

SAMPLE INFORMED CONSENT

VORINOSTAT WITH ¹³¹I-MIBG THERAPY FOR RESISTANT/RELAPSED HIGH-RISK NEUROBLASTOMA: A PHASE I STUDY

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

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. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your study doctor.

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. Your cancer has either grown back (relapsed) or has never gone away (persistent tumor) after 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 doses of vorinostat and ¹³¹I-MIBG without causing severe side effects
- To find out the side effects seen by giving ¹³¹I-MIBG and vorinostat on this schedule at different dose levels
- To measure the effects of vorinostat on proteins and genetic material in blood cells
- To determine if your tumor gets smaller after treatment with ¹³¹I-MIBG and vorinostat.

The research is being done because:

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

This study will combine an oral drug called vorinostat with the chemical agent called metaiodobenzylguanidine (MIBG).

Vorinostat is a drug that is FDA-approved to treat a certain type of cancer mainly seen in adults. Vorinostat affects the way the DNA that carries our genes is folded in cells. In the laboratory, vorinostat causes neuroblastoma cells to stop growing. This effect is even greater when vorinostat is combined with radiation.

MIBG is taken up by neuroblastoma tumor cells. MIBG can be combined together with radioactive iodine (¹³¹I) in the laboratory to form the radioactive compound ¹³¹I-MIBG. The ¹³¹I-MIBG compound delivers radiation to the neuroblastoma cancer cells and causes them to die.

Giving vorinostat together with the ¹³¹I-MIBG may help the ¹³¹I-MIBG to kill more neuroblastoma cells. ¹³¹I-MIBG lowers the number of blood forming cells (called stem cells) in the bone marrow when it is given at higher doses. Since the combination of vorinostat and ¹³¹I-MIBG is expected to increase this effect, all patients will get back their own stem cells to help the bone marrow recover from this therapy.

This study will be the first study to test giving vorinostat together with ¹³¹I-MIBG and will help determine the highest doses of vorinostat and ¹³¹I-MIBG that can safely be given together to patients with resistant/relapsed neuroblastoma.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 9 and 42 people will take part in this study.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Medical Tests Before You Begin the Study

You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Physical exam	Bone marrow tests [#]
Blood tests	Various scans*
Pregnancy test	Echocardiogram and EKG to check the heart function
Urine tests	Test of kidney function

[#] Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which 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.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. They are part of regular cancer care.

Physical exam	Bone marrow tests
Blood tests and scans	Various tests
Pregnancy test	Echocardiogram and EKG to check the heart function
Urine tests	Test of kidney function

Treatment Plan

Before you can get treatment on this study, stem cells must be available that meet the study requirements.

A map of the treatment course is shown here.

Therapy Days	V 1	V 2	V+M 3	V 4-14	HSC 17	Eval 56
V = Vorinostat M = ¹³¹ I-MIBG HSC = Stem cell infusion Eval = Repeat disease evaluation						

Vorinostat	V	Days 1-14
¹³¹I-MIBG	M	Day 3
Stem Cells	HSC	Given on Day 17
GCSF	GCSF	Given after stem cells until white blood count recovers
Evaluation	Eval	Evaluations after finishing treatment on Day 56

You will receive vorinostat by mouth once a day with food in the morning on Days 1-14. Vorinostat will be given as a liquid.

You will receive ¹³¹I-MIBG in the hospital on Day 3 (see below: Treatment with MIBG).

You will receive your stem cells back on Day 17 and start GCSF (Neupogen or filgrastim) until your white blood cells recover.

If you have a serious infection, vorinostat may be stopped early, your stem cells may be given early, and you may start GCSF early.

You will be assigned a certain vorinostat dose and a certain ¹³¹I-MIBG dose. This study will test up to 3 vorinostat doses and up to four ¹³¹I-MIBG doses in groups of 3-6 patients. The starting vorinostat dose for the first group of patients is about 20% lower than what is currently being given to patients receiving vorinostat alone without bad side effects. The dose of ¹³¹I-MIBG will then be increased in the second group of patients. If this is tolerated without serious side effects, then the vorinostat dose will be increased (“dose escalation”) in groups of 3-6 patients until serious side effects are seen. At that point, investigators will have found the highest dose of vorinostat that can be given along with ¹³¹I-MIBG without bad side effects.

Next, the ¹³¹I-MIBG dose will be increased in groups of 3-6 patients until serious side effects are seen. At that point, investigators will have found the highest doses of both vorinostat and ¹³¹I-MIBG that can be

safely given together without bad side effects. An additional six patients will be treated at the highest dose of vorinostat and ^{131}I -MIBG to learn more about the side effects and the response of the tumor with those doses.

You can receive this combination of vorinostat and ^{131}I -MIBG once as part of this study.

Treatment with ^{131}I -MIBG

Treatment with ^{131}I -MIBG will be done at a hospital that is set up to take care of patients that are treated with radioactive substances. This means that you may need to travel some distance to another hospital to get this treatment. Your doctor will talk with you about where the different hospitals are that can give the ^{131}I -MIBG treatment. Your nurse and other members of the team that take care of you can help you plan for the trip to get this treatment.

Patients will be admitted to a ^{131}I -MIBG treatment center on day 2 of therapy. On the following day (Day 3), ^{131}I -MIBG is given into a temporary IV or in your central venous catheter over 90-120 minutes. IV fluids for hydration and other medicines will be given through your central venous catheter.

Patients who get ^{131}I -MIBG are considered to be “hot” or radioactive and special precautions are taken to care for you during this time until the radiation level has gone down to a level where these precautions are no longer needed (usually 4 - 5 days). Special care precautions include:

- A single room in a bed surrounded by a lead shield to keep family and the staff who take care of you from being exposed to radiation from the ^{131}I -MIBG treatment. This usually takes about 5 days.
- The length of time family can visit inside the room in front of the protective lead shield that is around your bed will depend on how much radiation is measured in the room each day by the radiation specialist. Usually family can visit for a total of 30-45 minutes on the first day and longer on the days after that because there will be less radiation measured in the room each day.
- Family may visit anytime outside of the room behind a lead shield. You will be able to see who is visiting over this shield.
- No one will be able to spend the night in this special room with you during this time.

Your urine will be radioactive after treatment with ^{131}I -MIBG. A urinary catheter will be inserted through your urethra into the bladder to drain the radioactive urine from your body. This catheter will be removed 3 –5 days following the treatment.

You will also take 2 medicines by mouth, (potassium iodide and potassium perchlorate) to prevent thyroid damage from the radioactive iodine contained in the ^{131}I -MIBG compound. The two medicines will be taken together by mouth beginning the night before treatment for a total of 6-8 days then the potassium iodide alone will be continued for a total of 6 weeks.

When you have finished treatment with vorinostat and ^{131}I -MIBG

After you stop treatment with ^{131}I -MIBG and vorinostat, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ functions, tests will be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Bone marrow tests [#]
Blood tests	Various scans*
Urine tests	

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this consent.

Optional Tests in this Study

You will be asked if you want to participate in tests that are being done to see how the study drugs are affecting your body. **This part of the study is voluntary.** The results of these tests would not be told to you or your doctor or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study. You can decide not to let the doctors do these tests and still be able to be treated with vorinostat and ¹³¹I-MIBG as part of this clinical study. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these voluntary studies.

- **Determining Vorinostat's Effect on Proteins and Genes in Blood Cells**

Part of the research goal for this study is to look at changes in certain proteins and genes in the blood cells before and after you have been treated with vorinostat. For this test, 10 mL of blood (about 2 teaspoons) will be taken 4 times to measure certain proteins and genes in the blood cells. This testing will be done over the first 14 days of the treatment with vorinostat. You will not need separate clinic visits to participate in this part of the study. The total amount of blood drawn for testing will be 40 mL (about 8 teaspoons) over 14 days. The blood will be drawn or taken from your central line (or port). This amount of blood is considered safe to donate. Samples will be sent to the University of California in San Francisco, CA for analysis.

HOW LONG WILL I BE ON THIS STUDY?

You will receive one course of treatment on this study.

After you stop treatment, 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. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment; or whether you have developed any additional cancer. Your oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?

Yes. If you are thinking about stopping the study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely. There are certain time points in the study where it would be strongly recommended that you complete the medical supportive care required to avoid very bad and/or fatal side effects.

- Once you have gotten ¹³¹I-MIBG treatment, you will stay in the special room until you are no longer radioactive (usually 5 days), since you could expose others to radiation.
- Once you have gotten ¹³¹I-MIBG treatment, it would be strongly recommended that you complete the medical supportive care needed to avoid very bad and/or fatal side effects.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

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 a specific dose of a drug. In a Phase I study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who has serious side effects as a result of participating in this Phase I study.

In this study, researchers will be looking at side effects seen in patients taking different doses of vorinostat and ¹³¹I-MIBG. Since subjects will be assigned to different doses of vorinostat and ¹³¹I-MIBG, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or itching). Many side effects go away soon after you stop taking vorinostat and ¹³¹I-MIBG, but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. Because this combination has never been given to children before, there may be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study. While on the study, you are at risk for the side effects listed on the following pages.

Possible side effects of Vorinostat

Likely (happens to 21-100 children out of every 100 children)	Less Likely (happens to 5-20 children out every 100 children)	Rare (happens to < 5 children out every 100 children)
<ul style="list-style-type: none"> • Low blood counts, including low red blood cells (which can cause fatigue or pale appearance) and platelets (which can cause bruising or bleeding). • Fatigue • Weight loss • Poor appetite • Diarrhea • Nausea • Vomiting • 	<ul style="list-style-type: none"> • <u>Decrease in specific types of blood cells-(white blood cells which can cause increased risk of infection)</u> • Effects on blood coagulation lab tests • Decreased kidney function • High blood sugar • Fever • Chills • Hair loss • Constipation • Dehydration • Dry mouth • Heartburn • Taste changes • Infection • Low protein in the blood • Changes in liver blood tests • Changes in blood salts • Muscle spasm or 	<ul style="list-style-type: none"> • Skin breakdown • Changes in a specific part of the heart tracing known as an EKG. (Mild changes in a specific part of the heart tracing known as an EKG has been rarely reported in patients treated with vorinostat, though it is not clear whether vorinostat caused these changes or not.)

	weakness <ul style="list-style-type: none"> • Dizziness • Abdominal pain • Cough • Shortness of breath • Blood clot 	
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Other side effects have been reported in patients receiving vorinostat, but it is unknown whether the vorinostat caused the side effect. These side effects include: irregular heart rhythm; heart attack; blurry vision; trouble swallowing; gassiness; mouth sores; gum pain; swelling of arms/legs; trouble walking; chest pain; low blood sugar; aches and pains; tumor pain; trouble talking; headache; increased pressure in the brain; bleeding into the brain; stroke; confusion and memory changes; decreased skin sensation; fainting; tremor; anxiety; blood and/or protein in the urine; difficulties with urination; bleeding into the lungs; nose bleeds; trouble sleeping; stuffy nose; throat pain; increased sweating; nail changes; itchiness; other rashes; flushing; bruising; changes in blood pressure; and inflammation of blood vessels.

Possible side effects of ¹³¹I-MIBG

Likely (happens to 21-100 children out every 100 children)	Less Likely (happens to 5-20 children out every 100 children)	Rare (happens to < 5 children out every 100 children)
<ul style="list-style-type: none"> • Decrease in the number of red and white blood cells and platelets made in the bone marrow. You will need blood and platelet transfusions and sometimes stem cell infusions are necessary. The dose of ¹³¹I-MIBG used in this study will lower your blood counts. • Nausea • Dry mouth 	<ul style="list-style-type: none"> • Decreased function of the thyroid gland. This causes tiredness (fatigue), weight gain, constipation, and lower blood pressure. Treatment for life with a medicine to supplement the thyroid gland (i.e. Synthroid or related thyroid supplement) may be needed. • Not being able to get pregnant or father a child • High or low blood pressure during the ¹³¹I-MIBG infusion • Thinning of the hair • Vomiting • Infection due to low white blood cells 	<ul style="list-style-type: none"> • Pain in salivary glands or mouth • Decreased function of adrenal gland. This affects your activity level and growth. It causes tiredness (fatigue), weight changes and blood pressure changes. You may need to take medicine to supplement the adrenal gland. • Decreased heart function • Irritation of the liver. Because some of the radioactive ¹³¹I-MIBG is taken up by the liver, there is a possible risk of future liver damage from the ¹³¹I-MIBG alone. • Second cancer (such as leukemia) that is different from the kind of cancer you have now • Trouble breathing due to infection or damage to the lung

	<ul style="list-style-type: none"> • Fatigue due to low red blood cells • Bleeding/bruising due to low platelets • Loss of appetite 	<ul style="list-style-type: none"> • Overactive thyroid gland
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Possible risks from having a bladder catheter placed

In order to safely receive MIBG therapy, you will need to have a tube or catheter called a Foley catheter temporarily placed in your bladder. The catheter may cause you some discomfort and may increase your risk for getting a bladder infection.

Possible side effects of Potassium Iodide:

This medication is given for 45 days after the ¹³¹I MIBG infusion, to protect your thyroid gland.

Likely (happens to 21-100 children out every 100 children)	Less Likely (happens to 5-20 children out every 100 children)	Rare (happens to < 5 children out every 100 children)
	<ul style="list-style-type: none"> • Gastrointestinal distress (nausea / vomiting / diarrhea / stomach pain) 	<ul style="list-style-type: none"> • Tingling, pain or weakness in arms and legs • Flare up of acne in teenagers • Irregular heartbeat • Confusion • Tiredness • Fever • Allergic reaction (hives) • Burning of mouth / throat • Metallic taste • Rash • Decreased function of the thyroid gland with overuse • Swelling of lymph glands

Possible side effects of Potassium Perchlorate:

This medication is given for 5 days after the MIBG infusion, to protect your thyroid gland.

Likely (happens to 21-100 children out every 100 children)	Less Likely (happens to 5-20 children out every 100 children)	Rare (happens to < 5 children out every 100 children)
	<ul style="list-style-type: none"> ▪ Nausea and stomach irritation. Taking this medicine with food or meals may prevent these side effects. 	<ul style="list-style-type: none"> ▪ Unable to make red and white blood cells, platelets ▪ Hives ▪ Skin rashes

Possible side effects of G-CSF (Neupogen)

G-CSF is not an anti-cancer medicine. It helps the growth of white blood cells that fight infection.

Likely (happens to 21-100 children out every 100 children)	Less Likely (happens to 5-20 children out every 100 children)	Rare (happens to < 5 children out every 100 children)
<ul style="list-style-type: none"> • Bone pain 	<ul style="list-style-type: none"> • Pain or irritation at injection site • Increased blood tests for alkaline phosphatase, LDH and uric acid • Low platelet count • Fever 	<ul style="list-style-type: none"> • Allergic reactions (more common with giving the drug IV than as an injection under the skin) • Skin rash, itching, puffiness in the face • Shortness of breath or wheezing • Low blood pressure, fast heart rate • Low grade fever • Enlargement of the spleen. • Rupture of the spleen • Worsening of existing skin rashes • Sickle cell crises in patients with sickle cell disease • High white blood cell count in the blood • Irritation / inflammation of veins in the skin • Adult respiratory distress syndrome • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing neutropenia (not as seen in cancer patients) and long term administration.

Possible side effects associated with stem cells

- ANY TIME BEFORE STEM CELL INFUSION: The freezer where PBSC are stored could malfunction, the container holding them could break and the stem cells could be damaged so they could not be used. This is expected to be an extremely rare event. However, if this occurs, another stem cell collection may be attempted or the back-up stem cells (if available) may be used if they were not damaged.
- If stem cells needed to be shipped from one location to another, they could be lost or damaged during shipping such that they could not be used. This is expected to be an extremely rare event. If this occurs, another stem cell collection may be attempted or the back-up stem cells, if available, may be used.
- PURGED STEM CELLS ONLY: Purged stem cells are treated (purged) to take out neuroblastoma cancer cells and leave the normal cells. Purging may injure the normal stem cells so they will not grow to make a normal working bone marrow after they are infused. This is expected to be an extremely rare event, but could be fatal if it happened. There would be the option to give medicine(s) to stimulate bone marrow growth, or infuse additional back-up stem cells, if they are available.
- Some patients may need extra fluids given into the vein after getting their stem cells. This is to protect the kidneys from the red blood cells mixed in with the stem cells.

Possible side effects of stem cell infusion

Likely (happens to 21-100 children out every 100 children)	Less Likely (happens to 5-20 children out every 100 children)	Rare (happens to < 5 children out every 100 children)
	<ul style="list-style-type: none">• Fever and chills	<ul style="list-style-type: none">• Allergic reaction. Can cause difficulty breathing and low blood pressure.• High blood pressure• Infection• Infusion of tumor cells. Tumor cells may still be present in the harvested stem cells and they could regrow after stem cells are infused.

Possible risks to unborn child

Patients who agree to participate in this study should not become pregnant while on this study. This study and the medicines used in this study may be hazardous to an unborn child. Patients and their sexual partners should use abstinence and /or an effective method of contraception that is medically appropriate based on your personal doctor's recommendation at that time.

Possible risks to the caregiver(s) of the patient getting MIBG treatment

Caregivers (example: parent, other family member, guardian, friend, partner) will be exposed to radiation while you are being treated with MIBG. Caregivers who could possibly become pregnant during this time need to avoid contact with the patient because the radiation exposure may increase the unborn baby's risk of developing cancer or other health problems.

If your caregiver is pregnant, then special precautions should be used to avoid contact with you during and for 4 weeks after getting MIBG treatment. Should your caregiver or your caregiver's sexual partner be found to have been pregnant while you were getting MIBG treatment and did not know it at the time, please contact your doctor immediately.

Possible long term side effects of this treatment

- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.
- Patients who have more than one ¹³¹I-MIBG treatment will have greater doses of radiation to the normal organs than those patients having one treatment. It is possible that there may be later damage to the normal function of the liver or other organs.

Possible risks from having blood drawn

The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk. These have risks that will be discussed with you. You will be asked to sign a separate consent for any procedure that needs sedation.

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 chemotherapy medicines
- Treatment with MIBG alone.
- Treatment with other experimental agents 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?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- NANT Consortium
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Draximage (supplier of ¹³¹I-MIBG)
- Merck (supplier of vorinostat)

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

G-CSF, potassium iodine, and potassium perchlorate are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

Vorinostat will be provided by Merck, the company that makes this drug.

¹³¹I-MIBG will be supplied by Draximage the company that makes this drug, but your insurance company will be charged for this medicine.

The optional studies will be done at no cost to if you agree to participate in this voluntary study. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

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, car fare, travel to and from the hospital for MIBG treatment, parking, and baby sitter fees.

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.

You will not be paid for taking part in this study.

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.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?

Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from 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. If you

remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

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

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

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 the research to protect your rights) at _____ (telephone number).

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may visit the NCI Web sites at <http://cancer.gov/>

For NCI's clinical trials information, go to <http://cancer.gov/clinicaltrials/>

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

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

CONSENTS FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional. You may still participate in the study even if you do not agree to these tests.

- **Determining Vorinostat's Effect on Proteins and Genes in Blood Cells**

Circle YES, if you agree to let researchers take blood to study vorinostat's effect on proteins and genes in blood cells. These are extra blood draws. The results of these tests will be confidential and not made available to you or your treating physician.

Circle NO, if you do not want researchers to take extra blood samples to look at vorinostat's effect on proteins and genes in blood cells.

YES

NO

Signature

Participant: _____

Date: _____

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) 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: Tests that will be done on this study.

Observation	Before Entry	Day 1-9	Day 10-56	At the end of treatment
Physical Exam	X	Day 7	Weekly until Day 28 and then every other week	X
Blood Tests	X	Day 3, 7-9	Up to three times weekly until Day 14 and then weekly	X
Urine tests	X			X
Pregnancy test	X			
Heart tests (echocardiogram and EKG)	X	Day 7 EKG	Day 14 EKG	X
Bone Marrow Aspirate/biopsy	X			X
CT, MRI and/or MIBG scans	X			X
MIBG scan after MIBG treatment; no extra MIBG is given to you for this scan.		After you get out of your radiation isolation room		
Blood samples for vorinostat effects on proteins and genes in the blood (optional)		Four blood samples over days 1-4		

SAMPLE ASSENT FORM

VORINOSTAT WITH ¹³¹I-MIBG THERAPY FOR RESISTANT/RELAPSED NEUROBLASTOMA: A PHASE I STUDY

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]
[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. My name is _____.
2. You have a kind of cancer called **Neuroblastoma**. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using two medicines called **Vorinostat** and **MIBG** and to see what effects (both good and bad) these medicines have on patients and their cancer. Vorinostat is a medicine that is given by mouth as a liquid. MIBG is a radioactive medicine that is given into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm). The MIBG goes mostly to where the cancer is in your body to give it radiation. The doctors think that giving MIBG may kill neuroblastoma cancer cells and that vorinostat will make the MIBG work better.
3. If you agree to be in this study this is what will happen:
You will get this therapy only one time.

Stem Cells:

MIBG is a medicine that can lower the numbers of your normal blood cells. Stem cells make all the normal blood cells your body needs to be healthy. This includes white blood cells that fight infection, platelets that stop you from bleeding, and red blood cells that carry oxygen to your body. When MIBG is given at higher doses it can damage stem cells so they don't make enough of the normal blood cells we need to live. Your doctor will collect your stem cells and put them away in a freezer for a time that you might need them. Your stem cells will be given back to you like a blood transfusion after the MIBG and other treatment is finished. This is called Stem Cell Infusion or Stem Cell Rescue.

Vorinostat:

You will take vorinostat liquid by mouth once a day for 14 days.

MIBG:

You will get MIBG, which is a radioactive medicine given into an IV over 1 hour. Because of this radiation treatment you will need to stay in your room until you go home. This is usually about 5 days. Your parents cannot sleep in your room but they will be able to stay just outside your room and you will be able to see and talk to them anytime you want. They can visit inside your room for a short time each day.

Because not all hospitals can give the MIBG, you might have to go with your parents to another hospital to get the MIBG part.. Your doctor will talk with you and your parents about the different hospitals that can give the MIBG, and which one will be the best for you.

You will need to have a **Urinary Catheter** placed to help drain your urine while you are getting the MIBG treatment. A soft tube will be put inside your urethra (the hole where urine comes out of our bodies), and up into your bladder (the place where urine waits inside our bodies until we go to the bathroom). Because the MIBG will be in your urine, and can cause damage to your bladder, the catheter is necessary to prevent this from happening by keeping your bladder completely empty all the time.

Filgrastim/G-CSF:

The G-CSF helps the blood cells grow back faster after treatment. You will get G-CSF if your blood cells are low after getting MIBG. G-CSF is given through your IV or as an injection (shot) from a very small needle into your leg that your parents will learn how to give you. It is given one time a day until your blood cells have started to grow back. We will know when the blood counts are high enough to stop the G-CSF by doing a blood test.

Stem Cell Infusion:

Your stem cells will be given back to you two weeks after you finish MIBG treatment. We give the stem cells back through your central line over about 30 minutes either in the hospital or in the clinic. It is a lot like getting a platelet transfusion – the stem cells look like watery blood.

Coming to See the Doctors:

During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often)
- MRI, CT, and MIBG Scans (special pictures of your tumor)

- Bone marrow test (to look for tumor in your bone marrow)
- Tests for your heart, and your kidneys
- Check your pee
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
- You may have to come to the clinic to have blood and platelet transfusions when the blood counts are low or stay in the hospital if you have a fever with low blood counts.

You will come to visit your doctor every week or so to start with, then less often if everything is going well.

4. Sometimes things happen to kids in research studies that may make them feel bad. These are called “risks”. Some of the risks of this study are:

- You may feel sick to your stomach and you may throw up.
- You may feel tired.
- You may have a bad appetite.
- You might have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection. You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
- During MIBG, the urinary catheter may be uncomfortable, and some people feel embarrassed having it – but you will only need it for a few days. It may also be hard to be in a room for a long time by yourself until the radiation levels are low enough that it is safe for your parents and everyone else to be around you all the time.
- The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing.
- You could get a different kind of cancer, this doesn’t happen often, but can happen years later.
- It is possible that you could die from the treatment or cancer.

Not all of these things may happen to you. Or things may happen that the doctors don’t know about yet.

5. People also have good things that happen to them when they are in research studies. These are called “benefits”. The benefits to you of being in this research study are that this treatment might make your neuroblastoma tumor stay the same size or get smaller for some time. We hope to learn more about this new treatment which could help other children 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. Being in this study is up to you. 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 but there are two times where you would be at more risk for being sick or having side effects or being dangerous to other people if you stopped being in the study. 1. If you got MIBG and left the special room before the doctors said it was ok to leave, then you would still be radioactive and this would be dangerous to everyone who was around you since you would give them radiation from your body. 2. If you decided to stop treatment after getting MIBG but before you were given your stem cells back, the high dose of MIBG could kill your blood cells so they would not grow back on their own without getting back your stem cells. In this case you would not be able to make your own blood cells and could have bad infections or bleeding, and you could die from not having enough normal blood cells.

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. Study doctor's phone number: _____.

9. Optional Blood Samples

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

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

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

10.. Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Subject: _____

Signature of Subject:

Date

Signature of Investigator

Date

Signature of Person Conducting Discussion

Date