N15-02 Template Consent and Assents

There are 3 Consents and 2 Assents in this file

Consent:

1. **Cohort A1 & B1**
2. **Cohort B2**
3. **Cohort A2**

Assent

1. **Lorlatinib only**
2. **Lorlatinib in combination with cyclophosphamide/topotecan**

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APPENDIX VI: DOSE ESCALATION AND EXPANSION COHORT (A1 & B1) SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB (PF-06463922), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

PHASE 1 DOSE ESCALATION & EXPANSION COHORT (A1 & B1): FOR PATIENTS ONE YEAR OF AGE THROUGH 18 YEARS OF AGE

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 doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of lorlatinib that can be given to children and adolescents with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib given at different dose levels to children and adolescents 1-18 years of age.
- To determine if your tumor gets smaller after treatment with lorlatinib.
- To measure the levels of lorlatinib in the blood at different dose levels.
- To look at genetic changes in tumor DNA found in the blood during treatment with lorlatinib.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK). ALK may be important in the growth of certain types of cancer cells, such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a situation like yours. Lorlatinib has not been approved by the United States Food and Drug Administration (FDA). Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. Lorlatinib has not previously been used in children and adolescents. This study is called a phase 1 study because the goal is to find the highest dose of lorlatinib that we can give safely. Once we have found out the highest dose of lorlatinib that can be given safely, we will treat more children and adolescents with neuroblastoma with this Lorlatinib dose.

All patients enrolled on this phase 1 study have been previously tested and are known to have a defect in the ALK gene in their tumor before they start treatment. You or your doctor should have the results of this test before enrolling on this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be about 56 patients enrolling on the 4 study cohorts. You have been given this consent because the planned enrollment is on cohort A1 or B1. Between 9 and 18 people will take part in the phase 1 dose escalation part of the study (Cohort A1). When you join the study, you will be assigned a certain lorlatinib dose. This study will test up to three lorlatinib doses in groups of 3-6 patients. The starting lorlatinib dose for the first group of patients is about 25% lower than what was given to adults who received lorlatinib without bad side effects. If this is tolerated without serious side effects, then the lorlatinib dose will be increased ("dose escalation") in groups of 3-6 patients until the third dose level or if serious side effects are seen. At that point, investigators will have found the highest dose of lorlatinib that can be given without bad side effects (called maximum tolerated dose). This part of the trial is called cohort A1.

Once the maximum tolerated dose is determined, another group of 6 patients will be enrolled and treated at this dose of lorlatinib, known as the dose expansion part of the study (Cohort B1). The purpose of the dose expansion part of the study is to gather more information about side effects seen in patients treated at the maximum tolerated dose of lorlatinib. The dose expansion cohort (Cohort B1) will not enroll patients until the dose escalation part of the study (Cohort A1) is completed and the highest dose of lorlatinib that can be given safely without serious side effects is found.

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

Before You Begin the Study

Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the *ALK* gene which allows you to be considered for participation in this study (Cohorts A1 and B1).

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of 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 doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

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

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

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6] Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with lorlatinib. Neuropsychological testing will be done within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During the Study" for more details on what tests are done and when they are done during this study.

<u>During the Study</u>

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given for 28 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to take lorlatinib for an unlimited number of cycles unless you develop serious side effects or your tumor worsens.

One Treatment Cycle (Cohort A1: dose escalation group and Cohort B1: dose expansion group)			
Week 1	Week 2	Week 3	Week 4
Days 1 - 7	Days 8 - 14	Days 15 - 21	Days 22 - 28
Lorlatinib once a day →			

Lorlatinib will be given by mouth once a day followed by a small glass of water. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side effects that you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the

medication bottle (even if it is empty) weekly during cycle 1 and then after each treatment cycle of lorlatinib. This will help us to know how much of the drug you take and how it made you feel.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm [3]
Blood tests [1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor [4]
Pregnancy test (urine or blood) [2]	Neuropsychological testing[5]

[1] Some blood tests (cholesterol and fat digestion) may be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2] A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female at least 10 years old or who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3] Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4] Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5] **Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. A table at the end of the consent lists how often neuropsychological testing will be done during the study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child.

- All patients 3 years of age and older will do computerized tests using an iPad. While the patient is taking these tests, the patient's parent or legal guardian will complete written questionnaires about the patient's mood and emotions, behavior, daily living/functional skills and social skills with others. The parent/legal guardian can be in the same room during the testing but they cannot help their child with their tests.

- Patients 18 years of age will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.

- Patients under 3 years of age will have an evaluation of overall functioning including language, motor and cognitive development done by a licensed psychologist. This testing will take 60 to 90 minutes to complete. Parents/legal guardians will also complete written questionnaires at the same time.

Patient age at testing in years	Testing being done	Length of testing time for Patients	Length of testing time for Parents/legal guardians
1	Patient: licensed psychologist Parent/legal guardian: written questionnaires	~ 60 - 90 minutes	~ 20 minutes
2			~ 60 - 90 minutes
3 - 5	Patient: computerized tests using an iPad Parent/legal guardian: written questionnaires	~ 10 minutes	~ 50 minutes
6		~ 30 – 40 minutes	~ 50 minutes
7 - 9		~ 30 – 40 minutes	~ 50 - 55 minutes
10 - 17		~ 35 – 45 minutes	~ 50 - 55 minutes
18	Patient: computerized tests using an iPad and written questionnaires	~ 80 – 90 minutes	NA

NANT Biology Study (N2004-05)

You will also be expected to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with Lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

When You Have Finished Treatment with Lorlatinib

After you stop treatment on this study, 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 function, tests are recommended by the study to 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	Neuropsychological testing[1]
Blood tests	Bone marrow tests & various scans to check your tumor[2]

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans (CT/MRI, MIBG or PET) are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this consent (Consent Addendum 1).

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). These blood samples will be collected on patients enrolling in both the dose escalation (Cohort A1) and the dose expansion (Cohort B1) phases of the study. About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 2 separate days during course 1 (Day 1 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 and a half teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study.

Other Biology Research Tests in this Study - Optional

You will be asked if you want to participate in 3 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you 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.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. For this study, researchers would like to take 2 additional teaspoons of blood (10mL) at study entry and at each time a disease evaluation is done (after cycle 2, 4, 6 and then every 4^{th} cycle after that) to look at what genetic changes in your tumor can be seen in your blood over time. The blood will be sent to a commercial laboratory for genetic testing.

- **Comparing genetic changes between leftover tumor from a surgical procedure prior to tumor relapse (at diagnosis or when you had surgery done after diagnosis) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

HOW LONG WILL I BE ON THIS STUDY?

You can get an unlimited number of treatment cycles with lorlatinib as long as you are not having bad side effects and as long as your tumor is not getting worse.

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 doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also 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 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 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 have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib. Since subjects will be assigned to different dose levels of lorlatinib, 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 reaction to lorlatinib). Many side effects go away soon after you stop taking the study medications 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. There may also 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 below:

Possible Risks of Lorlatinib

Likely **> 20% of patients (%)**	**Less Likely** **5-20% of patients (%)**	**Rare** **< 5% of patients**
• Blood cholesterol increased • Swelling in extremities • Blood triglycerides increased • Weakness, numbness, tingling, burning, prickling or pain, usually in your hands and feet	• Fatigue • Liver enzymes increased • Constipation • Pancreas enzymes increased • Nausea • Ringing in ears • Weight increased • Mood swings • Low level of red blood cells making you feel tired or weak • Pain in joints • Difficulty thinking clearly • Memory impairment • Vomiting • Distorted sense of taste • Gait disturbance • Irritability • Difficulty speaking, communicating	• Abnormal dreams • Hair loss • Amnesia • Weakness or lack of energy • Kidney enzyme increased • Confusion • Diarrhea • Disturbance in attention (Attention deficit/hyperactivity disorder) • Abnormal heart rhythm • Hallucination • Increased blood lipids • Seizure • Low platelet count • Abdominal pain • Anxiety • Balance disorder • Blood enzyme in brain,

	• Visual impairment	skeletal muscle and heart increased • Carpal tunnel syndrome • Swelling in the eyes • Decreased appetite • Dehydration • Depressed mood • Acne • Dizziness • Skin rash • Dry mouth • Shortness of breath • Decrease in heart function • Fluid retention

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. It is unknown if lorlatinib could be hazardous to an unborn child. Patients and their sexual partners should avoid sex and / or use two effective methods of contraception that is medically appropriate based on your personal doctor's recommendation at that time and should be used for as long as you participate in this study. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of Treatment with Lorlatinib

Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

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.

Unknown Risks

The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

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?

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

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available
- No neuroblastoma 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:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- 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), Health Canada, or European regulatory agency(ies) involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

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.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with lorlatinib is being done as part of research and will be paid for by the study. The special research blood and tissue studies will be done at no cost to you. 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 treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not 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 website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

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 you 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/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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

CONSENT FOR EXTRA STUDIES FOR RESEARCH

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

1. **Using extra blood to look for genetic changes seen in tumor cells**
   Initial next to YES if you agree to let researchers take 2 extra teaspoons (10mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on the study. The results of these tests will be confidential and not made available to you or your treating physician.

   Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

   _____Yes _____No

2. **Comparing genetic changes between tumor leftover from a surgical procedure prior to relapse (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with lorlatinib.**

   Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want leftover tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

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.

_____
Print Patient Name

_____ _____/_____/_____
Print Name 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 Date

Consent Addendum I: Tests That Will Be Done On This Study

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine Blood tests (Blood counts, electrolytes, liver, kidney function)	X	Weekly for other tests and twice weekly for blood counts	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle and weekly for blood counts	X
Blood tests for cholesterol triglycerides and function of the pancreas (amylase/lipase)	X	Weekly	Start of cycle	Start of each cycle	X
Pregnancy test (All females 10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to two weeks after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				
	Tests done during Disease Evaluation				
Bone marrow aspirate and biopsy	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X
CT/MRI scans and/or MIBG/PET scans					
Blood and bone marrow for NANT Biology study[#]					

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information

Consent Addendum II

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX VII: LORLATINIB IN COMBINATION WITH CONVENTIONAL CHEMOTHERAPY (COHORT B2) SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB, AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

LORLATINIB IN COMBINATION WITH CONVENTIONAL CHEMOTHERAPY (COHORT B2): FOR PATIENTS ONE YEAR OF AGE THROUGH 18 YEARS OF AGE

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 doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of lorlatinib that can be given to children and adolescents with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib when given in combination with cyclophosphamide and topotecan) in children and adolescents.
- To determine if your tumor gets smaller after treatment with lorlatinib when given in combination with cyclophosphamide and topotecan.
- To measure the levels of lorlatinib in the blood when given together with cyclophosphamide and topotecan in children and adolescents.
- To look at genetic changes in tumor DNA found in the blood during treatment.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy. This part of the study will combine three drugs: lorlatinib, cyclophosphamide and

topotecan. You may have taken cyclophosphamide and/or topotecan before (but not all three together) for treatment of your neuroblastoma.
This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK). ALK may be important in the growth of certain types of cancer cells such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a situation like yours. Lorlatinib has not been approved by the United States Food and Drug Administration (FDA). Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. Lorlatinib has not previously been used in children and adolescents.

Cyclophosphamide and topotecan are chemotherapy drugs that are FDA-approved for the treatment of certain adult cancers, but have not been approved to treat children with neuroblastoma. These drugs have been used in combination to treat many children with neuroblastoma and in some patients this combination has reduced the amount of neuroblastoma present. Even if you have previously received treatment with cyclophosphamide and topotecan, you can still participate in this study.

All patients enrolled on this study are known to have a defect in the ALK gene in their tumor before they start treatment. You or your doctor should have the results of this test before being able to enroll on this study.

The highest dose of lorlatinib that can be given safely to children and adolesecents was determined from the dose escalation part of the study that has been completed (Cohort A1). Lorlatinib has not been given in combination with chemotherapy in patients with childhood tumors. In this part of the study (Cohort B2), we will look at whether this dose of lorlatinib can be given safely in combination with cyclophosphamide and topotecan to children and adolescents with relapsed/refractory neuroblastoma.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
There will be about 56 patients enrolling on the 4 study cohorts. Of this number, about 12 children and adolescents will be enrolled on this part of the study where lorlatinib is given together with cyclophosphamide and topotecan (Cohort B2).

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

Before You Begin the Study
Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the *ALK* gene which allows you to be considered for participation in this study (Cohort B2).

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of 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.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.
[3]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

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

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6]Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with Lorlatinib. Neuropsychological testing will be done at within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During the Study" for more details on what tests are done and when they are done during this study.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given once a day for 28 days and will be given together with cyclophosphamide/topotecan on the first 5 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to receive treatment with lorlatinib and cyclophosphamide/topotecan for up to 24 cycles unless you develop serious side effects or your tumor worsens.

One Treatment Cycle **Cohort B2: Lorlatinib with chemotherapy**									
Week 1							Week 2	Week 3	Week 4
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8-14	Days 15 -21	Days 22-28
***Lorlatinib once a day** →									
CPM	CPM	CPM	CPM	CPM					
TOPO	TOPO	TOPO	TOPO	TOPO	MGF				

CPM: Cyclophosphamide
TOPO: Topotecan
MGF: Myeloid growth factor
*Lorlatinib should be given at least one hour before chemotherapy on days 1-5 of each cycle.

Lorlatinib

Lorlatinib will be given by mouth once a day followed by a small glass of water.. Lorlatinib should be given at least one hour before chemotherapy on days 1 – 5 of each cycle. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side effects that you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then at the end of each treatment cycle. This will help us to know how much of the drug you take and how it made you feel.

Cyclophosphamide & Topotecan

You will receive both cyclophosphamide and topotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) on days 1 through 5 of each cycle. You will receive each medicine over 30 minutes and the cyclophosphamide will be given first. These medicines are typically given in the clinic.

Myeloid Growth Factor

In addition, you will be given a medicine to help boost your white blood cell count. White blood cells help fight infection and having low white blood cells can increase your risk of developing an infection. This drug will be started on day 6 of each treatment cycle. Filgrastim or G-CSF is a shot given into the skin each day until the white blood cell count increases. Pegfilgrastim is a long-acting version of filgrastim that is given as shot into the skin just once on day 6 of the cycle. Your doctor will talk with you about which of these study drugs you will receive.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib in combination with chemotherapy and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm [3]
Blood tests [1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor [4]
Pregnancy test (urine or blood) [2]	Neuropsychological testing [5]

[1] Some blood tests (cholesterol and fat digestion) may be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2] A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female at least 10 years old or who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3] Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4] Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5]**Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. Testing methods are based on the age of the patient and include

computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

The results of the neuropsychological testing will be told to your doctor and entered as part of your medical record. Neuropsychological results will be used to make decisions about your care while enrolled on this study. If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child. Please see the table at the end of the consent form that tells how often these tests will be done during the study.

- All patients 3 years of age and older will do computerized tests using an iPad. While the patient is taking these tests, the patient's parent or legal guardian will complete written questionnaires about the patient's mood and emotions, behavior, daily living/functional skills and social skills with others. The parent/legal guardian can be in the same room during the testing but they cannot help their child with their tests.

- Patients 18 years of age will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.

- Patients under 3 years of age will have an evaluation of overall functioning including language, motor and cognitive development done by a licensed psychologist. Parents/legal guardians will also complete written questionnaires at the same time.

<table>
<tr><th>Patient age at testing in years</th><th>Testing being done</th><th>Length of testing time for Patients</th><th>Length of testing time for Parents/legal guardians</th></tr>
<tr><td>1</td><td rowspan="2">Patient: licensed psychologist
Parent/legal guardian: written questionnaires</td><td rowspan="2">~ 60 - 90 minutes</td><td>~ 20 minutes</td></tr>
<tr><td>2</td><td>~ 60 - 90 minutes</td></tr>
<tr><td>3 - 5</td><td rowspan="4">Patient: computerized tests using an iPad
Parent/legal guardian: written questionnaires</td><td>~ 10 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>6</td><td>~ 30 – 40 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>7 - 9</td><td>~ 30 – 40 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>10 - 17</td><td>~ 35 – 45 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>18</td><td>Patient: computerized tests using an iPad and written questionnaires</td><td>~ 80 – 90 minutes</td><td>NA</td></tr>
</table>

NANT Biology Study (N2004-05)

You will also be expected to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with Lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

When You Have Finished Treatment with Lorlatinib

After you stop treatment on this study, 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 are

recommended by the study to 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	Neuropsychological testing[1]
Blood tests	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor[2]

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this form (Consent Addendum 1).

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). These blood samples will be collected on patients enrolling in both the dose escalation (Cohort A1) and the dose expansion (Cohort B1) phases of the study. About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 2 separate days during course 1 (Day 1 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 and a half teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study.

Other Biology Research Tests in this Study - Optional

You will be asked if you want to participate in 2 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you 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.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. About 10mL (two teaspoons) of blood will be drawn at study entry and at each time disease evaluation testing is done (after cycles 2, 4, 6 and then every 4th cycle) to look at what genetic changes in your tumor may be seen over time from the small pieces of tumor DNA found in your blood. The blood will be sent to a commercial laboratory contracted to perform this testing for the study.

- **Comparing genetic changes between leftover tumor from a surgical procedure prior to tumor relapse (at diagnosis or when you had surgery done after diagnosis) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

HOW LONG WILL I BE ON THIS STUDY?
You can get up to 24 cycles with lorlatinib and chemotherapy as long as you are not having bad side effects and as long as your tumor is not getting worse.

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 your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also 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 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 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 have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib as well as lorlatinib given together with chemotherapy.

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. Many side effects go away soon after you stop taking the study medications 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. There may also 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 below:

Possible Risks of Lorlatinib:

Likely > 20% of patients (%)	Less Likely 5-20% of patients (%)	Rare < 5% of patients
• Blood cholesterol increased • Swelling in extremities • Blood triglycerides increased • Weakness, numbness, tingling, burning, prickling or pain, usually in your hands and feet	• Fatigue • Liver enzymes increased • Constipation • Pancreas enzymes increased • Nausea • Ringing in ears • Weight increased • Mood swings • Low level of red blood cells making you feel tired or weak • Pain in joints • Difficulty thinking clearly • Memory impairment • Vomiting • Distorted sense of taste • Gait disturbance • Irritability • Difficulty speaking, communicating • Visual impairment	• Abnormal dreams • Hair loss • Amnesia • Weakness or lack of energy • Kidney enzyme increased • Confusion • Diarrhea • Disturbance in attention (Attention deficit/hyperactivity disorder) • Abnormal heart rhythm • Hallucination • Increased blood lipids • Seizure • Low platelet count • Abdominal pain • Anxiety • Balance disorder • Blood enzyme in brain, skeletal muscle and heart increased • Carpal tunnel syndrome • Swelling in the eyes • Decreased appetite • Dehydration • Depressed mood • Acne • Dizziness • Skin rash • Dry mouth • Shortness of breath • Decrease in heart function • Fluid retention

Possible Side Effects of Cyclophosphamide:

Likely	Less Likely	Rare But Serious
• Loss of appetite • Nausea • Vomiting • Fewer white blood cells in the blood. ○ A low number of white blood cells may make it easier to get infections. • Hair loss • Decreased ability of the body to	• Abdominal pain • Diarrhea • Fewer red blood cells and platelets in the blood ○ A low number of red blood cells may make you feel tired and weak. ○ A low number of platelets may cause you to bruise and bleed more easily.	• Temporary blurred vision • Nasal stuffiness with fast IV infusions • Irregular heart rate with fast IV infusions • Skin rash • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills

fight infection • Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children	• Bleeding and inflammation of the urinary bladder • Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children	and fever • Abnormal hormone function which may lower the level of salt in the blood • Heart muscle damage which may occur with very high doses and which may be fatal • Darkening of areas of the skin and finger nails • Fingernail changes • Slow healing of wounds • Infections • Infertility which is the inability to have children • Damage and scarring of lung tissue which may make you short of breath • A new cancer or leukemia resulting from this treatment. • Damage or scarring of urinary bladder tissue

Possible Side Effects of Topotecan:

Likely	Less Likely	Rare But Serious
• Diarrhea • Nausea • Vomiting • Constipation • Fewer white blood cells, red blood cells and platelets in the blood. o A low number of white blood cells can make it easier to get infections o A low number of red blood cells can make you feel tired and weak o A low number of platelets causes you to bruise and bleed more easily • Fever including fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics • Pain which may be in your abdomen, back or bones • A feeling of weakness and/or tiredness • Temporary hair loss	• Loss of appetite • Headache • Lack of muscle strength or weakness • Rash, hives, itching or a red bumpy rash • A mild lowering of the blood pressure which usually does not require treatment • Shortness of breath • Inflammation and/or sores in the mouth, throat and/or esophagus • Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage • An infection in the blood which will require admission to the hospital and treatment with antibiotics	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath. • Chest pain • Shaking chills • Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage • Numbness and tingling in the fingers and toes • Muscle or joint aches and pains • Bleeding into the tumor which may cause damage depending on the location of the tumor • Small amount of blood and/or protein in the urine or an elevation in blood creatinine which may indicate mild kidney damage

Growth Factors are not anti-cancer medicines. It helps the growth of white blood cells that fight infection (filgrastim/pegfilgrastim).

Possible Side Effects of Neupogen (Filgrastim):

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)
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen or rupture of the spleen. • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome) • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug. • Worsening of skin rashes • Low Fever • Inflammation of blood vessels leading to a raised purple rash and bruising • Higher than normal white blood count. • Low blood pressure and/or increased heart rate • Wheezing or shortness of breath • Skin rash, hives or facial swelling

Possible Side Effects of Neulasta (Pegfilgrastim):

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)
• Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • Enlarged spleen • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may

		be due to the white blood cells, stimulated by Pegfilgrastim, travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome)

Possible Risks to Unborn Child
Patients who agree to participate in this study should not become pregnant while on this study. It is unknown if lorlatinib could be hazardous to an unborn child. Patients and their sexual partners should avoid sex and / or use two effective method(s) of contraception that is medically appropriate based on your personal doctor's recommendation at that time and should be used for as long as you participate in this study. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of This Treatment
Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

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.

Unknown Risks
The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

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?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No neuroblastoma 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:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- 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) or Health Canada, involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.

- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

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.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. Cyclophosphamide and topotecan is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with Lorlatinib is being done as part of research and will be paid for by the study.
The special research blood and tissue studies will be done at no cost to you. 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 treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not 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 you 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/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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

CONSENT FOR EXTRA STUDIES FOR RESEARCH

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

1. **Using extra blood to look for genetic changes seen in tumor cells**
   Initial next to YES if you agree to let researchers take 2 extra teaspoons (10mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on this study. The results of these tests will be confidential and not made available to you or your treating physician.

   Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

   _____Yes _____No

2. **<u>Comparing genetic changes between tumor leftover from a surgical procedure prior to relapse (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.</u>**

   Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want leftover tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

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

_____ _____/_____/_____
Print Name 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 Date

Consent Addendum I: Tests That Will Be Done On This Study

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine blood tests (Blood counts, electrolytes, liver, kidney function)	X	Weekly for other tests and twice weekly for blood counts	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle and weekly for blood counts	X
Blood tests for cholesterol, triglycerides and function of the pancreas (amylase/lipase)	X	Weekly	Start of cycle	Start of each cycle	X
Pregnancy test (All females10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to two weeks after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6 and every 4th cycle thereafter)	
Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				
	Tests done at Disease Evaluation				
Bone marrow aspirate and biopsy	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X
CT/MRI scans and/or MIBG/PET scans					
Blood and bone marrow for NANT Biology study[#]					

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study (NANT 2004-05) consent form for more information.

Consent Addendum II

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX VIII: DOSE EXPANSION COHORT A2: PATIENTS > 18 YEARS OF AGE SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB, AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

PHASE 1 DOSE EXPANSION COHORT (A2): PATIENTS OLDER THAN 18 YEARS OF AGE AND INCLUDING THOSE PATIENTS <= 18 YEARS OF AGE WITH A BSA >= 1.73M2. FOR PATIENTS TREATED ON THE ADULT DOSE OF LORLATINIB

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

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 doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The Purposes Of This Study Are:

- To find the highest dose of lorlatinib that can be given to children and adolescents with refractory or relapsed neuroblastoma without causing severe side effects for those children/adolescents enrolling on dose level 3 of the dose expansion cohort A1
- To learn about the side effects of the drug lorlatinib when given to adults.
- To determine if your tumor gets smaller after treatment with lorlatinib.
- To measure the levels of lorlatinib in the blood
- To look at genetic changes in tumor DNA found in the blood during treatment.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The Research Is Being Done Because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK) gene. ALK may be important in the growth of certain types of cancer cells such as neuroblastoma. Lorlatinib is considered experimental because it has not been

proven to work in a situation like yours. Lorlatinib has not been approved by the United States Food and Drug Administration (FDA). Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. In these previous studies, the recommended dose of lorlatinib that can be given safely was determined for adults. Adults and children/adolescents whose body size may be the size of adults that meets the adult dosing criteria will receive this dose of lorlatinib. All patients enrolled on this study are known to have a defect in the ALK gene in their tumor before they start treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be about 56 patients enrolling on the 4 study cohorts. There is no maximum number of patients to be enrolled on this cohort. It is expected that 6 patients greater than 18 years of age and children/adolescents with a higher BSA meeting the adult dosing criteria will take part in the phase 1 expansion part of the study called Cohort A2. Children and adolescents with a BSA between $1.43m^2$ and $1.72m^2$ will only be assigned to this cohort when cohort A1 (dose escalation cohort) is enrolling patients on dose level 3. When you join the study, you will be given lorlatinib at the adult recommended phase 2 dose of 100mg orally once a day for 28 days. This is the highest dose level at which investigators have found lorlatinib to be given safely without serious side effects.

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

Before You Begin the Study

Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the ALK gene which allows you to be considered for participation in this study.

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of 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 doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8-10 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

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

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

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.
[6]Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with Lorlatinib. Neuropsychological testing will be done at within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During this Study" for more details on what tests are done and when they are done during this study..

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given for 28 days. This entire period is called a cycle with each treatment cycle being 28 days long.. You may continue to take lorlatinib for an unlimited number of cycles unless you develop serious side effects or your tumor worsens.

One Treatment Cycle (Cohort A2: adults and children/adolescents higher BSA group meeting adult dosing criteria)			
Week 1	Week 2	Week 3	Week 4
Days 1 - 7	Days 8 - 14	Days 15 - 21	Days 22 - 28
Lorlatinib once a day →			

Lorlatinib will be given by mouth once a day followed by a small glass of water. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side affects you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then after each treatment cycle of lorlatinib. This will help us to know how much of the drug you take and how it made you feel.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm[3]
Blood tests[1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor[4]
Pregnancy test (urine or blood)[2]	Neuropsychological testing[5]

[1]Some blood tests (cholesterol and fat digestion) can only be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2]A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5]**Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. A table at the end of the consent lists how often neuropsychological testing will be done during the study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

The results of the neuropsychological testing will be told to your doctor and entered as part of your medical record. Neuropsychological results will be used to make decisions about your care while enrolled on this study. If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child.

- All patients 3 years of age and older will do computerized tests using an iPad. While the patient is taking these tests, the patient's parent or legal guardian will complete written questionnaires about the patient's mood and emotions, behavior, daily living/functional skills and social skills with others. The parent/legal guardian can be in the same room during the testing but they cannot help their child with their tests.
- Patients 18 years of age and older will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.
- Patients under 3 years of age will have an evaluation of overall functioning including language, motor and cognitive development done by a licensed psychologist. Parents/legal guardians will also complete written questionnaires at the same time.

<table>
<tr><th>Patient age at testing in years</th><th>Testing being done</th><th>Length of testing time for Patients</th><th>Length of testing time for Parents/legal guardians</th></tr>
<tr><td>1</td><td rowspan="2">Patient: licensed psychologist
Parent/legal guardian: written questionnaires</td><td rowspan="2">~ 60 - 90 minutes</td><td>~ 20 minutes</td></tr>
<tr><td>2</td><td>~ 60 - 90 minutes</td></tr>
<tr><td>3 - 5</td><td rowspan="4">Patient: computerized tests using an iPad
Parent/legal guardian: written questionnaires</td><td>~ 10 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>6</td><td>~ 30 – 40 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>7 - 9</td><td>~ 30 – 40 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>10 - 17</td><td>~ 35 – 45 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>18 – 25</td><td rowspan="2">Patient: computerized tests using an iPad and written questionnaires</td><td rowspan="2">~ 80 - 90 minutes</td><td rowspan="2">NA</td></tr>
<tr><td>26+</td></tr>
</table>

NANT Biology Study (N2004-05)
You will also be expected to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with Lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

When you have finished treatment with Lorlatinib
After you stop treatment on this study, 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 are recommended by the study to 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	Neuropsychological testing[1]
Blood tests	Bone marrow tests and Various scans (CT/MRI, MIBG or PET) to check your tumor[2]

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this form (Consent Addendum 1).

Additional Tests in this Study
We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required
During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). These blood samples will be collected on patients enrolling in both the dose escalation (Cohort A1) and the dose expansion (Cohort B1) phases of the study. About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 2 separate days during course 1 (Day 1 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 and a half teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study.

Other Biology Research Tests in this Study – Optional

You will be asked if you want to participate in 2 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you 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.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. About 10mL (two teaspoons) of blood will be drawn at study entry and at each time disease evaluation testing is done (after cycles 2, 4, 6 and then every 4th cycle) to look at what genetic changes in your tumor may be seen over time from the small pieces of tumor DNA found in your blood. The blood will be sent to a commercial laboratory contracted to perform this testing for the study.

- **Comparing genetic changes between leftover tumor from an earlier procedure (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

HOW LONG WILL I BE ON THIS STUDY?

You can get an unlimited number of treatment cycles with lorlatinib as long as you are not having bad side effects and as long as your tumor is not getting worse.

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 your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also 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 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 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 have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib. 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 reaction to lorlatinib). Many side effects go away soon after you stop taking the study medications 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. There may also 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 below:

Possible Risks of Lorlatinib

Likely **> 20% of patients (%)**	**Less Likely** **5-20% of patients (%)**	**Rare** **< 5% of patients**
• Blood cholesterol increased • Swelling in extremities • Blood triglycerides increased • Weakness, numbness, tingling, burning, prickling or pain, usually in your hands and feet	• Fatigue • Liver enzymes increased • Constipation • Pancreas enzymes increased • Nausea • Ringing in ears • Weight increased • Mood swings • Low level of red blood cells making you feel tired or weak • Pain in joints • Difficulty thinking clearly • Memory impairment • Vomiting • Distorted sense of taste • Gait disturbance • Irritability • Difficulty speaking, communicating • Visual impairment	• Abnormal dreams • Hair loss • Amnesia • Weakness or lack of energy • Kidney enzyme increased • Confusion • Diarrhea • Disturbance in attention (Attention deficit/hyperactivity disorder) • Abnormal heart rhythm • Hallucination • Increased blood lipids • Seizure • Low platelet count • Abdominal pain • Anxiety • Balance disorder • Blood enzyme in brain, skeletal muscle and heart increased • Carpal tunnel syndrome • Swelling in the eyes • Decreased appetite • Dehydration • Depressed mood • Acne • Dizziness • Skin rash • Dry mouth • Shortness of breath • Decrease in heart function • Fluid retention

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. It is unknown if lorlatinib could be hazardous to an unborn child. Patients and their sexual partners should avoid sex and / or use two effective method(s) of contraception that is medically appropriate based on your personal doctor's recommendation at that time and should be used for as long as you participate in this study. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of Treatment with Lorlatinib
Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

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.

Unknown Risks
The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

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, young people and adults with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No neuroblastoma 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:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- 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) or Health Canada, involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

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.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with lorlatinib is being done solely as part of research and will be paid for by the study.

The special research blood and tissue studies will be done at no cost to you. 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 treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not 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 website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

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 you 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/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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

CONSENT FOR EXTRA STUDIES FOR RESEARCH

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

1. <u>Using extra blood to look for genetic changes seen in tumor cells</u>

Initial next to YES if you agree to let researchers take 2 extra teaspoons (10mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on this study. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

_____Yes _____No

2. **<u>Comparing genetic changes between tumor leftover from an earlier procedure (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.</u>**

Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

Initial next to NO if you do not want left over tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

_____Yes _____No

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.

_____
Print Patient Name

_____ _____/_____/_____
Signature of Patient Date

_____ _____/_____/_____
Signature of Physician or Responsible Investigator Date

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests that will be done on this study.

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine blood tests (Blood counts, electrolytes, liver, kidney function)	X	Weekly for other tests and twice weekly for blood counts	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle and weekly for blood counts	X
Blood tests for cholesterol, triglycerides and function of the pancreas (amylase/lipase)	X	Weekly	Start of cycle	Start of each cycle	X
Pregnancy test (All females 10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4,6,8,10,12 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to one week after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6 and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				
	Tests done at Disease Evaluation				
Bone marrow aspirate and biopsy CT/MRI scans and/or MIBG/PET scans Blood and bone marrow for NANT Biology study[#]	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information.

Consent Addendum 2

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX IX: SAMPLE ASSENT FORM

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohorts A1 and B1: Taking Lorlatinib only

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. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using a medicine called **lorlatinib** to see what effects (both good and bad) this medicine has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. The doctors think that giving this drug may help get rid of neuroblastoma cancer cells.

3. If you agree to be in this study this is what will happen:

You will take lorlatinib by mouth every day followed by a small glass of water. Lorlatinib is given in cycles that last about one month (28 days). You can continue taking lorlatinib for as many cycles as you can unless there are side effects or your tumor gets worse. Lorlatinib works differently than some of the other medicines you have gotten before to treat your neuroblastoma. Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing.

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). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
- A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- 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.
    - The doctors will have you answer questions about how you are doing using an iPAD. This should take about 30 minutes to do. At the same time you are using your iPAD, your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of this testing needs to be done more often.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

4. **When you are in a research study, sometimes good things and bad things can happen.** 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 lightheaded, jittery, irritable or hungry while you are fasting before certain tests
    - You may have swelling in your arms and legs
    - You may have tingling, or prickly feeling or numbness in your hands and feet
    - You may have a hard time concentrating, remembering things or talking to others.
    - You may have ringing in your ears
    - You may feel tired
    - You may feel sick to your stomach and you may throw up
    - You may not feel like eating
    - 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 you could die from the treatment or cancer.

Not all of these things may happen to you. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.

- Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:
    - 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

5. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

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" <u>you</u> 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 <u>you</u>.

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 you see me.

- Study doctor's phone number: _____

9. Special Study Tests:

You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over the first 2 days of treatment. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: 2 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. This would be done when you start the study and then everytime after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

- _____ YES, you can draw the extra blood
- _____ NO, I don't want to have the extra blood drawn

#2: The doctors will compare old and new tumor samples collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

- _____ YES, you can use my tumor samples to look at the ALK gene
- _____ NO, I don't want my tumor samples used to look at the ALK gene

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 Patient: _____

_____ Yes, I want to be in the study.

_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

APPENDIX X: SAMPLE ASSENT FORM

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohort B2: Taking Lorlatinib combined with chemotherapy (cyclophosphamide/topotecan)

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. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using three experimental medicines called **lorlatinib, cyclophosphamide and topotecan** and to see what effects (both good and bad) these medicines has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. Cyclophosphamide and topotecan are medicines that are given into the bloodstream either through your central line or a small tube placed in a vein in your hand or arm. The doctors think that giving these three drugs together may help get rid of neuroblastoma cancer cells.

3. **If you agree to be in this study this is what will happen:**

   The medicines will be given in cycles that each last about one month (28 days). Your doctor will explain the schedule for each cycle to you and your parents. You can continue to get this treatment for up to 24 courses (about 2 years) unless you have bad side effects or your tumor gets worse. These medicines work differently than some of the other medicines you have gotten before to treat your neuroblastoma.

   Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing when used together the chemotherapy medinces cyclophosphamide and topotecan.

   Lorlatinib:
   You will take lorlatinib by mouth every day followed by a small glass of water.

   Cyclophosphamide and topotecan:
   You will take cyclophosphamide and topotecan by I.V. once a day for the first 5 days of every cycle. You will be in the clinic on those days. You do not need to be in the hospital to get these chemotherapy medicines.

Other medicines (not chemotherapy):
You will need to take Neupogen (given once a day as an injection) or Neulasta (given once each cycle as an injection). These medicines are given to help your normal blood cells get better after getting chemotherapy medicines like cyclophosphamide and topotecan.

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). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
- A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- 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.
    - The doctors will have you answer questions about how you are doing using an iPAD. This should take about 30 minutes to do. At the same time you are using your iPAD, your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of this testing needs to be done more often.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

4. **When you are in a research study, sometimes good things and bad things can happen.**
Sometimes things happened to children in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:
    - You may feel lightheaded, jittery, irritable or hungry while you are fasting before certain tests
    - You may have swelling in your arms and legs
    - You may have tingling, or prickly feeling or numbness in your hands and feet
    - You may have a hard time concentrating, remembering things or talking to others.
    - You may have ringing in your ears
    - You may feel tired
    - You may feel sick to your stomach and you may throw up
    - You may not feel like eating
    - 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.

- You may get sores in your mouth that makes it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
- You may get diarrhea.
- 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. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.

Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:

- 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

5. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

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" <u>you</u> 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 <u>you</u>.

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 you see me.

    - Study doctor's phone number: _____

9. <u>Special Study Tests:</u>

You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over the first 2 days of treatment. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: 2 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. This would be done when you start the study and then everytime after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

- _____ YES, you can draw the extra blood
- _____ NO, I don't want to have the extra blood drawn

#2: The doctors will compare old and new tumor samples collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

- _____ YES, you can use my tumor samples to look at the ALK gene
- _____ NO, I don't want my tumor samples used to look at the ALK gene

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 Patient: _____

_____ Yes, I want to be in the study.

_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or **Date**
RESPONSIBLE INVESTIGATOR