Dose Finding

A Phase I Open Label Safety Study to Evaluate the Pharmacokinetic Profile and Tolerance of Mibefradil Dose Finding in Subjects with Recurrent High-Grade Glioma Undergoing Standard, Repeated Temozolomide Treatment

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

You are being asked to take part in this study because you have a brain tumor that has grown or has recurred.

WHY IS THIS STUDY BEING DONE?

This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. For this reason, we are trying to find new drugs to improve treatment for this tumor. The study you are being asked to join uses a drug called mibefradil. Mibefradil is a type of drug known as a calcium channel blocker. Mibefradil has previously been used to treat patients with high blood pressure. It was later found that mibefradil's action on a particular type of calcium channel causes cancer cells to line up in a way that may increase the effect of temozolomide (TMZ), a drug that is used for the treatment of glioma. Mibefradil is considered experimental because it has not been approved by the U. S. Food and Drug Administration (FDA) for treatment of brain tumors.

This is a dose-finding study. This means that we want to find the best dose of mibefradil to give prior to treatment with TMZ. TMZ is an FDA-approved chemotherapy for high-grade gliomas and is considered part of "standard of care" therapy for this disease. We will test the best dose of mibefradil to give for 7 days prior to taking TMZ for 5 out of every 28 days.

You will be assigned a dose of mibefradil when you enter the study. You will be told what your dose is and it will not be increased. You will be given the same or a lower dose throughout your treatment. You will be given a lower dose if you experience side effects that require reduced dosing. We will also be looking at the side effects of mibefradil and temozolomide.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A minimum of 6 and a maximum of 48 people will take part in the study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study you will have the following tests and procedures:

Before treatment starts, you will have a complete physical exam and blood tests. Your physical examination will include a medical history and measurement of your height, weight, blood pressure, temperature, respiratory rate, heart rate, and performance status, which measures the degree of your ability to complete daily activities (e.g., dressing and eating). You will have a complete neurological exam to test your ability to think, your muscle strength, balance, and other functions of the brain. An ECG (electrocardiogram or measurement of the electrical activity of the heart) will also be done. To measure the extent of your brain cancer, you will have an

MRI (magnetic resonance imaging) scan of the brain, which is a method of obtaining pictures of internal soft bodily tissue through the use of powerful magnets and radio waves.

As part of your screening tests, about 3 tablespoons of blood will be drawn from one of your veins to conduct laboratory tests (e.g., standard blood count including a count of your platelets, and blood chemistries). You will also be asked to have a pregnancy test if you are a woman that is able to have children. If you are pregnant you will not be permitted to participate in this study.

Treatment cycles are 28 days (4 weeks).

Before treatment starts or on Day 1 of the first cycle, prior to your first dose of mibefradil, you will be fitted with a portable electrocardiogram (ECG) device which will continuously monitor the electrical activity of your heart and your heart rate while you are taking mibefradil. You will be instructed how to use it and must follow these instructions exactly. You must wear the monitor continuously during the days you are taking mibefradil, even while you are sleeping (Days 1-8). (The monitor can be removed for bathing.)

You will also receive a home blood pressure monitoring device and be instructed how to take and record your blood pressure and pulse while you are taking mibefradil; you will have to check and record your blood pressure/pulse at least one time per day during Days 1-8 in the first cycle.

In Cycle 1 you will take mibefradil by mouth over eight consecutive days (Days 1-8), starting at approximately 5pm on the first day (Cycle 1 Day 1). You do not need to take mibefradil on an empty stomach. You will take 2 doses of mibefradil on Day 1 (at 5pm and 10pm) and 2 doses on Day 8 (at 7am and 12pm); on the days in between (Days 2-7) you will take four doses of mibefradil each day on a four-times-a-day schedule at 7am, 12pm, 5pm, and 10pm.

After 8 days of treatment with mibefradil, **you will take temozolomide (TMZ) for 5 days** (Days 9-13). You will begin temozolomide approximately 24 hours after your last dose of mibefradil. Temozolomide must be taken on an empty stomach. You cannot eat or drink anything except water for at least one hour before and for one hour after taking your TMZ pills.

After the 5 days of treatment with TMZ you will not receive any other treatment for the remainder of each 28-day cycle.

After the first cycle, in subsequent cycles, **you will take mibefradil by mouth for seven consecutive days** (Days 1-7), on a four-times-a-day schedule, at 7am, 12pm, 5pm, and 10pm. After 7 days of treatment with mibefradil, **you will take temozolomide (TMZ) for 5 days** (Days 8-12). You will begin temozolomide approximately 24 hours after your last dose of mibefradil.

You will be asked to record the date, time, and the number of pills you take each day of the study in a pill diary for each medication, as you take your dose. You will need to bring the diaries and any extra pills and medication containers with you to your monthly visit to the study physician.

You should not take any over-the-counter (OTC) medications and nutritional supplements, including herbal or "Chinese" medications while you are on this study, with the exception of certain over-the-counter medications that your study doctor will discuss with you. Consult with your study doctor before taking any new medication, including anything recommended or prescribed by a doctor not involved with your treatment for brain cancer, due

to the possibility of interactions with the study medication. **Mibefradil interacts with many common medications so it is very important that you follow these instructions.**

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions.

As part of this study, we will be collecting extra blood samples in order to check the amount of mibefradil in your blood and to look at the activity of mibefradil in your blood. These blood samples will be drawn in the clinic on Days 2, 5, 8, 9, and 10 in the first cycle only. A total of 29 extra blood samples will be drawn, 9 samples each day on Days 2, 5, and 8, and 1 sample on each of Days 9 and 10. Approximately 1 teaspoon of blood will be drawn for each sample. These extra blood tests are for research purposes only and would not be part of your standard care. The costs associated with collecting and processing these blood samples will not be charged to you or your insurance company.

During the study, physical and neurologic exams will be repeated, your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate), and ECG monitoring will take place. Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week for as long as you receive TMZ.

After the second cycle another MRI will be obtained. If this MRI shows that the tumor size is the same or smaller, you will begin a third four-week cycle of treatment. An MRI will be obtained before every other cycle (every 8 weeks) to see if your tumor is growing. These brain scans (MRI) are part of routine cancer care.

HOW LONG WILL I BE IN THE STUDY?

Treatment with mibefradil and temozolomide will be continued on the same schedule for up to 6 or more four-week cycles, unless your tumor grows or you have side effects that require discontinuation, or you want to stop treatment.

An MRI will be obtained after you complete the first 2 cycles (8 weeks). If this MRI shows that the tumor size is the same or smaller, you will begin a third 4-week cycle of treatment. As long as your tumor does not grow and as long as you do not experience any bad side effects you may continue to receive additional 4-week cycles, up to 6-12 cycles in total (24 to 48 weeks). If at any time the MRI shows that your tumor is growing you will stop mibefradil treatment and you and your doctor will discuss other treatment options.

If you must permanently stop taking temozolomide for any reason, you will also stop taking mibefradil and will be off-treatment. If you must stop taking mibefradil you will be taken off-treatment but may continue to receive additional cycles of TMZ treatment as standard care if your doctor feels it is beneficial to you.

Your participation in this clinical trial is completely voluntary. You can stop participating at any time. If you decide not to participate it will not affect your medical care at this institution. If you join this study you may withdraw from it at any time. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor and visit your regular doctor first.

Your study doctor may end your participation in the study if it is judged to be in your best interest or if you are unable to follow the rules of the study.

When you withdraw from the study for any reason, all medication and study drug bottles must be returned to the study site. You will also be asked to return to the site so that the study doctor may perform a final safety evaluation.

Every two (2) months after your participation in the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease.

WHAT ARE THE RISKS OF THE STUDY?

Because of the risk of adverse reactions, you will need to inform your study doctor of any side effects or new health problems you experience during participation in this study. Also, due to the risk of side effects resulting from different combinations of drugs (called drug-drug interactions), you must discuss any medications you are taking with your doctor and ensure they are safe to take while you are on the study (your doctor will have a list of permitted and prohibited medications for this study). You may not take any over-the-counter (OTC) medications without your doctor's approval and may not take any nutritional supplements, including herbal or "Chinese" medications while you are on this study. You must also notify the study doctor of any other medical treatments or procedures that may be necessary for you to undergo.

You may experience all, some, or none of the side effects described below. Side effects may be mild, moderate, or severe, and although they usually subside, they could also be permanent. There may be other side effects that you experience that are not commonly observed in other subjects receiving mibefradil or temozolomide.

Some side effects may not show up until several weeks after treatment is given. Your doctor may order other medications to make side effects less severe or to make you feel more comfortable.

In the event that you experience any severe or unusual adverse reaction during the course of this study, you should immediately contact the study doctor.

Risks of Mibefradil

Likely side effects include (> 20% of subjects experience these):

- Low heart rate or pulse
- Dizziness when you stand up
- Feeling light-headed
- Getting tired more easily

Less Likely side Effects include (≤ 20% of subjects experience these):

- Feeling that your heart is "skipping beats"

Rare but serious side effects (≤ 3% of subjects experience these)**:**

- Fainting

Risks of Temozolomide

Temozolomide (TMZ) is a chemotherapy drug. TMZ may cause the following:

Likely side effects:

- Nausea and vomiting, especially on the first day of each cycle. It may be necessary to use medication to prevent this.
- Constipation
- Loss of appetite,
- Lowering of your blood counts, which may result in low white blood cells, platelets, and red blood cells. If you have very low white blood cells, you are at a higher risk for infections. Lung infections have occurred in subjects receiving daily treatment with temozolomide combined with radiation and steroids (e.g., dexamethasone). To prevent this, your doctor may ask you to take preventative medication during this time. Apart from this, if you develop fever it may be necessary to treat you with antibiotics. Low platelets may result in a bleeding tendency, if necessary this can be treated with platelets transfusions. Low red blood cells can also be treated with transfusions.
- Fatigue, lethargy, insomnia, weakness
- Headache
- Hair loss and rash

Less Likely side effects:

- Kidney problems and high blood sugar
- Abnormal liver tests and diarrhea

Note: For more comprehensive information regarding less likely and rare side effects please refer to the temozolomide package insert.

Risks associated with blood drawing may include: pain, bruising, bleeding or other discomfort at the blood drawing site. Anemia (low red blood cells), fainting or infection at the blood drawing site may occur (very unlikely).

This study may also have risks to you that cannot be determined at this time. You will be told of any potential risks that may be discovered while you are participating in this study.

Reproductive risks: Because there may be a risk of birth defects if a fetus is exposed to mibefradil or temozolomide, you should not use this drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A pregnancy test will be performed on women who are able to become pregnant before the start of the study medication. An adequate method of birth control must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study. Ask about counseling and more information about preventing pregnancy.

Risks of MRI

The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

Gadolinium Risk

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung.

NSF/NFD is a serious progressive disease and can result in death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the study doctor to give you this information.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Financial risks: There may be extra costs associated with this study. Some of the costs may not be covered by the hospital or your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

For more information about risks and side effects, ask the researcher or contact:

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other subjects with brain tumors in the future.

WHAT OTHER OPTIONS ARE THERE?

Should your disease become worse, or if you have severe side effects, this therapy may be discontinued and other means of treating you will be discussed. You may choose at this time, or any time in the future to have no further therapy other than care for relief of your symptoms (supportive care). You may also consider other

treatments for your disease such as further surgery, radiation therapy or chemotherapy. Other research options may also be available to you.

Please talk to you doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as needed in this study. _____ has a policy to protect health information that may identify you. Federal and state laws also protect your privacy. _____ has procedures in place to support these policies and laws.

a. What information about you may be used or given out in this study?

Information that identifies you and relates to your health or medical condition may be used or given out in this study. Information that identifies you can include your name, address, telephone number, date of birth, Social Security number and other details about you. Information that relates to your health or medical condition includes:

Information obtained from the activities and procedures outlined in this consent form, which may include:

i) things done to see if you can join this study, such as physical examinations, blood and urine tests and any other information that you share with us, including information about your health history and your family health history; and

ii) information obtained during the study, such as how you respond to the study activities or procedures, information we learn in study visits, phone calls, surveys, physical examinations, blood and urine tests, x-rays and other tests and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?

Some people may see your health information and may give out your health information during this study. These include the researcher and the research staff, the institutional review boards and their staff, legal counsel, audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?

Other organizations may see your health information during this study. These include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections and the Food and Drug Administration
- Doctors and staff at other places that are participating in this study and are part of the ABTC (Adult Brain Tumor Consortium)
- The pharmaceutical sponsor, Tau Therapeutics LLC
- The sponsors of this study and people that the sponsors may contract with for this study.
- DCTD/NCI (Division of Cancer Treatment and Diagnosis/National Cancer Institute
- The Data Safety Monitoring Board
- An outside institutional review board
- The Adult Brain Tumor Consortium (ABTC)

d. Why will this information be used and given out?
Your information will be used and given out to carry out this study and to evaluate the results of this study when seeking approval from regulatory authorities to market the studied drug. It may also be used in study reports or for scientific presentations, but in a way that will not identify you by name. Your personal health information will be kept confidential and, unless required by law, will not be made publicly available. Your identity and contact details will not be disclosed unless required by law. Rather, your identity and contact details will be replaced by a code, such as a number. After this study has been completed, it is possible that your coded health information will be used for future research.

e. What if you decide not to give your permission to use and give out your health information?
You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. May you withdraw or cancel your permission?
You may cancel your agreement to allow your health information to be used or given out at any time by sending a written notice to the Institutional Review Board Office, _____. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after that date. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?
If your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and may be used or given out without your permission.

h. Does this consent form have an end date?
This authorization to use and give out health information continues until the end of this study and any necessary data analysis follow-up activities for this study.

i. What is the role of the IRB?
Research studies involving human volunteers are reviewed by an Institutional Review Board (IRB). The IRB is made up of doctors, nurses, scientists, non-scientists and people from the community. The IRB is responsible for protecting participant's rights.

WHAT ARE THE COSTS?

The pharmaceutical sponsor will provide you with mibefradil free of charge for this study. Should this agent become commercially available or approved for this indication during the course of this study, you may be asked to purchase subsequent doses of the drug needed to complete the study in the event that the company no longer provides the drug. Even though it probably won't happen, it is possible that the manufacturer may not continue to provide mibefradil to the pharmaceutical sponsor for some reason. If this were to occur, other possible options are:

- You might be able to get mibefradil from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no mibefradil available at all, no one will be able to get more and the study would close.

If a problem with getting mibefradil occurs, your study doctor will talk to you about these options.

Temozolomide is commercially available for recurrent brain tumor.

Taking part in this study may lead to added costs to you or your insurance company. Some of the costs of the blood tests and brain scans may not be covered by your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

In the case of injury or illness which is a direct result of participation in this study, emergency medical treatment is available and will be provided at the usual charge. The pharmaceutical sponsor, Tau Therapeutics LLC, will reimburse for reasonable costs for necessary medical care that is not covered by your medical insurance or other governmental programs providing such coverage.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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.

We will talk to you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher _____ (NAME{S}) at _____ (TELEPHONE NUMBER) .

For questions about your rights as a research participant, contact the_____ (NAME OF CENTER) Institutional Review Board (which is 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)

Visit the NCI's Web site 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/cancertopics/

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

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

SIGNATURE

I agree to take part in this study.

Participant _____

Date _____

Investigator _____

Date _____

Witness _____

Date _____

Dose Expansion

A Phase I Open Label Safety Study to Evaluate the Pharmacokinetic Profile and Tolerance of Mibefradil Dose Finding in Subjects with Recurrent High-Grade Glioma Undergoing Standard, Repeated Temozolomide Treatment

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

You are being asked to take part in this study because you have a brain tumor that has grown or has recurred.

WHY IS THIS STUDY BEING DONE?

This research is being done because this type of tumor is almost never cured with surgery, radiation, or chemotherapy. For this reason, we are trying to find new drugs to improve treatment for this tumor. The study you are being asked to join uses a drug called mibefradil. Mibefradil is a type of drug known as a calcium channel blocker. Mibefradil has previously been used to treat patients with high blood pressure. It was later found that mibefradil's action on a particular type of calcium channel causes cancer cells to line up in a way that may increase the effect of temozolomide (TMZ)), a drug that is used for the treatment of glioma. Mibefradil is considered experimental because it has not been approved by the U. S. Food and Drug Administration (FDA) for treatment of brain tumors.

The purpose of this study is to find out what effects (good and bad) mibefradil taken prior to treatment with TMZ has on your brain tumor. TMZ is an FDA-approved chemotherapy and is considered part of "standard of care" therapy for this disease. We will look at the effects of mibefradil given for 7 days prior to taking TMZ for 5 out of every 28 days.

You will be told what your mibefradil dose is and it will not be increased. You will be given the same or a lower dose throughout your treatment. You will be given a lower dose if you experience side effects that require reduced dosing. We will also be looking at the side effects of mibefradil and temozolomide.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Ten people will take part in the study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study you will have the following tests and procedures:

Before treatment starts, you will have a complete physical exam and blood tests. Your physical examination will include a medical history and measurement of your height, weight, blood pressure, temperature, respiratory rate, heart rate, and performance status, which measures the degree of your ability to complete daily activities (e.g., dressing and eating). You will have a complete neurological exam to test your ability to think, your muscle strength, balance, and other functions of the brain. An ECG (electrocardiogram or measurement of the electrical activity of the heart) will also be done. To measure the extent of your brain cancer, you will have an MRI (magnetic resonance imaging) scan of the brain, which is a method of obtaining pictures of internal soft bodily tissue through the use of powerful magnets and radio waves.

As part of your screening tests, about 3 tablespoons of blood will be drawn from one of your veins to conduct laboratory tests (e.g., standard blood count including a count of your platelets, and blood chemistries). You will also be asked to have a pregnancy test if you are a woman that is able to have children. If you are pregnant you will not be permitted to participate in this study.

As part of this study, you will undergo research imaging using fluorothymidine Positron Emission Tomography (FLT PET) scanning at 3 time points: you will have the first two scans within 10 days before the first dose of mibefradil (at least 24 hours apart), and the third on the last day of mibefradil dosing (Day 7) in the first cycle of treatment (a cycle is 28 days).

An FLT PET scan is a procedure in which a small amount of radioactive thymidine ([F-18]FLT, an investigational radiopharmaceutical that is one of the building blocks of genetic material) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the thymidine is used. Because cancer cells often use more thymidine than normal cells, the pictures can be used to tell how active cancer cells are and if mibefradil is changing this activity. FLT PET is considered investigational because it has not been approved by the U. S. Food and Drug Administration (FDA) as a standard imaging technique for brain tumors.

You may not eat or drink anything for 4 hours before each scan. Your vital signs will be monitored more frequently while you are undergoing the FLT PET scan procedure and you must remain in the clinic for at least two hours after the end of the scan.

These FLT PET scans are for research purposes only and would not be part of your standard care. The costs associated with these scans will not be charged to you or your insurance company.

Prior to the first dose of mibefradil you will be fitted with a portable ECG device which will continuously monitor the electrical activity of your heart and your heart rate while you are taking mibefradil. You will be instructed how to use it and must follow these instructions exactly. You must wear the monitor continuously during the days you are taking mibefradil, even while you are sleeping (Days 1-7). The ECG monitor can be removed for bathing.

You will also receive a home blood pressure monitoring device and be instructed how to take and record your blood pressure and pulse while you are taking mibefradil; you will have to check and record your blood pressure/pulse at least one time per day during Days 1-7.

Treatment cycles are 28 days. **You will take mibefradil by mouth for seven consecutive days** (Days 1-7), on a four-times-a-day schedule at 7am, 12pm, 5pm, and 10pm. You do not need to take mibefradil on an empty stomach.

After 7 days of treatment with mibefradil, **you will take temozolomide (TMZ) for 5 days** (Days 8-12). You will begin temozolomide approximately 24 hours after your last dose of mibefradil. Temozolomide must be taken on an empty stomach. You cannot eat or drink anything except water for at least one hour before and for one hour after taking your TMZ pills.

After the 5 days of treatment with TMZ you will not receive any other treatment for the remainder of each 28-day cycle.

After the first 28-day cycle, in subsequent cycles, you will continue to take doses of mibefradil on Days 1-7, on the same schedule as Cycle 1. Five days of treatment with TMZ will follow each 7-day treatment with mibefradil.

You will be asked to record the date, time, and the number of pills you take each day of the study in a pill diary for each medication, as you take your dose. You will need to bring the diaries and any extra pills and medication containers with you to your monthly visit to the study physician.

You should not take any over-the-counter (OTC) medications and nutritional supplements, including herbal or "Chinese" medications while you are on this study, with the exception of certain over-the-counter medications that your study doctor will discuss with you. Consult with your study doctor before taking any new medication, including anything recommended or prescribed by a doctor not involved with your treatment for brain cancer, due to the possibility of interactions with the study medication. **Mibefradil interacts with many common medications so it is very important that you follow these instructions.**

You should avoid consuming grapefruit and grapefruit juice while taking the study medication due to possible interactions.

During the study, physical and neurologic exams will be repeated, your vital signs will be measured (including temperature, heart rate, blood pressure, respiratory rate), and ECG monitoring will take place. Routine blood tests will be done. If at any point your blood counts are low, these blood tests will be repeated more often. Your blood counts will be checked at least once every week for as long as you receive TMZ.

After the second cycle another MRI will be obtained. If this MRI shows that the tumor size is the same or smaller, you will begin a third four-week cycle of treatment. An MRI will be obtained before every other cycle (every 8 weeks) to see if your tumor is growing. These brain scans (MRI) are part of routine cancer care.

HOW LONG WILL I BE IN THE STUDY?

Treatment with mibefradil and temozolomide will be continued on the same schedule for up to 6 or more four-week (28-day) cycles, unless your tumor grows or you have side effects that require discontinuation, or you want to stop treatment.

An MRI will be obtained after you complete the first 2 cycles (8 weeks). If this MRI shows that the tumor size is the same or smaller, you will begin a third 4-week cycle of treatment. As long as your tumor does not grow and as long as you do not experience any bad side effects you may continue to receive additional 4-week cycles, up to 6-12 cycles in total (24 to 48 weeks). If at any time the MRI shows that your tumor is growing you will stop mibefradil treatment and you and your doctor will discuss other treatment options.

If you must stop taking temozolomide for any reason, you will also stop taking mibefradil and will be off-treatment. If you must stop taking mibefradil you will be taken off-treatment but may continue to receive additional cycles of TMZ treatment as standard care if your doctor feels it is beneficial to you.

Your participation in this clinical trial is completely voluntary. You can stop participating at any time. If you decide not to participate it will not affect your medical care at this institution. If you join this study you may withdraw from it at any time. However, if you decide to withdraw from the study, we encourage you to talk to the study doctor and visit your regular doctor first.

Your study doctor may end your participation in the study if it is judged to be in your best interest or if you are unable to follow the rules of the study.

When you withdraw from the study for any reason, all medication and study drug bottles must be returned to the study site. You will also be asked to return to the site so that the study doctor may perform a final safety evaluation.

Every two (2) months after your participation in the study has ended, someone from the study will contact you or your medical records will be reviewed to follow your disease.

WHAT ARE THE RISKS OF THE STUDY?

Because of the risk of adverse reactions, you will need to inform your study doctor of any side effects or new health problems you experience during participation in this study. Also, due to the risk of side effects resulting from different combinations of drugs (called drug-drug interactions), you must discuss any medications you are taking with your doctor and ensure they are safe to take while you are on the study (your doctor will have a list of permitted and prohibited medications for this study). You may not take any over-the-counter (OTC) medications without your doctor's approval and may not take any nutritional supplements, including herbal or "Chinese" medications while you are on this study. You must also notify the study doctor of any other medical treatments or procedures that may be necessary for you to undergo.

You may experience all, some, or none of the side effects described below. Side effects may be mild, moderate, or severe, and although they usually subside, they could also be permanent. There may be other side effects that you experience that are not commonly observed in other subjects receiving mibefradil or temozolomide.

Some side effects may not show up until several weeks after treatment is given. Your doctor may order other medications to make side effects less severe or to make you feel more comfortable.

In the event that you experience any severe or unusual adverse reaction during the course of this study, you should immediately contact the study doctor.

Risks of Mibefradil

Likely side effects include (> 20% of subjects experience these):

- Low heart rate or pulse
- Dizziness when you stand up
- Feeling light-headed
- Getting tired more easily

Less Likely side Effects include (≤ 20% of subjects experience these):

- Feeling that your heart is "skipping beats"

Rare but serious side effects (≤ 3% of subjects experience these)**:**

- Fainting

Risks of Temozolomide

Temozolomide (TMZ) is a chemotherapy drug. TMZ may cause the following:

Likely side effects:

- Nausea and vomiting, especially on the first day of each cycle. It may be necessary to use medication to prevent this.
- Constipation
- Loss of appetite,
- Lowering of your blood counts, which may result in low white blood cells, platelets, and red blood cells. If you have very low white blood cells, you are at a higher risk for infections. Lung infections have occurred in subjects receiving daily treatment with temozolomide combined with radiation and steroids (e.g., dexamethasone). To prevent this, your doctor may ask you to take preventative medication during this time. Apart from this, if you develop fever it may be necessary to treat you with antibiotics. Low platelets may result in a bleeding tendency, if necessary this can be treated with platelets transfusions. Low red blood cells can also be treated with transfusions.
- Fatigue, lethargy, insomnia, weakness
- Headache
- Hair loss and rash

Less Likely side effects:

- Kidney problems and high blood sugar
- Abnormal liver tests and diarrhea

Note: For more comprehensive information regarding less likely and rare side effects please refer to the temozolomide package insert.

Risks associated with blood drawing may include: pain, bruising, bleeding or other discomfort at the blood drawing site. Anemia (low red blood cells), fainting or infection at the blood drawing site may occur (very unlikely).

This study may also have risks to you that cannot be determined at this time. You will be told of any potential risks that may be discovered while you are participating in this study.

Reproductive risks: Because there may be a risk of birth defects if a fetus is exposed to mibefradil or temozolomide, you should not use this drug if you and your partner are planning to have a baby during this study or two months following the end of the study. A pregnancy test will be performed on women who are able to become pregnant before the start of the study medication. An adequate method of birth control must be used during the study and for eight (8) weeks after your last dose of study drug. You should not nurse a baby while on this study. Ask about counseling and more information about preventing pregnancy.

Risks of MRI

The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise

the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

Gadolinium Risk
The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly.

There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people. Insertion of the needle (small plastic tube) to give you gadolinium may cause minor pain, bruising and/or infection at the injection site.

People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This disease causes fibrosis, which is the formation of too much connective tissue in the skin and internal organs throughout the body. People develop skin thickening that may prevent bending and extending joints, resulting in decreased movement of the joints. The skin changes can cause feelings of burning, itching and pain that can be severe. In addition, people may experience fibrosis that spreads to other parts of the body such as the diaphragm, muscles in the thigh and lower abdomen, and the lining of blood vessels in the lung.

NSF/NFD is a serious progressive disease and can result in death. If you have severe kidney failure and receive gadolinium, the risk of developing NSF/NFD is 1-5 % (up to 1 to 5 per 100 people). We may require a blood sample (about 1 tablespoon) to check your kidney function before you receive gadolinium contrast for your MRI.

Please notify a doctor, nurse or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects. If you do not know if you have kidney problems or if you do not know if your kidney problems fall in the severe category, you can ask the study doctor to give you this information.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Risks of FLT PET scans: Although a radiotracer chemical (thymidine) is used in this test, the amount of radiation you are exposed to is low. The dose of tracer used is so small that it does not affect the normal processes of the body. However, the radiotracer may expose the fetus of subjects who are pregnant or infants of women who breastfeed to the radiation. You may not participate in this study if you are pregnant or nursing. You and your doctor need to consider this risk compared with the need for and potential information to be gained from the FLT PET scan.

While considered extremely rare, the risks of undergoing FLT PET procedures are:
- Injection-related risks that may include infection, or accidental extravasation of the dose that may lead to discomfort, localized pain, or infection.
- Risks related to allergic reaction/anaphylaxis that may be life threatening.

Financial risks: There may be extra costs associated with this study treatment. Some of the costs may not be covered by the hospital or your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

For more information about risks and side effects, ask the researcher or contact:

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other subjects with brain tumors in the future.

WHAT OTHER OPTIONS ARE THERE?

Should your disease become worse, or if you have severe side effects, this therapy may be discontinued and other means of treating you will be discussed. You may choose at this time, or any time in the future to have no further therapy other than care for relief of your symptoms (supportive care). You may also consider other treatments for your disease such as further surgery, radiation therapy or chemotherapy. Other research options may also be available to you.

Please talk to you doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information that identifies you may be used and/or given out as needed in this study. _____ has a policy to protect health information that may identify you. Federal and state laws also protect your privacy. _____ has procedures in place to support these policies and laws.

a. What information about you may be used or given out in this study?

Information that identifies you and relates to your health or medical condition may be used or given out in this study. Information that identifies you can include your name, address, telephone number, date of birth, Social Security number and other details about you. Information that relates to your health or medical condition includes:

Information obtained from the activities and procedures outlined in this consent form, which may include:

i) things done to see if you can join this study, such as physical examinations, blood and urine tests and any other information that you share with us, including information about your health history and your family health history; and

ii) information obtained during the study, such as how you respond to the study activities or procedures, information we learn in study visits, phone calls, surveys, physical examinations, blood and urine tests, x-rays and other tests and any other medical information we learn from you as a participant in this study.

b. Who may use and give out information about you?

Some people may see your health information and may give out your health information during this study. These include the researcher and the research staff, the institutional review boards and their staff, legal counsel,

audit and compliance staff, officers of the organization and other people who need to see the information to help this study or make sure it is being done as it should.

c. Who may see your health information?
Other organizations may see your health information during this study. These include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections and the Food and Drug Administration
- Doctors and staff at other places that are participating in this study and are part of the ABTC (Adult Brain Tumor Consortium)
- The pharmaceutical sponsor, Tau Therapeutics LLC
- The sponsors of this study and people that the sponsors may contract with for this study.
- DCTD/NCI (Division of Cancer Treatment and Diagnosis/National Cancer Institute
- The Data Safety Monitoring Board
- An outside institutional review board
- The Adult Brain Tumor Consortium (ABTC)

d. Why will this information be used and given out?
Your information will be used and given out to carry out this study and to evaluate the results of this study when seeking approval from regulatory authorities to market the studied drug. It may also be used in study reports or for scientific presentations, but in a way that will not identify you by name. Your personal health information will be kept confidential and, unless required by law, will not be made publicly available. Your identity and contact details will not be disclosed unless required by law. Rather, your identity and contact details will be replaced by a code, such as a number. After this study has been completed, it is possible that your coded health information will be used for future research.

e. What if you decide not to give your permission to use and give out your health information?
You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

f. May you withdraw or cancel your permission?
You may cancel your agreement to allow your health information to be used or given out at any time by sending a written notice to the Institutional Review Board Office, _____. If you do this, you are leaving this study. If you leave this study, no new health information about you will be gathered after that date. However, information gathered before that date may be used or given out if it is needed for this study or any follow-up for this study.

g. Is your health information protected after it has been given to others?
If your health information is given to someone not covered by these policies and laws, that information may no longer be protected, and may be used or given out without your permission.

h. Does this consent form have an end date?
This authorization to use and give out health information continues until the end of this study and any necessary data analysis follow-up activities for this study.

i. What is the role of the IRB?

Research studies involving human volunteers are reviewed by an Institutional Review Board (IRB). The IRB is made up of doctors, nurses, scientists, non-scientists and people from the community. The IRB is responsible for protecting participant's rights.

WHAT ARE THE COSTS?

The pharmaceutical sponsor will provide you with mibefradil free of charge for this study. Should this agent become commercially available or approved for this indication during the course of this study, you may be asked to purchase subsequent doses of the drug needed to complete the study in the event that the company no longer provides the drug.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide mibefradil to the pharmaceutical sponsor for some reason. If this were to occur, other possible options are:

- You might be able to get mibefradil from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no mibefradil available at all, no one will be able to get more and the study would close.

If a problem with getting mibefradil occurs, your study doctor will talk to you about these options.

Temozolomide is commercially available for recurrent brain tumor.

Taking part in this study may lead to added costs to you or your insurance company. Some of the costs of the blood tests and brain scans may not be covered by your insurance company. We encourage you to work closely with your insurance company to find out exactly what is covered for this research study.

In the case of injury or illness which is a direct result of participation in this study, emergency medical treatment is available and will be provided at the usual charge. The pharmaceutical sponsor, Tau Therapeutics LLC, will reimburse for reasonable costs for necessary medical care that is not covered by your medical insurance or other governmental programs providing such coverage.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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.

We will talk to you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher _____ (NAME{S}) at _____ (TELEPHONE NUMBER) .

For questions about your rights as a research participant, contact the_____ (NAME OF CENTER) Institutional Review Board (which is 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)

Visit the NCI's Web site 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/cancertopics/

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

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

SIGNATURE

I agree to take part in this study.

Participant _____

Date _____

Investigator _____

Date _____

Witness _____

Date _____