

SAMPLE INFORMED CONSENT

A PHASE I STUDY OF ZOLEDRONIC ACID (ZOMETA) WITH CYCLOPHOSPHAMIDE IN CHILDREN WITH RECURRENT OR REFRACTORY NEUROBLASTOMA AND CORTICAL BONE INVOLVEMENT OF TUMOR

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 using human patients). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

You are being asked to participate in this study because you have been diagnosed with neuroblastoma, a type of cancer that usually affects children. Your neuroblastoma is present in your bone(s) after either growing back (relapsed) or never going away (persistent tumor) after having gotten standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest dose of monthly intravenous Zometa that can be given with daily low doses of cyclophosphamide by mouth without causing severe side effects.
- To find out the side effects seen by giving Zometa and cyclophosphamide on this schedule at different dose levels.
- To measure blood and urine levels of Zometa during treatment
- To determine if your tumor gets smaller after treatment with Zometa and cyclophosphamide.
- To measure the effects of Zometa on markers of bone breakdown found in urine, blood, and bone marrow
- To measure the effects of Zometa on the immune system.

The research is being done because:

Currently there is no known effective treatment for your type of cancer. Therefore new ways of treating your tumor are being tried in the hope that it will shrink your tumor or prevent it from coming back. One potential new way to treat tumors is to change the normal cells around the tumor, making it more difficult for tumors to survive. Zometa is a drug that works against a type of cell in the bone called osteoclasts. Osteoclasts are important for neuroblastoma tumor cells to spread to the bone and form painful tumors there.

When the investigators used Zometa with cyclophosphamide in laboratory experiments to treat neuroblastoma in animals, they found that the combination slowed the growth of tumors in bones and other places as well. Therefore investigators have put the two
N2004-01 Sample Consent Ver 10-18-04

drugs, Zometa and cyclophosphamide, together for this study. Zometa has been used before in adults but this is the first time it will be used in a clinical trial in children. Cyclophosphamide is a standard chemotherapy drug that is used to treat neuroblastoma. This clinical trial will help find the highest Zometa dose that can be safely given together with cyclophosphamide to patients with resistant neuroblastoma that have bone disease.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 12 and 24 people will take part in this study.

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

Before you begin the study, you will need to have the following exams, tests or procedures done to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

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

[#]Bone marrow tests are done to check the response of your tumor to the treatment by inserting a needle into the hip bone to remove the marrow which is inside the bone. Sedation and pain medicine will be provided during this test.

^{*} Various scans are done for checking the response of your tumor to the treatment. These may include CT and /or MRI scans and MIBG scans or bone scans and plain x-rays. Your study doctor will recommend scans or x-rays specific for your case and will answer your questions`.

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

Physical exam	Bone marrow tests (see above #)
Blood tests	Various scans (see above *)
Urine tests	

Because you are in this study, physical exams, blood and urine tests, bone marrow tests and various scans that are part of your regular cancer care will be done more often.

- During first month of treatment: Physical exams, blood and urine tests will be done at least once a week.
- After the first month of treatment: Physical exams and blood tests will be done at least once a month. Bone marrow tests and various scans will be done before the second and fourth month, then at least every 3 months.

You will be asked if you want to participate in research tests that are being done to see how the study is affecting your body. **This part of the study is voluntary.** You can decide not to let the doctors do these tests and still be able to be treated with Zometa and cyclophosphamide as part of this clinical study. The test results do not affect your treatment with Zometa and cyclophosphamide and will not be told to your doctor or become part of your medical record. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these voluntary studies.

- **Determining Levels of Zometa in Blood and Urine (called Pharmacokinetics)** Part of the research goal for this study is to look at the level of Zometa in the blood and urine. These tests will be done with the first dose of Zometa during the first three days of treatment. Two ml of blood (about ½ of a teaspoon) will be withdrawn 6 times (total of 12 ml or 1 tablespoon) before during and after the infusion. The last blood sample will be taken 24 hours after the Zometa started. If you agree to these tests, you will need a second IV for the blood draws. Urine will be collected over the entire 2 days after the Zometa is given. You will be given containers for collecting urine and these containers will be returned to your doctor. You may agree to allow us to collect samples of your blood and urine or just samples of your blood. Novartis, the company that makes Zometa, will be performing these tests for the researchers. They will keep the results of the tests together with information on similar tests performed in other patients who received Zometa. The information that Novartis receives will not have your name or other information on it that could identify you.

- **Determining Osteoclast Activity in Blood and Urine**
How well the bone cells called osteoclasts are working can be measured by tests on the blood and urine. Extra blood and urine will be taken 3 times; before the first, second and fourth dose of Zometa is given. Since Zometa is given once a month, it will take 3 months to finish this test. Three mls (one half teaspoon) of blood will be drawn each time for a total of 9 ml (less than two teaspoons). You will be asked to collect urine for these tests as well. You will be asked to save the urine from the second time you go to the bathroom that day. If your child is not potty trained, you will be asked to throw away the diaper your child was sleeping in, and place a baggie for urine collection. This will be done at the same times we would ask to collect your blood. You can be told the results of these tests.

- **Determining Growth Factors from the Bone**
Chemicals released by the bone that may help the tumor to grow can be measured by tests on the blood and bone marrow. Extra blood and bone marrow would be taken 3 times; before the first, second and fourth dose of Zometa is given. Five mL of blood (1 teaspoon) will be drawn each time for a total of 3 teaspoons or 15ml. If your doctor is planning to do a bone marrow test to look for tumor before your first dose of Zometa, we would like to take an extra 5 mls of bone marrow for these tests as well and from the bone marrows performed before the 2nd and 4th doses. We will not do an extra bone marrow just to do these tests.

- **Determining Zometa's Effects on the Immune System**
In adults, Zometa has caused a change in some parts of the immune system that may make it better at fighting tumor cells. We would like to measure changes in the immune system as you take Zometa. This can be done by tests on your blood. Extra 5 to 10 mls (one to two teaspoons) of blood will be taken 4 times; before starting treatment, 4 days after starting treatment, one month after starting treatment and 3 months after starting treatment. The amount of blood to be taken will depend on your size and other blood being drawn that day.

The chart at the end of this form tells you when all tests (regular and voluntary research tests) need to be done.

Treatment Plan:

You will take two drugs: Zometa and cyclophosphamide.

Cyclophosphamide will be taken by mouth once a day, every day. Everyone on this study will get the same dose of cyclophosphamide. It will either be a liquid or a pill,

depending on your weight and if you can take pills. It is important to take this drug in the morning and to try to drink fluids all day long.

Zometa is given by IV once a month over 15 minutes. When you enroll on this study, you will be assigned to get a certain dose of Zometa. Each dose will be given to a group of 3-6 patients. The first group of patients will get the lowest dose of Zometa, which is about 20% lower than what is currently being given to adult patients without bad side effects. The dose of Zometa will be increased (“dose escalation”) in each of the following groups of 3-6 patients until side effects are seen. If you receive Zometa for more than one dose, your dose will not increase. We will tell you what dose you will receive and answer your questions about “dose escalation”.

The following administration schedule for Zometa (**Z**) and cyclophosphamide (**C**) will be used:

Week	1	1	2	3	4	
Day	1	2-7	8-14	15-21	22-28	Start next course
	Z					
	C	CCCCC	CCCCCCC	CCCCCCC	CCCCCCC	

You will also be asked to take calcium and Vitamin D to reduce the chances that you will have some side effects because of the Zometa. All patients will take at least one dose of these medicines each day, some patients may need to take more. These medicines should not be taken with the cyclophosphamide, it is better to wait 3 or more hours after the cyclophosphamide before taking calcium and Vitamin D.

HOW LONG WILL I BE ON THIS STUDY?

You can continue to get Zometa every 28 days and cyclophosphamide every day as long as your neuroblastoma responds to the treatment or you do not have bad side effects from taking either drug. After you stop treatment with Zometa and cyclophosphamide, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Evaluations for this study will continue unless your tumor gets worse or you start treatment on another study. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive, whether you have developed any side effects from the treatment or any additional cancer. This information may be gotten from your oncologist or family doctor at regular intervals.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing might be most helpful to you.

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

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

This is a phase I study. A phase I study looks at how common and serious side effects can be for each patient at each specific dose of drug. In this study researchers will be looking at side effects seen in patients taking different doses of Zometa given together with cyclophosphamide. 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. Your health care team may give you medicines to help lessen the side effects. Many side effects go away soon after you stop taking Zometa and cyclophosphamide. In some cases side effects can be serious, long lasting or may never go away. There is also a risk of death. 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 from taking the study drugs Zometa and cyclophosphamide.

Side effects of Zometa:

Side effects seen *occasionally* with Zometa

- Fever
- Flu-like symptoms
- Effects on how well the kidneys work. This problem is usually seen after several doses of the drug.

Side effects seen *rarely* with Zometa

- Shaking
- Nausea
- Low body levels of magnesium, potassium, calcium or phosphorus
- Damage to bone called osteonecrosis. This problem may be more likely after dental work and/or giving chemotherapy along with Zometa or other drugs like it.

Side effects of cyclophosphamide

Side effects seen *frequently* with cyclophosphamide

- Poor appetite, nausea or vomiting
- Low blood counts including need for transfusion, bleeding, and higher risk of infections
- Hair loss
- Difficulties getting pregnant or fathering a child, early menopause

Side effects seen *occasionally* with cyclophosphamide

- Metallic taste in mouth
- Bleeding from the urinary bladder
- Syndrome of inappropriate ADH secretion. This problem would make it difficult to keep fluids and salts balanced correctly in the body

Side effects seen *rarely* with cyclophosphamide

- Blurred vision
- Irregular heart beats or damage to the heart muscle
- Stiffening (fibrosis) of the lungs
- Stiffening (fibrosis) of the urinary bladder
- Secondary cancers, different from the kind of cancer you have now

Side effects of oral calcium

Side effects seen occasionally with oral calcium

- Constipation

Side effects seen rarely with oral calcium

- Abnormal heart beats
- Dry mouth
- Headache
- Stomach upset including nausea, vomiting, heartburn
- Changes in levels of calcium and phosphorus in the blood stream
- Irritability

Side effects of oral vitamin D

Side effects seen occasionally with oral calcium

- Constipation
- Dry mouth

Side effects seen rarely with oral vitamin D

- Headache
- Stomach upset including nausea, vomiting, heartburn
- Changes in levels of calcium and phosphorus in the blood stream, sometimes forming small deposits of calcium in the blood vessels or kidneys
- Irritability, sleepiness, or psychosis
- Bone pain
- Muscle aches or weakness
- Itching
- Loss of appetite
- Increases in blood pressure
- Increases in cholesterol levels
- Abnormal liver labs
- Fever
- Decreased sexual drive
- Increased thirst and urination
- Sensitivity to light

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

Risks from taking blood or bone marrow samples: The risks from having your blood taken are minimal but can result in a infection or a blood clot (infections). Experienced doctors or nurses will perform these blood draws to minimize this risk. Bone marrow tests also can lead to infection, and they often require you to get sedation (sleep) medicines. Bone marrow tests may cause pain during the procedure or bleeding at the site on your hip where the test was done. These have risks that will be discussed with you. You will sign a separate consent for any procedure that needs sedation.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about using Zometa and cyclophosphamide together as a treatment for cancer. This information could help future cancer patients.

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

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

- Treatment with the same medicines but not on study
- Treatment with chemotherapy medicines.
- Treatment with other experimental agents that may be available.
- No therapy at this time with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

You may read your record. 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 will 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 such groups as:

- New Approaches To Neuroblastoma Therapy (NANT) Consortium at Childrens Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you (your child) by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The Federal Government – National Cancer Institute (NCI) and the Food and Drug Administration (FDA) that are involved in keeping research safe for people may look at records of patients participating in this study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Both Zometa and cyclophosphamide are commercially available so you and/or your insurance company will need to pay for the medicine needed to complete the study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The tests for Zometa pharmacokinetics in blood and urine, bone growth factor tests of blood and bone marrow and blood tests of the immune system function will be done at no cost to you if you agree to participate in these voluntary tests. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw the blood, urine or bone marrow samples from you.

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, parking, and baby sitter fees.

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 due to injury while being on the study.

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

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

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

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

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

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

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review 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/>

1. For NCI's clinical trials information, go to <http://cancer.gov/clinicaltrials/>
2. For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

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

CONSENT FOR EXTRA STUDIES FOR RESEARCH

We are asking to collect extra blood, urine and bone marrow to perform 4 different kinds of research tests during this study.

#1: Blood Levels and Urine Levels of Zometa (Pharmacokinetics)

In this test researchers would like to take 6 extra blood samples (total of about 1 tablespoon) over the first two days of treatment. If you agree to this test, you will most likely need to have an extra IV placed to draw this blood. Your doctor can tell you if this is the case.

Researchers would also ask you to collect your urine in containers beginning right before the zometa infusion is given continuing for 2 entire days afterwards.

Researchers would like to have either blood and urine samples together from the same patient or blood samples only. They do not want urine samples without blood samples for this test.

Novartis, the company that makes Zometa, will do these tests. They will not be given any information that can identify who you are.

The results of these tests will be confidential and not made available to you or your treating physician.

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood and urine collected for blood and urine levels of Zometa

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

_____ **NO**, I do not agree to have blood and urine collected for blood and urine levels of Zometa

Signature: _____ **Date:** _____

#2 Blood and Urine for Measures of Normal Bone Cell (Osteoclasts) Activity

Researchers would like to take 3 extra blood (total 9ml) and urine samples 3 times during treatment; before treatment starts, after one month and the final set of samples after 3 months of treatment.

These tests are commercially available to you or your treating physician. The results can be given to you but they will not change the treatment plan.

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood and urine collected for normal bone cell activity

_____ **NO**, I do not agree to have blood and urine collected for normal bone cell activity

Signature: _____ **Date:** _____

#3 Blood and Bone Marrow for Measuring Growth Factors from the Bone

Researchers would like to take 3 extra blood and bone marrow samples (total 1 tablespoon of each) 3 times during treatment; before treatment starts, after one month and the final set of samples after 3 months of treatment.

You would not have any extra bone marrow tests done to collect these samples. You may also agree to just having the blood collected and not the bone marrow.

The results of these tests will be confidential and would not be made available to you or your doctor.

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood and bone marrow collected for measuring bone growth factors

_____ **YES**, I agree to only have blood collected for measuring bone growth factors

_____ **NO**, I do not agree to have blood and bone marrow collected for measuring bone growth factors

Signature: _____ **Date:** _____

#4 Blood for Measuring Effects of Zometa on the Immune System

Researchers would like to take 4 extra blood samples to do this test. The amount of blood taken for each sample would be between 5-10ml each. The samples would be collected before starting treatment, 4 days after starting treatment, one month after starting treatment and 3 months after starting treatment.

The results of these tests will be confidential and would not be made available to you or your doctor.

Mark the correct box and sign your name and the date

_____ **YES**, I agree to have blood collected for measuring immune system effects

_____ **NO**, I do not agree to have blood collected for measuring immune system effects

Signature: _____ **Date:** _____

STATEMENT OF CONSENT

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

Patient Name

Signature of Parent or Guardian

____/____/____
Date

Signature of Parent or Guardian

____/____/____
Date

Signature of Patient (If > 7 years old)

____/____/____
Date

Signature of Physician or
Responsible Investigator

____/____/____
Date

Signature of Witness

____/____/____
Date

Signature of Translator
(If applicable)

____/____/____
Date

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

STUDY	Before Study	During Treatment Course 1	Before Treatment Course	Next	During all other treatment courses	Finish Treatment
Physical Exam	X	X	X			X
Blood tests	X	Weekly	X		Every other week	X
Pregnancy test	X					
Urine test	X	Weekly	X			X
Tumor imaging (CT/MRI & MIBG scan)	X		After course 1, 3, and every 3 courses			X
Bone imaging (Bone scan and x-rays)	X		After course 1, 3, and every 3 courses			X
Bilateral bone marrow aspirate/biopsy	X		After course 1, 3, and every 3 courses			X
Urine test (VMA/HVA)	X		After course 1, 3, and every 3 courses			X

The tests below this line would only be done if you gave permission for them to be done

Zometa levels Blood and Urine Samples		Days 1, 2, 3				
Measurement of normal bone cell (Osteoclast) Activity Blood and Urine samples		X	After course 1 and 3			
Measurement of growth factors Blood and Bone Marrow samples	X		After course 1 and 3			
Measures of effects of Zometa on the immune system Blood samples		Day 4	After course 1 and 3			