INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Description of Study

You have von Hippel-Lindau (VHL) disease with at least one tumor that is large enough that you may be at risk for the tumor spreading to other organs (metastasis). You are invited to join this phase II study of an investigational (research) drug call 17AAG (17-allylamino 17-demethoxygeldanamycin).

17AAG is a drug that contributes to the destruction of several proteins inside the cell. Some of these proteins are thought to play a role in causing cancer and encouraging growth of a tumor once it develops. In laboratory experiments, 17AAG has been shown to kill or slow the growth of cancer cells. Studies then showed that 17AAG killed or slowed the growth of human cancer cells in mice. Several studies in humans were done to evaluate the safety of the drug.
on these studies, a reasonably safe dose and treatment schedule has been determined. The main purpose of the study is to find out if 17AAG can shrink your kidney tumors.

Under this study, people will receive 17AAG and also have several imaging studies designed to measure the tumor’s response to the drug. Normally imaging studies such as the MRIs and CT scans measure the size or dimensions of tumors. The MRI imaging studies done with this study will also measure the actual biologic activity of the tumor and the blood vessels within and around the tumor. This is done for research.

There are other aspects we would like to study:
1) We will measure the effect of 17AAG on other tumors you may have that are caused by VHL. Examples of other VHL related tumors are tumors of the pancreas, eye, adrenal gland, brain and spinal cord.
2) We will study the effects of 17AAG on the amount of blood vessels in the tumors and the biologic (metabolic) activity of the tumor.
3) We will study how 17AAG affects the cells circulating in your bloodstream.
4) We will continue to evaluate the safety of this drug, and
5) If you have your kidney tumor(s) removed, we will examine the tumor to find out the impact of 17AAG on the tumor.

17 AAG
17 AAG belongs to a new class of anticancer drugs. It changes the function of a protein inside the cell known as heat shock protein 90 (Hsp90). Hsp90 affects the levels of several proteins including some that may be important in the formation of tumors. It is believed that some of these proteins may also be involved in the continued growth of tumors once they develop. 17AAG has been shown to contribute to the destruction of several of these proteins by processes which involve Hsp90. Kidney tumors in von Hippel-Lindau disease appear to have high levels of some of these proteins in their cells.

Pre-treatment eligibility evaluation
In order to determine if you are eligible for the 17AAG study, you will be evaluated in the out-patient clinic at the Warren G. Magnuson Clinical Center (NIH) in Bethesda MD.

The eligibility evaluation involves:
• An appointment to meet with our medical team. This includes a discussion about your health history including any allergies you may have and a review of the medications you are currently taking. You will also have a physical examination. If you have a history of allergy to eggs, please discuss this with the doctors as it may be dangerous for you to receive 17 AAG. We will discuss the study and answer your questions.
• CT scans (a type of imaging study which uses radiation) and a brain MRI (an imaging study that uses radio waves) will be done to allow us to see the size and extent of your kidney tumor(s) and to determine if your tumor has spread beyond the kidneys. If you are unable to have an MRI scan because you have metal clips, a pacemaker, shrapnel injury or other metal inside your body, you may have a CT scan instead.
• 2-3 tubes of blood (4 teaspoons) and urine samples will be taken.
• A visit with a heart doctor (cardiologist) for a basic heart evaluation.
• An electrocardiogram (EKG) which is a test that analyzes the electrical activity of your heart.
• A MUGA test, which is a nuclear medicine imaging study that looks at the function of your heart.
• Pulmonary Function Testing (PFT’s) which measures your lung function by breathing into a machine.
• Pulse oximetry before and after exercise which measures your oxygen level. This is done by using a non-invasive finger probe clipped to your finger.
If you have not had the following tests to evaluate your VHL health status within the recent past, you may be asked to have them done before entering the study.

- a 24 hour urine collection,
- an ultrasound of the testicles in men,
- a hearing test,
- an eye exam, and
- an MRI or CT scan of the spine.

These are all clinical tests that are usually done to monitor someone with von Hippel-Lindau disease. These evaluation studies are not considered research. If you have had these tests done very recently, you may not need to repeat them.

Pre-treatment Research Imaging

If you are eligible for this study and you decide to enroll, you will have an MRI scan before treatment begins. In order to measure the tumor’s response to 17AAG, we will compare the tumor’s biologic activity and blood supply before treatment to its’ biologic activity and blood supply after treatment. These can be done on an out-patient basis.

MRI (Magnetic Resonance Imaging)

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves that demonstrates structural and chemical changes in tissue. This technique is more sensitive than x-ray in some diseases and carries no radiation risk. A kind of MRI (high speed) may be done to measure the amount of blood vessels in the tumor. We may also look at the blood supply to the tumor. This MRI scan is a routinely used imaging technique and has been performed on many people. After an IV (small flexible plastic catheter) is inserted, contrast dye will be given to you just like the MRIs you have had in the past. If you have severe problems with claustrophobia, you can receive medication (sedation) to help you relax. The scanner is also quite noisy and you will be provided with ear plugs.

Treatment with 17AAG

After the MRI scan is done, treatment with 17AAG will begin. You will be given 17AAG once a week for three weeks (three weeks out of every four weeks) for three months. 17AAG is given by intravenous (IV) infusion (IV drip). You will be admitted to the Mark O. Hatfield Clinical Research Center in Bethesda Maryland where you will stay overnight. Your heart will be monitored during the infusion and for 24 hours afterwards. To do this, leads (wires) are attached to soft pads on your chest. Before and after each infusion of 17AAG, your temperature, respiratory (breathing) rate, blood pressure and heart rate will be taken. You will have an EKG before and after each infusion of 17-AAG. The infusion will generally take 2 hours to complete, but may take longer.

After approximately 3 months, you will have the same kind of tests that you had before treatment began. The kinds of tests that may be done include a CT scan, MRI, eye exam, and other tests to evaluate the effect of 17 AAG on your tumors.

You may continue to receive 17AAG for another 12 weeks if your kidney tumor(s) have become smaller. But if your kidney tumor(s) have not gotten smaller or they have grown during the 3 months of treatment, we will ask you to undergo surgery to remove your kidney tumor(s). We will recommend surgery in order to reduce the chance of cancer spreading to other parts of your body. In this study, some people will receive one round of the treatment, while others may receive a second round of 17AAG. The decision to have a second round will be based upon your tumor’s response to 17AAG.
After 12 weeks of treatment with 17AAG, you will have the research MRI scans done again. The repeat imaging studies will be done to measure any changes that may have happened since the pre-treatment scans. Repeat scans will measure changes in the amount of glucose the tumor absorbs, the blood flow in and through the tumor, and the amount of blood vessels in the tumor. If your treatment is continued beyond 12 weeks, these tests will be repeated again at the completion of the second round of treatment with 17 AAG.

Research Blood Samples
We will draw samples of blood four times during your first week of treatment at NIH for research purposes (several tablespoons each time). After the 1st week, blood will be drawn before each dose of 17 AAG. These blood samples will be used to determine the effects of 17 AAG on your blood counts, liver function etc. and to monitor the safety of the treatment. Some of this blood will also be used to perform the research tests explained earlier. You will be seen in the Urologic Oncology clinic every four weeks and more often as needed. We will review your laboratory studies, side effects, and perform a physical examination. We will also answer any questions you have.

Risks and discomforts

Delay in surgical resection of kidney tumor(s)
Von Hippel-Lindau patients with kidney tumors that have reached the size of your tumor(s) would normally be advised to undergo surgery to remove them. Surgical removal of tumors is done to lessen the risk of spread to other organs. Removing your kidney tumors does not mean that your cancer has been ‘cured’. Even if you have surgery to remove your kidney tumor(s), it is possible that you will develop new tumors and may need surgery again in the future. We feel that delaying surgery for approximately 12 weeks is unlikely to greatly increase the risk of tumor spread from your kidneys. A delay in surgery will happen if you choose to participate in this study and your tumors do not decrease in size with 17AAG. However, if any of your kidney tumors should be very large (>4cm), we will advise surgery at the earliest possible time and will exclude you from the current study.

17AAG
17AAG is an experimental drug. Possible side effects from 17AAG listed below are based on studies of the drug in humans. These side effects may be a minor inconvenience or could be severe enough to be life-threatening or fatal. In addition, there is always the risk that you could have side effects that have not been seen before. You will be closely watched for any side effects. If serious side effects occur, the drug will be stopped and you will be treated for the side effect.

The following side effects have been seen in people who received 17AAG and are thought to be caused by the drug: The most common side effect which resulted in stopping 17AAG was the development of abnormal blood tests suggesting some damage to cells in the liver, gall bladder or bile duct. Other side effects experienced by some patients included fatigue, nausea & vomiting, constipation, diarrhea, loss of appetite, fever, muscle aches and lowering of blood counts. Lowering of white blood cells makes you less able to fight infections; low platelet counts can increase your risk of bleeding and low red cell counts can result in anemia which makes you more tired and affects your ability to perform strenuous activity. Some people have experienced episodes of an irregular heart rhythm such as a rapid or slow heart beat. And some have had a decrease of their blood pressure and fainted. Some patients receiving 17-AAG have developed difficulty in breathing while at rest, during exercise, or while lying down, cough, lung abnormalities (infiltrates) on chest X-ray or CT scan, sudden difficulty breathing, and possibly death related to lung problems. Please contact your doctors immediately if you experience any problems with your breathing, or develop a cough.
It may be possible for people to be allergic to 17AAG. Allergic reactions may cause reddening of the skin, skin rash, chest tightness, back & abdominal pain, a change in blood pressure, difficulty breathing, etc. Should these occur, the infusion will be stopped and you will be given medications to control the side effect. If you have an allergic reaction, you may: 1) either be treated with 17AAG again, 2) you may be treated with medications to reduce the risk of an allergic reaction, or 3) 17AAG may be stopped permanently depending on the severity of the reaction. If you have a severe allergic reaction, you may need to be admitted to the hospital.

Other side effects have occurred, but it is not clear that these are caused by 17AAG. These include infection, difficulty in breathing and low amounts of oxygen in the blood, hoarseness of voice, cough, altered sense of taste, abdominal pain / cramping, mouth ulcers, mouth dryness, weight loss, breath / body odor, fever, headache, dizziness / light-headedness, blurred vision, abnormal levels of calcium, potassium, magnesium, and bicarbonate, soreness & redness of mouth and gums, fluid retention, increased blood pressure, increased blood sugar, blood tests indicating a tendency to bleed, joint swelling / pain, bone pain, hair loss, rash, dry skin, nail changes, itching, nerve damage resulting in muscle weakness and numbness & tingling in the fingers and toes, inflammation of the pancreas, urinary frequency / urgency, and blood tests indicating kidney damage.

Precautions will be taken to try to prevent side effects from occurring, and medicines can be given to stop or treat nausea, vomiting and diarrhea. Transfusions can be given if you develop low red cell or platelet counts. You will also be monitored for changes in heart rhythm, and asked to tell your doctors immediately if you develop any problems with breathing, cough, or shortness of breath.

Other Procedures
Other procedures done during the study may cause risks or discomfort. The risks associated with drawing blood are mild pain from the needle sticks and a chance of bruising or infection at the point used for blood draws. There are also risks associated with the method used for tumor evaluation. For instance, during the CT scan, you will be exposed to radiation. CT scans (done in the eligibility evaluation) can also be associated with extremely rare allergic reactions to the contrast agents used to see things during the scans. When you have this type of scan, you will be checked carefully by the radiologist for these allergic reactions and will be treated immediately if one happens. If you decide to have a port or vascular access device inserted, the risks and benefits will be discussed with you by the doctor inserting the device.

The risks/discomforts associated with MRI include those resulting from placement of an IV and the risk of a reaction to the contrast agent. At the NIH we have observed a reaction rate (reactions are asthma, hives, low blood pressure or seizures) in less than 0.5 % of all patients who have received this contrast. Some patients also experience claustrophobia during MRI. Should this happen to you, conscious sedation can be given to you to decrease or eliminate your symptoms. You will not be able to undergo MRI if you have a pacemaker, cerebral aneurysm clips, shrapnel injury or implantable electronic devices. If you know or think you may have any of these, please discuss this with your doctors. Individuals with fear of confined spaces may become anxious during MRI. You will hear a thumping noise created by the radio waves forming the images. You will feel no pain, but you may find the noise and the closed-in space discomforting. You will be observed at all times by the operators and will be able to speak to them; you can be moved out of the machine at your request.

If you are asked to undergo surgery to remove your kidney tumor(s), the procedure will be discussed with you by the surgeons performing the procedure and you will be asked to sign a separate consent form. The surgery is not considered research; you will receive standard-of-care surgery. It is not known if treatment with 17 AAG is going to make your surgery and healing process more difficult or dangerous. For this reason, we will not perform surgery for at least 2
weeks after the last dose of 17AAG. We believe that this delay will minimize the risk of 17AAG negatively affecting your surgery.

**Pregnancy / Contraception**
If you are a woman and are pregnant or breast feeding, you cannot take part in this study because there may be a potential of harm to the fetus. If you are a woman capable of becoming pregnant, you must have a negative pregnancy test within one week before starting the study. You must agree not to become pregnant while you are taking part in this study. If you become or are found to be pregnant while you are on this study, you must let the doctor listed on this form know immediately.

If you are a sexually active man and have not had surgery to become sterilized, you must agree not to have sexual intercourse or to use barrier contraception during the study. This is to prevent the possibility of a pregnancy from sperm that might have been damaged by 17AAG treatments.

**Use of medications while on study**
In addition to side effects that you may experience, 17AAG may have negative interactions with medications you may be taking. There are medications (prescription and non-prescription) and dietary supplements (including “complementary” or “alternative” medications) that may interact with 17AAG. These may be potentially dangerous when combined with 17AAG and will need to be avoided while you are on-study. You will be given a list of these drugs and we ask you to carefully review the list and advise the investigators if you are currently taking any of these drugs. The investigators will review all the medications and supplements you are currently taking before your participation on this study. You should not take any new medications or dietary supplements without discussing it with the investigators first.

**Alternative to Participation**
Your doctor is very willing to discuss the benefits and side effects of other ways to treat your tumors including the option of surgical resection of your tumor(s), treatment of your symptoms only, and other investigational protocols that may be available for your condition.

**Potential Benefits to Subjects**
You are being offered this experimental drug (17 AAG) because it may be of benefit to you in treating your VHL disease. One potential benefit may be shrinkage of your tumors that would enable you to delay or avoid surgery. Another possible benefit might be changes to the tumor environment (such as decreased blood supply) that may make surgical removal of your tumor(s) easier. However, there is no guarantee that this drug is of benefit to humans or that you will benefit from taking part in the study. The drug you receive may even be harmful to you.

**Potential Benefits to Society**
The knowledge gained from this study may benefit others. Your participation may help to determine if 17 AAG treatment can be safely and effectively given to other patients with VHL.

**Compensation for Participation**
There will be no financial compensation for participating in this study.

**Financial Obligation**
The study drug, 17AAG, will be provided to you free of charge by the National Cancer Institute/ Cancer Therapy Evaluation Program. There is no cost to you for the drug itself or for any test or procedure performed solely for research purposes. NIH will pay for the cost of the blood tests, x-rays, scans, drug preparation and pharmacy fees, other
laboratory tests and doctor’s fees associated with your research-related care while you are enrolled in this study. You or your insurance company will have to pay for all non-research related costs that are associated with your routine care for your underlying disease.

**Drug Sponsor/ Manufacturer**
The manufacturer of this study is Kosan Biosciences, Inc. 17 AAG will be obtained from Kosan Biosciences, Inc. for use in this study at the National Cancer Institute by the Cancer Therapy Evaluation Program. It is possible that the information obtained from your participation on this study may become valuable for commercial research and development purposes (including patentable inventions), which may be of significant benefit to society, the sponsor of this study, individual researchers, or other third parties. You will not receive direct financial benefit from such research and development. Blood/urine/tissue specimens obtained during your participation in this study may be sent to Kosan Biosciences, Inc. in order to test for information required for this study. All samples will be coded and no personal information will be included to protect your privacy.

**Emergency Care and Compensation for Injury**
If you are injured as a result of research procedures you will receive treatment at no cost to you.

**Research Subject’s Rights**
You will be told if no benefit occurs to you as a result of participation in this treatment program. A copy of the informed consent is on file at the Center for Cancer Research, National Cancer Institute and a copy will be made available to you. Your signature on this form indicates that you agree to participate in this medical research study under the direction of the principal investigator as listed above. Your records will be kept confidential with the exception of the FDA, CTEP, and the pharmaceutical (drug) company which manufactures 17AAG (Kosan Biosciences, Inc.) who may have access to your records, and the staff of the National Cancer Institute who may inspect and study your medical records. Your participation in this study does not constitute a promise of long-term care at the NIH Clinical Center.

Your participation in this study is voluntary, and you may refuse to participate or withdraw at any time. If you do take part in this study, you may not be allowed to take part in certain other research protocols. This is because researchers may not understand the effect of one research drug on another. The Principal Investigator or an Associate Investigator may end your participation in this study if they feel that termination is medically indicated due to side effects, progression of disease or compliance. Upon completing this study, you may be given the choice of taking part in other research protocols that may be appropriate for you or you will be referred to the care of your primary physician.

**Consent for tissue/ blood (specimen) banking**
During the course of this study, you may donate several different types of your tissue. Tissue blocks or slides from surgery you may have at the end of the study may be obtained with your permission. Samples of your blood and urine may be collected.

Some of the studies will be done as part of routine health care because you have VHL. These studies are clinical in nature and are done for your personal health. By federal regulation your name must be placed on some of the samples. You may receive results of these studies because they are performed in a certified laboratory.

Several types of research studies will be done on your blood and tissues. If you have kidney tumor surgery, we want to study the biochemistry and molecular changes in the tumor. Because these studies are basic research, you will not learn of specific results of the tests done in the research laboratories.
Your tissues that will be used for research purposes will not have your name on them. To maintain your confidentiality, your name will be removed and replaced by a code. Your coded tissues will be stored in the Urologic Oncology Branch at the National Institutes of Health in Bethesda MD.

The results of tissue/blood (specimen) bank research may help find new ways to learn about, prevent, or treat cancer and other diseases. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. If you have any questions, please talk to your doctor or nurse, or call the National Cancer Institute's Cancer Information Service at 1-800-422-6237 (1-800-4-CANCER).

1. Remaining tissue from my tissue/blood specimens may be kept for use in research to learn about, prevent, or treat cancer.
   
   Yes  No

2. Remaining tissue from my tissue/blood specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
   
   Yes  No

3. Someone from Dr. Marston Linehan's laboratory (at the NCI) may contact me in the future to ask me to take part in more research.
   
   Yes  No
OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have/your child has any problems or questions about this study, or about your/your child’s rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. W. Marston Linehan, Building 10, Room 2B-47, Telephone 301-496-6353.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

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<th>COMPLETE APPROPRIATE ITEM(S) BELOW:</th>
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<tr>
<td><strong>A. Adult Patient’s Consent</strong></td>
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<tr>
<td>I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.</td>
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<td>Signature of Adult Patient/Legal Representative Date</td>
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| **C. Child’s Verbal Assent (If Applicable)** |
| The information in the above consent was described to my child and my child agrees to participate in the study. |
| Signature of Parent(s)/Guardian Date |

THI S CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JANUARY 14, 2008 THROUGH JANUARY 13, 2009.

| Signature of Investigator Date | Signature of Witness Date |