INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

Pilot Study of Cabozantinib for Recurrent or Progressive Central Nervous System Tumors in Children

You/your child are invited to participate in a research study of the use of Cabozantinb for treatment of children with a central nervous system tumor. If you are the parent or guardian of a child under 18 years old, you will be asked to read and sign this document to give permission for your child to participate. Your child may also be asked to sign an assent form agreeing to participate in the study. You/your child were selected as a possible subject because you/your child have a refractory or recurrent central nervous system tumor**.** Please read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted by Dr. Scott Coven, Department of Pediatrics – Hematology/Oncology. It is funded by Indiana University; the drug Cabozantinib is provided by the manufacturer, Exelixis.

STUDY PURPOSE

The purpose of this study is to find out if the drug, Cabozantinib, is safe and tolerable in pediatric patients with refractory and/or recurrent central nervous system tumors who have previously received prior treatment. We are also looking to see if the drug has an effect on the rate at which the tumor grows at 6 months.

NUMBER OF PEOPLE TAKING PART IN THE STUDY

If you agree to participate, you will be one of 11 subjects who will be participating in this research. Participation in the study can last for up to one year.

PROCEDURES FOR THE STUDY

If you agree to be in the study, you will do the following things:

Before starting the study…
Prior to enrolling on this clinical trial, your study doctor will make sure you are eligible to receive this treatment. The following tests will be done:

- Urine Pregnancy Test for females of child-bearing potential (this test must be negative, not pregnant) If your child is 14 and older, pregnancy results will be provided to your child only. If your child is 13 or younger and has a positive pregnancy test, you and your child will be informed of the results, as well as applicable state agencies.
- Physical Exam and Medical History
- Laboratory tests including blood tests and urine tests to monitor your health during treatment
- MRI (Magnetic Resonance Imaging) scan - These are scans that will be performed to evaluate the tumor prior to starting your treatment
- ECG – to monitor the electrical activity of your heart

If these tests show that you are eligible to participate in the clinical trial, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this clinical trial.

During Study Treatment:

The start of receiving Cabozantinib will be within 14 days of study enrollment. Cabozantinib should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each Cabozantinib dose).

Cabozantinib should NOT be re-taken if vomiting occurs after taking a scheduled dose. Dosing may continue the next day as scheduled. You will take Cabozantinib once a day.

While participating in this trial, you will be followed at this center to monitor the safety of this treatment and to evaluate if the tumor is responding well. Once the treatment begins, you will have follow-up visits as outlined below:

Study Schedule:

STUDIES TO BE OBTAINED	Pre-Study[1]	Cycle 1	Cycle 2, 3	Cycle 4-12	Completion of Study
History	X	Day 28	Days 15, 28	Day 28	X
Physical exam with vital signs and pulse ox	X	Days 15 and 28	Days 15, 28	Day 28	X
Height, weight, BSA	X	Day 28	Days 15, 28	Day 28	X
Blood pressure[2]	X	Days 15 and 28	Days 15, 28	Day 28	X
Performance Status	X	Day 28	Days 15, 28	Day 28	X
Subject Diaries (Study drug and steroid use)	X	Day 15 & 28	Day 15 & 28)	Day 28	X
CBC, differential, platelets	X	Days 15 and 28	Days 15, 28	Day 28	X
CMP[3] with Ca, Mg, Phos, lipase, amylase	X	Days 15 and 28	Days 15, 28	Day 28	X
PT, PTT, INR	X	Day 28	Day 28	Day 28	X
Urinalysis	X	Day 28	Day 28	Day 28	X
Urine protein/creatinine	X	Day 28	Day 28	Day 28	X
Pregnancy test[4]	X[5]		Day 28 Cycle 2	Day 28 Cycles 4, 6, 8, 10, 12	X
Thyroid stimulating hormone	X	Day 28	Day 28 Cycle 3	Day 28 Cycles 6, 9, 12	X
12- lead ECG[5]	X	Day 28	Day 28 Cycle 3	Day 28 Cycles 6	
MRI of brain +/- spinal cord if clinically indicated[6]	X		Day 28 Cycle 3	Day 28 Cycles 6 and 9	X

1. All studies to determine eligibility must be performed within 2 weeks prior to enrollment. Consent must be obtained prior to enrollment but does not expire at 2 weeks.
2. Baseline BP should be obtained by collecting 3 serial BP measurements at least 5 minutes apart and then averaging the second and third BP measurements.
3. CMP should include: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase
4. For females of childbearing age
5. If the subject starts a medication with substantial evidence that the drug prolongs the QT interval, then ECG monitoring must performed at the end of each cycle while on the medication
6. For subjects with Complete or Partial response confirmatory MRI per RANO criteria will be performed within 6 weeks

MRI Scans will be performed to evaluate how well your tumor is responding to this treatment. Thesescans will be performed during treatment and prior to cycle 4, Cycle 7, prior to cycle 10 and after cycle 12. If you remain on study beyond 12 cycles of treatment, you will have an MRI scan done to evaluate your disease every 6 cycles, annually thereafter, and/or one final scan done when you stop participating in this study.

Additional exams, blood draws, etc. may be required if clinically indicated for standard of care.

WHAT RISKS OR DISCOMFORTS ARE INVOLVED?

You may have side effects while on the study. 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 study doctor may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the Cabozantinib. In some cases, side effects can be serious, long-lasting, or may never go away. There also is a risk of death. We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to Cabozantinib include those which are:

Very Common

- Abdominal pain
- Alteration of thyroid function tests
- Blisters, rash, or pain in hands or feet
- Changes in blood tests used to monitor the liver, which may indicate liver damage
- Change in voice
- Changes to the way things taste
- Constipation
- Diarrhea[#]
- Fatigue
- Hair color changes or hair loss
- High blood pressure
- Inflammation of mucus membranes
- Loss of appetite
- Mouth and/or throat sores or swelling
- Nausea
- Rash
- Vomiting
- Weakness
- Weight loss

Cabozantinib can cause diarrhea or other digestive problems. Not all subjects will have bad diarrhea or other digestive problems. Using the supportive care drug loperamide (also known as Imodium) may help prevent diarrhea. Loperamide should be used at the first sign of diarrhea.

Common

- Abnormal thickening of the outer layer of the skin
- Change in the feeling of touch
- Cough
- Bleeding, including bleeding from stomach or intestines which may look like coffee grounds or black sticky bowel movements and bleeding within the brain
- Blood clot in a large vein, usually in the leg
- Blood clot that travels from a vein to the lung
- Confusion and disorientation
- Decreased amounts of red blood cells (anemia), which may cause feelings of tiredness or shortness of breath
- Decreased amounts of calcium or sodium in the blood

- Decreased or increased amounts of potassium in the blood
- Decreased amounts of magnesium or phosphorus in the blood
- Decreased level of albumin in the blood
- Decreased platelet counts, which increases the risk of bleeding or makes bleeding more difficult to stop
- Decreased white blood cell counts, which may increase chances of infection
- Dermatitis acneiform, a type of acne
- Dehydration
- Difficulty swallowing
- Dizziness
- Dry mouth
- Dry skin
- Fever
- Fungal infections including mouth, lung, and other locations
- Hemorrhoids and bleeding hemorrhoids
- Headache
- Increased amounts of pancreas enzymes in the blood, which may indicate damage to the pancreas
- Increased levels of bilirubin in the blood, which may indicate complications with the liver
- Increased levels of creatinine in the blood, which may indicate complications with the kidneys
- Mouth or throat pain
- Muscle spasm
- Muscle weakness
- Pain in a joint or muscle
- Pain in extremities
- Protein in the urine, which may indicate kidney damage
- Shortness of breath
- Stomach acid coming up from the stomach into the esophagus
- Swelling of the limb(s)
- Ulcer
- Upset stomach or indigestion

Uncommon:

- Abnormal electrical activity in the heart that could cause a potentially serious change in heart rhythm
- Abnormal opening between two organs or from an organ to the outside of the body
- Abscesses (infected cavities filled with pus)
- Blood clot in an artery
- Chest discomfort originating from the heart
- Clouding of the lens in the eye that affects vision
- Damage to skeletal muscle tissue
- Decreased brain function or decreased alertness and ability to think
- Decrease in all blood counts (red blood cells, white blood cells and platelets)
- Destruction of bone tissue, in particular, bone in the jaw
- Feelings of unease or fear
- Gallstones
- Heart attack
- Heart failure

- Holes in the stomach or intestines
- Infections
- Inflammation of the intestine, appendix, gall bladder or thin tissue lining the inner wall of the abdomen and most of the abdominal organs
- Reduced kidney function
- Loss of consciousness, fainting episode
- Pneumonia and inflammation of the lungs
- Rapid heart rhythm
- Re-opening of wounds after surgery
- Respiratory failure
- Seizure
- Stroke / mini-stroke
- Tear or inflammation in skin that lines the anus
- Uncoordinated movements

Rare but Medically important

- Air in the chest between lungs and chest wall
- Allergic reaction
- Anemia caused by destruction of red blood cells
- Blocked intestines
- Brain dysfunction caused by brain swelling
- Cancer of the mouth or skin
- Damage to the outermost surface of the eye
- Inflammation and blockage of channels that carry bile from the liver
- Severe swelling of the mouth, lips, tongue, eyes and throat, or difficulty swallowing or breathing
- Temporary paralysis of the intestines
- Throat swelling
- Very high blood pressure that comes on suddenly and quickly and which can lead to serious injury to the heart and brain

If you have a drop in the red blood cell count, the cells that carry oxygen around the body, you may feel tired. If your red blood cell count drops very low, you may need a blood transfusion.

If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the bloodstream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Cabozantinib may have an effect on the growth plates of bones of children who are still growing. In a study, a small number of children who received cabozantinib developed growth plate thickening. However, all children with this thickening still experienced bone growth; it is unclear if treatment with cabozantinib has an effect on bone length.

Reproductive risks:

Because the drug in this study can possibly cause abnormalities in an unborn baby and infants, you should not become pregnant or father a baby or breastfeed while you are on this study. Also, because Cabozantinib remains in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 6 months after your last dose of Cabozantinib, although the optimal or the maximal time required for drug clearance cannot be precisely predicted. Let your doctor know immediately if you become

pregnant or find out that you are going to be the father of a child. We can provide counseling about preventing pregnancy for either male or female study participants. In addition, the effect of the study drug on the ability to have children in the future is uncertain. The study drug may make it more difficult or impossible to have children in the future.

MRI Risks:
This may cause some discomfort if you are uncomfortable in tight spaces. During this procedure, it is necessary for you to lie still for long periods of time. There are some loud noises you will hear from the machine, and ear plugs are available for you to use while in the MRI machine. Although this procedure may be uncomfortable, this is not painful.

Risks of blood drawing or placing an intravenous catheter for blood drawing:
Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

There is a possible risk of loss of confidentiality, but standard measures are in place to protect your medical and research information.

For more information about risks and side effects, ask your study doctor.

BENEFITS OF TAKING PART IN THE STUDY

You may not directly benefit from participation in this study, however, a possible benefit may be that the tumor stops growing or becomes smaller. It is hoped that the information gained from this study will benefit future subjects with central nervous system tumors.

ALTERNATIVES TO TAKING PART IN THE STUDY

Instead of being in the study, alternative strategies will be offered at the discretion of your primary oncology team.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your identity will be held in confidence in reports in which the study may be published

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, Indiana Clinical Research Center (ICRC), IU Clinical Trials Data Safety Monitoring Committee and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA), the National Cancer Institute (NCI) etc., who may need to access your medical and/or research records.

A description of this clinical trial will be available on **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.

COSTS

Taking part in this study may lead to added costs to you or your insurance company. You or your insurance

company will be responsible for the following costs

- MRIs
- Laboratory testing
- ECG
- Physical Exams

You will not be responsible for these study-specific costs:

- The drug: Cabozantinib

PAYMENT

You will not receive payment for taking part in this study.

WILL MY INFORMATION BE USED FOR RESEARCH IN THE FUTURE?

Information or specimens for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent. Specimens will not be used for whole genome sequencing.

COMPENSATION FOR INJURY

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact the researcher, Dr. Scott Coven at 317-944-2143 during normal business hours. If you cannot reach the researcher during regular business hours (i.e., 8 a.m. to 5 p.m.), please call the IU Human Subjects Office at 317-278-3458 or 800-696-2949. After business hours, please call the Pediatric Hematologist/Oncologist on call at (317) 944-5000.

In the event of an emergency, you may contact the Pediatric Hematologist/Oncologist on call at (317)944-5000.

If you are unable to reach the investigator at the above number, in an emergency you may contact the Indiana University Hospital Pharmacy at 317-944-0362.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or offer input, contact the IU Human Subjects Office at 317-278-3458 or 800-696-2949.

VOLUNTARY NATURE OF THIS STUDY

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with Dr. Scott Coven or any other Pediatric Hematologist/Oncologist at IU Health.

Your participation may be terminated by the investigator without regard to your consent in the following circumstances:

A. If you fail to follow the investigator's instructions including not completing the procedures required by the studyand/or are unable or unwilling to come for the required doctor visits including any required follow-up visits
B. If you experience a serious and unexpected side effect that may require evaluation.
C. If your disease gets worse while on this treatment.
D. If your tumor is not responding to Cabozantinib
E. If you experience side effects that are considered to outweigh benefits of your participation.
F. If the investigator feels it is in the best interest of your health and welfare.
G. If the sponsor no longer provides the drug.
H. If you begin another treatment for your central nervous system tumor.

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent to participate in this research study.

I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Subject's Printed Name:_____

Subject's Signature:_____ **Date**:_____
(must be dated by the subject)

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____ **Date**:_____

Printed Name of Parent:_____

Signature of Parent:_____ **Date**:_____

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____ **Date:**_____