Required Medical Tests

You will have a series of standard medical tests before, during, and following treatment with intravenous emulsion fenretinide. Researchers will use these tests to measure the effectiveness of the treatment and what it is doing to your body.

MEDICAL TESTS BEFORE AND DURING TREATMENT

Physical exam

Blood tests

Pregnancy test

Urine tests

Tests of heart function

Tests of vision

Chest x-ray (only before treatment starts)

Bone marrow tests[#]

Various scans*

[#]: Bone marrow tests are done by inserting a needle into the hipbone to remove the marrow that is inside the bone.

*: Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG scans. We will recommend scans specific for your case and we will answer your questions about these scans.

Medical Tests Following Treatment

Physical exam	Bone marrow tests [#]
Blood tests	Various scans*
Urine tests	
Tests of heart function	

The chart at the end of this form tells you when these tests need to be done.

During the first week of treatment for every course: Physical exams, blood and urine tests will be done at least twice a week. A blood test for triglycerides (fat in the blood) will be done two times a day during IV fenretinide infusion. (total: 10 times).

- Bone marrow tests and various scans may be done after the second course, then after every four courses of treatment thereafter.

Other Special Studies:

In addition to the routine studies listed above, we would like to do other studies while you are enrolled on the study. These tests are called "pharmacokinetic studies" (the level of the drug in your blood is measured) and "intracellular fenretinide studies" (in this case, measuring the amount of fenretinide that gets into your white blood cells). Each of these special studies is described in detail below.

Because one of the main reasons to do this study is to find out if more fenretinide can be delivered into the body by giving it into the veins rather than by mouth using capsules, "the pharmacokinetic" blood tests are REQUIRED for you to participate in the study and get treatment with IV emulsion Fenretinide.

However, while they are very helpful to us, the "intracellular fenretinide" studies are voluntary. You may choose NOT to participate in the "intracellular fenretinide" studies and can still be treated on this study with IV emulsion Fenretinide. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in the "intracellular fenretinide" studies.

The results of these studies (pharmacokinetic and "intracellular fenretinide") will not affect your treatment while enrolled on this study. The results will not be told to you or your doctor and will not become part of your medical record.

Determining Blood Levels of Intravenous Emulsion Fenretinide (called Pharmacokinetics)

This test is REQUIRED.

One of the main goals of this study is to determine what fenretinide levels are reached in the blood when it is given intravenously. We know how much drug gets into the blood when fenretinide is given by mouth using capsules. We are trying to find out if we can get higher levels of fenretinide in the blood by giving it intravenously.

To determine this, blood will be taken during the first two courses of treatment with IV emulsion Fenretinide. During the first course, a half-teaspoon of blood (2 - 3 ml) will be taken about nine times while you are getting the intravenous fenretinide (over 5 days), and then two more times after the drug is stopped. This allows us to see how much and how fast the fenretinide builds up in the blood, and how quickly it leaves the blood once the drug infusion is stopped. During the second course, a half teaspoon

of blood will be taken up to 3 times: before you start the treatment with IV emulsion Fenretinide, at 48 hours into the treatment if you agree to participate in the “intracellular fenretinide studies” (below), and after the treatment is finished. Researchers will compare how the body processes the IV emulsion Fenretinide in Course 2 to what they saw in Course 1 and see if there are any differences. The total amount of blood drawn for drug level testing in Course 1 and Course 2 is about 36 ml.

Some patients may be able to have these specimens drawn from their central line. Everyone else will need to have a separate IV placed in a vein to draw the blood samples. This IV will be taken out after all the blood samples have been drawn. Your doctor and nurse will talk with you about whether your central line can be used to draw the blood samples or if you will need a separate IV placed.

This part of the study is required. Deciding not to take part in this part of the study means you will not be able to get treatment with the study drug, IV emulsion Fenretinide.

**Determining Levels of Fenretinide in White Blood Cells (called “intracellular fenretinide levels”)
This test is VOLUNTARY.**

To get some idea of how well intravenous emulsion fenretinide may get into tumor cells, we will measure how well it gets into normal white cells in the blood. If intravenous emulsion fenretinide is taken up well by normal white blood cells, we believe that it will also be taken up well by tumor cells. During Course 2 of treatment, about 4 teaspoons (20 – 23 ml) will be taken 2 times (before and during the fenretinide infusion) to test normal white blood cells. Some patients may be able to have these specimens drawn from their central line. Everyone else will need to have these specimens drawn through a vein. We would only do this test if your body is big enough for us to take this much blood without a problem or if you consent to having these blood specimens taken from a vein if your central line cannot be used.

This extra study is voluntary. If you do not agree to have these samples taken, you can still receive IV emulsion fenretinide as part of this trial.

HOW LONG WILL I BE ON THIS STUDY?

You can continue to get IV emulsion fenretinide every 21 days for a total of six courses as long as your neuroblastoma responds to the treatment or you do not have bad side effects from taking IV emulsion fenretinide. If your tumor is responding, and there is enough drug available, you may be able to receive more than six courses of therapy with the agreement of your treating doctor. After you stop treatment with IV emulsion fenretinide, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Evaluations for this study will continue unless your tumor gets worse or you start another treatment for your neuroblastoma. Researchers will continue to collection information about you for a lifetime. Information will be collected about whether you are still alive, whether you have developed any side effects from the treatment or any additional cancer. This information may be gotten from your oncologist or family doctor at regular intervals.

You can remove yourself from this study at any time. In addition, your doctor may remove you from this study at any time if he/she does not feel it is in your best medical interest to continue with treatment.

WHAT ARE THE RISKS OF THE STUDY?

This is a phase I study. A phase I study looks at how common and serious side effects can be for each patient at each specific dose of drug. In this study, researchers will be looking at side effects seen in patients taking different doses of IV emulsion Fenretinide. We know what side effects were seen in patients taking Fenretinide capsules by mouth. We do not know if these same side effects will be seen or

how severe they will be in patients taking IV emulsion Fenretinide. Because this drug has never been given to children before, there may be risks we do not know about.

The following side effects (toxicities) were seen in people who took Fenretinide capsules by mouth, fenretinide in an oral powder called “fenretinide/Lym-X_Sorb oral powder”, or other patients receiving intravenous fenretinide emulsion.

Likely side effects seen in 21 - 100 out of every 100 children.

- Itching and dry skin
- Night blindness
- Dry mouth
- Higher levels of fats in the blood
- Increased sensitivity of the skin to sunlight

Less likely side effects seen in 5 - 20 out of every 100 children.

- Rash and skin peeling
- Dry eyes
- Conjunctivitis or red eye
- Other visual changes
- Joint and muscle pain
- Headache
- Dizziness or lightheadedness
- Irritation of the liver seen in blood tests results of liver function.
- Protein or blood in the urine
- Nausea and vomiting
- Diarrhea
- Belly pain or cramping
- Higher blood levels of enzymes that help digestion (lipase and amylase).
- Irritation of the pancreas called pancreatitis. You can have belly pain, nausea, vomiting and higher blood levels of fat (triglycerides) and enzymes called lipase and amylase that help with digestion. Pancreatitis and high blood levels of fats were seen in adult patients with leukemia/lymphoma who are enrolled in a study using IV emulsion fenretinide.
- Decrease in the number of red and white blood cells and platelets made in the bone marrow.
- Feeling tired as a result of low red blood cells in the blood.
- Infection as a result of the low number of white blood cells in the blood.

Rare side effects seen in less than 5 out of every 100 people

- Arthritis or joint swelling
- Increased pressure in the brain (Pseudotumor cerebri)
- Hot flashes or flushing
- Allergic reaction. An unexpected allergic reaction to IV emulsion Fenretinide could occur, and in severe cases could be life threatening.
- Abnormal growth of leg bones with long-term use (several years) of fenretinide.
- Increase of calcium in the blood.
- Low amount of a protein in your blood called albumin
- Low amount of a chemical called phosphorous in your blood
- Temporary decrease in the ability of the kidney to filter the blood.
- Buildup of fluid around the lung.
- Temporary increase of pressure within the blood vessels of the lung.
- Bleeding as a result of low platelets.

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drug used in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them.

Risks starting from starting an IV and taking blood samples: The risks from starting an IV or having your blood taken are minimal but can cause pain and result in an infection or a blood clot. Experienced doctors or nurses will start the IV if needed and perform these blood draws to minimize this risk.

Side effects seen in animal studies with IV emulsion fenretinide: The following side effects were seen in some animals (dogs) in which a high dose of IV emulsion fenretinide was tested:

Lung: hemorrhages (bleeding) and emboli (blood clots)

It was not clear if these lung findings were related to the intravenous emulsion fenretinide, or to complications from the use of a central venous catheter in the animals.

Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or itching). Many of the side effects above went away shortly after the oral fenretinide was stopped, but it is always possible that side effects may be long lasting or permanent. Some side effects may be life threatening and it is possible that death could occur as a rare side effect following treatment with intravenous emulsion fenretinide. Patients are watched carefully and treatment will be stopped if bad side effects develop.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Yes, there are other options for treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines.
- Treatment with other experimental therapies that may be available.
- No therapy at this time with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

You may read your record. The records are available to those people caring for you at this hospital. However, all efforts will be made to keep your information confidential. Unfortunately, we cannot guarantee absolute confidentiality. Information about you may be shared if required by law.

Organizations that may look at and/or copy your research records for quality assurance and data analysis include such groups as:

- New Approaches To Neuroblastoma Therapy (NANT) Consortium at Childrens Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you (your child) by a number.
- Independent auditor monitoring quality assurance for the NANT Consortium

- The Investigational New Drug Sponsor (the supplier) of intravenous emulsion fenretinide, Dr. C. Patrick Reynolds, MD PhD, Texas Tech University Health Sciences Center.
- The U.S. Federal Government – the National Cancer Institute (NCI) and/or the Food and Drug Administration (FDA) may examine records of patients participating in this study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The Rapid Access to Interventional Development (RAID) program of the National Cancer Institute (NCI) through a grant to C. Patrick Reynolds, MD PhD, of Texas Tech University Health Sciences Center as the Investigational New Agent (IND) sponsor will provide IV emulsion fenretinide free of charge for this study.

The pharmacokinetic studies will be done at no cost to you and the “intracellular fenretinide” blood tests will be done at no cost to you if you agree to participate in this voluntary study. Payment for extra blood tests for triglycerides will be supported by funds from the NANT Consortium.

Taking part in this study may lead to added costs that may be covered by your insurance company. Please ask about any expected added costs or insurance problems.

The Rapid Access to Interventional Development (RAID) program of the National Cancer Institute (NCI) does not cover the cost of getting the intravenous emulsion fenretinide ready and giving it to you, so you or your insurance company may have to pay for this.

Intravenous Emulsion Fenretinide is being provided under a limited research grant. Therefore, a continuing supply of the drug cannot be guaranteed. If there is a problem getting Intravenous Fenretinide, your study doctor will talk with you about possible options.

You and/or your insurance company will be charged for continuing medical care or hospitalization.

You will receive no payment for taking part in this study.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, carfare, parking, and baby sitter fees.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor _____ [*investigator’s name(s)*], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [*telephone number*].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment due to injury while being on the study.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study call the _____ *[name of center]* Institutional Review Board (a group of people who review research to protect your rights) at _____ *[telephone number]*.

WHERE CAN I GET MORE INFORMATION?

For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will also get a copy of this consent form. If you want more information about this study, please ask your study doctor.

CONSENTS FOR STUDIES FOR RESEARCH

#1 Blood Levels of fenretinide known as Pharmacokinetics

Researchers would like to take about half a teaspoon of blood (2 – 3 ml) a total of eleven times (9 times during and 2 times after) the first course of treatment with IV emulsion fenretinide and two or three times during the second course of treatment. These are extra blood draws and if your central line cannot be used, you will need to have a separate IV started in a vein for these blood samples to be taken. The results of these tests will be confidential and not made available to you or your treating physician.

IF YOU DO NOT AGREE THAT THESE TESTS MAY BE PERFORMED, YOU MAY NOT PARTICIPATE IN THIS STUDY

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood collected for blood levels of fenretinide

_____ **NO**, I do not agree to have blood collected for blood levels of fenretinide. I understand that by refusing to let these blood samples be collected that I cannot participate in this study.

Signature: _____ **Date:** _____

#2 Blood Levels of fenretinide in normal white blood cells known as “intracellular fenretinide levels.”

Researchers would like to take about 4 teaspoons (20 – 23 cc) of blood two times (just before the start, and in the middle of the infusion) during the second course of treatment with IV emulsion fenretinide. These are extra blood draws and if your central line cannot be used, you will need to have these specimens drawn through a vein. The results of these tests will be confidential and not made available to you or your treating physician.

THESE TESTS ARE STRICTLY VOLUNTARY. YOU MAY STILL PARTICIPATE IN THE STUDY EVEN IF YOU DO NOT AGREE TO THESE TESTS.

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood for fenretinide levels in normal white blood cells

_____ **NO**, I do not agree to have blood for fenretinide levels in normal white blood cells.

Signature: _____ **Date:** _____

STATEMENT OF CONSENT

I have been given a copy of all _____ pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Patient Name

Signature of Parent or Guardian

_____/_____/_____
Date

Signature of Parent or Guardian

_____/_____/_____
Date

Signature of Patient (If > 7 years old)

_____/_____/_____
Date

Signature of Physician or
Responsible Investigator

_____/_____/_____
Date

Signature of Witness

_____/_____/_____
Date

Signature of Translator
(If applicable)

_____/_____/_____
Date

CONSENT ADDENDUM

A blank box means the test is not done at that time point in the study.

TESTS THAT WILL OR MAY BE DONE ON THIS STUDY

STUDY	Before Study	During Treatment Course One (3 weeks)	Before Next Treatment Course	During all other treatment courses (3 weeks each course)	Finish Treatment
Physical Exam	X	Daily x 5 days in Week 1	X	Daily x 5 days in Week 1	X
Blood tests	X	11 times in Week 1; 1 time in Week 2	X	up to 11 times in Week 1	X
Pregnancy test	X		X		
Urine test	X	2 times in week 1	X	2 times in week 1	X
Vision testing	X		After Course 4, before Course 7, then every 4 courses if normal at start, otherwise before every course		
Heart test (echocardiogram/MUGA and EKG)	X				X
Chest x-ray	X				
Head Imaging (CT/MRI)	X				
Tumor imaging (CT/MRI & MIBG scan)	X		After Course 2 and 6, and then every 4 courses		X
Bilateral bone marrow aspirate/biopsy for routine morphology	X		After Course 2 and 6, and then every 4 courses		X
Urine test (VMA/HVA)	X		After Course 2 and 6, and then every 4 courses		X
Fenretinide Blood levels (REQUIRED)		Day 0,1,2,3,4,5,6		Course 2 only, for up to three blood draws during the drug infusion	
The tests below this line would only be done if you gave permission for them to be done					
Intracellular fenretinide levels				Course 2 only for 2 blood draws during the drug infusion	

SAMPLE ASSENT TO PARTICIPATE IN A RESEARCH STUDY

Using intravenous emulsion fenretinide to Treat Patients with Recurrent or Resistant Neuroblastoma

Subject's Name:	_____	
Hospital#:	_____	Birth Date: _____

1. My name is _____.
2. You have a kind of cancer called **neuroblastoma**, which has either come back, or not gone away with the treatments you have already had. In the past, Doctors have found that giving a drug called **Fenretinide** by mouth may help to treat children with neuroblastoma like yours. In the past Fenretinide has only been available as large pills that can be very difficult to swallow (especially for small children). This study will use another form of Fenretinide (called "intravenous emulsion fenretinide") that can be given by vein. It will be given continuously for five days. It is also hoped that this way of giving Fenretinide might mean that patients taking it absorb (soak up) more of the Fenretinide. We are asking you take part in this research study because we are trying to learn more about what effects (both good and bad) a research treatment using the intravenous emulsion fenretinide has on patients with neuroblastoma.
3. If you agree to be in this study this is what will happen:

Coming to see the Doctor: You will need to come and see the doctor frequently while you are receiving the intravenous emulsion fenretinide. Tests will be done before, during and after the time when you receive the intravenous emulsion fenretinide. These tests include;

- Looking in your ears, eyes, listening to your lungs, heart and stomach – this is called a Physical Exam.
- Blood and urine tests.
- Test your heart and eyes.
- Scans (like MRI, MIBG, and CT scans).
- An X-Ray of your chest before you start the Fenretinide.
- Bone Marrow tests – you will have had these before as part of your treatment for your neuroblastoma.

Asking Questions: It is very important that you ask any questions you might have. Your Doctors, Nurses and all the people that work with you here at the Hospital will always try to answer your questions. If they don't know the answer, they will find someone who does.

Taking Fenretinide: You will be given intravenous emulsion fenretinide continuously in the hospital for five days straight every three weeks. This block of three weeks is called a **cycle**.

Blood Samples: Because we want to learn how well the intravenous emulsion fenretinide works, and how well your body absorbs (or soaks up) the Fenretinide we will need to take blood samples from you. These samples will be collected during the first, and second cycles of treatment. If you do not have a central line you will have to have an i.v. started or be poked with a needle in your arm or hand. We can use numbing cream or "cold spray" so it doesn't hurt; The blood samples we just talked about are **required** – you must do them to be on the study.

There are also two other **optional** blood samples that you can choose to do or not. If you agree, we will take two extra blood samples on the 1st and 2nd days of your second cycle of intravenous emulsion fenretinide. These are fairly large samples (about 4 teaspoons each time). This would only be done if you were well enough and big enough to have the blood taken without hurting your body. You do not have to do this part of the study if you don't want to.

4. Sometimes things happen to children in research studies that may make them feel bad. These are called "risks". The risks of this study are:

- Dry skin, or a rash.
- Your skin could be more sensitive to getting sunburned.
- Dry, or irritated eyes.
- Problems seeing when it is dark when you're getting the medicine and for a few days afterward – it is very important that if you are worried that you cannot see properly that you tell your Mom and Dad.
- Swollen joints, sore joints or muscles.
- Headache, dizziness or feeling lightheaded. It is very important that you tell your Mom and Dad when you have a headache.
- Nausea, vomiting, tummy pain, tummy cramping or diarrhea.
- Increased pressure in your brain which may cause headache, vomiting or double vision.
- You might have an allergic reaction to the Fenretinide.
- **Risks from starting an IV and taking blood samples:** This can be painful. Sometimes you can get an infection or a blood clot in the IV so that the IV stops working and would need to

be taken out and restarted in another place. Doctors or nurses who have started IV's many times will start your IV and take the blood samples.

- Low number of red blood cells which may cause you to feel tired.
 - Low number of white blood cells which may lead to infection
 - Low number of platelets which may cause you to bleed more easily.
 - Higher amounts of a chemical called calcium in your blood (calcium is also in milk).
 - Low amount of a protein in your blood called albumin
 - Low amount of a chemical called phosphorous in your blood
 - Some fluid could build up around your lungs for a while.
 - Your kidneys may not filter your blood as well as they normally do for a while.
5. People also have good things that happen to them when they are in research studies. These are called "benefits". This treatment may help your neuroblastoma but you shouldn't think that your neuroblastoma will completely go away if you take part in this study. We hope to learn more about this treatment that will help other kids like you with neuroblastoma.
6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.
7. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to you.
8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me, or ask me next time.

Optional Blood Samples

Please check to show if you do or do not agree to allow us to take the two extra blood samples.

_____ Yes, it is okay to take the extra two blood samples.

_____ No, it is not okay to take the extra 2 blood samples

9. Signing your name on the next page means that you agree to be in this study. Your doctors will continue to treat you whether or not you participate in this study. You and your parents will be given a copy of this form after you have signed it.

Name and Signature of Subject

Date

Signature of Investigator

Date

