CONSENT FOR CANCER RESEARCH

Project Title: CASE 1305 Fluorescence-guided Detection of Malignant Gliomas: A Dose Ranging Study Using 5-Aminolevulinic Acid (ALA) Induced Protoporphyrin IX (PpIX) in a Phase II Clinical Trial

University Hospitals Cleveland Medical Center Principal Investigator: Andrew Sloan, MD

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at University Hospitals (UH).

You have been asked to consider enrolling in a clinical trial (a type of research study) at University Hospitals Cleveland Medical Center. Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have a malignant brain tumor. You should take your time to make your decision and discuss it with your family and friends.

PURPOSE OF STUDY

The purpose of this study is to see whether 5-Aminolevulonic acid (5-ALA) can be used to locate the true outline or "edges" of the tumor. If the tumor outline could be accurately identified at the time of surgery, the fullest extent of tumor could be removed while sparing the normal brain tissue. You are asked to participate in a research study of the use of the drug, (5-ALA) to locate brain tumors in the operating room because you are likely to have, or have been diagnosed with a brain tumor, for which surgical removal (or "resection") is the standard of care treatment. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the proposed study procedures. The information provided in this document describes the purpose, procedures, benefits, discomforts, risks and precautions associated with this study. It also describes your right to refuse to participate or to withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should understand enough about its risks and benefits to be able to make an informed decision. This is known as the informed consent process. Please ask the study doctor or study staff to explain any words you don't understand before signing this consent form. Please make sure that all of your questions have been answered to your satisfaction before signing this document.

This study is investigating the accuracy of brain tumor margin (i.e., the edge or border of the tumor touching the normal brain tissue) detection using a fluorescent drug, 5-aminolevulinic acid (ALA) induced protoporphyrin IX (PpIX). About 120 patients are expected to participate in this trial. Accurately removing a brain tumor is challenging for a neurosurgeon. Most of the tumor can usually be found using an operating microscope and white light illumination, but the majority of brain tumors do not have clear edges and infiltrate or "spread into" normal brain tissue. This makes the finding and removal of the tumor edges particularly difficult. Accurately removing the entire tumor is of great importance; in case of a situation where all of the tumor is not removed the remaining tumor tissue may lead to the tumor growing again in the same area and a return of

your disease. On the other hand if too much of the brain is removed, the patient could suffer brain damage.

Fluorescence-guided detection using ALA may assist the neurosurgeon in accurately locating tumor edges that otherwise could go undetected under white light illumination. The use of ALA induced PpIX fluorescence in brain tumors is experimental, which means that the U.S. Food and Drug Administration (FDA) has not approved it for use to locate brain tumors. However, the use of the drug ALA for the purposes of this study is on file with the FDA (IND #72,005). ALA is a molecule that already exists in the cells of the human body. It is converted by the body to another molecule, PpIX. The higher concentration of PpIX in tumors has allowed other studies to identify cancerous and non-cancerous tissues. When you shine blue light on cancerous tissue, and if PpIX is present, it can emit red fluorescent light which can then be detected with a camera sensitive to that reddish color. This is what we call "Fluorescent-guided detection" because we are detecting cancerous tissue with fluorescent light.

ALA-based fluorescence of the tumor has been used in research studies of brain and bladder cancers to help surgeons locate and remove tumor tissue. In this study, we will not change the extent of surgery to be performed. We will only use the information from the study to determine the best ALA dose for accurate tumor margin (i.e., the border or edges of the tumor with the normal brain) detection so that no tumor is left behind. In future studies, we would potentially use this information to more accurately locate and surgically remove as much as possible, if not all, of the brain tumor. The purpose of this study is to determine whether in the future the use of intraoperative fluorescence imaging with ALA will enable more accurate tumor edge visualization. If that is the case it is expected that the use of ALA would allow more complete tumor resection, thereby improving life expectancy.

For this study, there will be 2 groups of patients: one made up of patients who have just recently been diagnosed with a malignant brain tumor and the other made up of patients whose malignant brain tumor has come back after previous treatment. Regardless of which group you are in, you will be randomized to one of 2 ALA dose levels: 10 mg/kg (milligrams of drug per kilogram of your body weight) or 20 mg/kg (milligrams of drug per kilogram of your body weight). Randomization is a process by which you are assigned a dose level by chance using a process similar to the flip of a coin. Neither you nor the study staff will select the group to which you will be assigned. However, this information can be obtained if you have a medical emergency.

STUDY PROCEDURES

If you agree to take part in the study you will contribute data to the study beginning at your next visit, the day of your surgery, and two days after your surgery if you tolerate the drug without any serious side effects. If a side effect of the drug is detected or suspected, the doctors will watch

you closely and monitor your health until symptoms of the side effects are under control.

If you enroll as a study participant, your next visit would take place in the preadmission department of University Hospitals Cleveland Medical Center, in the same way that it would if you were not taking part in the study. During this visit, the study doctor will ask you about your medical history and any medicine (e.g., vitamins, herbal products, prescription medications, etc.) that you are currently taking, and he or she will examine you. You will meet with a nurse practitioner to receive information in preparation for your surgery. Based on your physician's assessment of your past medical history, you may also be asked to meet with an anesthetist. Standard preoperative laboratory tests will be conducted prior to surgery, including the drawing of about 3 teaspoons of blood. For this study, we will also test the blood drawn to see if your liver is functioning normally.

As a study participant, your next (second) visit will occur the morning of your surgery. This procedure will be done at the Dahms Clinical Resources Unit (DCRU). You may need to check into the DCRU the evening before surgery to receive the ALA. Be sure to ask your study doctor or a member of his team if you are not sure when you should arrive. Before surgery, the study doctor will ask you about any new medications that you are taking and/or any medical problems you have had since your last visit. As a study participant you will be randomly assigned to an ALA dose level. You will drink the ALA diluted in water before surgery.

Your skin will be very sensitive to light after you take the ALA. Therefore, there will be precautions taken to be sure you are not exposed to either indoor or outdoor lights. After taking the ALA, you will be placed into a dark room with the shades closed and the lights turned off. When you leave the room, you will have any areas of exposed skin covered with a blanket and goggles or
sunglasses will be placed over your eyes. A member of the study team will review with you the steps you should take to avoid exposure to light and will provide you with an instruction sheet as you will need to avoid both indoor and outdoor light for at least 24 hours after taking the ALA.

As a study participant, fluorescence measurements will be taken two times during your tumor removal surgery. The first time will be when half of the tumor is removed. The second time will be at the end of the of tumor removal. At each time, a low power light will be used to light up the area and a fluorescence image will be taken. After your surgery has been completed, the removed tumor tissue will be examined by a pathologist, a doctor who examines tissue under a microscope, as would be done if you were not on the study. During the surgery, 6 small biopsies of the tumor will be taken. The biopsies will be taken from the center of the tumor, the tumor edge, area surrounding the tumor (if can be obtained safely), and areas seen to fluoresce (light up) during surgery. Approximately 0.1 gram of tissue is removed with each biopsy. Therefore, about one eighth of a teaspoon of tissue will be removed for later study. It is important to note that the

tissue removed for these biopsies would have been removed with or without your participation in this clinical trial. It would have been removed either because it was part of the tumor or to approach or expose the tumor. Therefore, obviously, removal of this tissue will not affect the surgical outcome because it would have been removed. These procedures and fluorescence biopsies will be completed as quickly as possible. If possible other aspects of the standard surgical procedure will be completed at the same time.

As a study participant, during your stay in the hospital following the procedure, a doctor will check to see if you have had any side effects from the ALA. Two 7 milliliter (1 ½ teaspoons each) blood samples will be collected to test your liver function 48 hours after your surgery. If these tests are abnormal, they will be checked weekly for 2 weeks and then monthly until they are normal again. You will not need to stay in the hospital for the sole purpose of these blood tests.

You will receive a separate consent form for the surgery itself.

RISKS

Your participation in this study will add approximately 5-10 minutes to the surgery during which your tumor is removed and anywhere from 2 to up to 12 hours at the DCRU to receive the ALA. These procedures and fluorescence biopsies will be completed as quickly as possible. If possible other aspects of the standard surgical procedure will be completed at the same time.

Your participation in the study involves the risks associated with taking the medication ALA. These risks include:

Skin and Eye Sensitivity: A 100% chance of skin and eye sensitivity to sunlight or other sources of very strong light for about 24 hours. This means that if you were to put your hand or face in direct sunlight for as short as 5-10 minutes during the first 24 hours after taking ALA, you might get a very bad sunburn or do damage to your vision. As a study participant you will receive written instructions about how to avoid very strong light in the first 24 hours after surgery.

Nausea or Vomiting: A 40% chance of mild nausea or occasional vomiting in the first 12 hours after ALA ingestion.

Abnormal Liver Test: A 20-40% chance for a rise in the value of some liver function blood tests. As a study participant you will have blood tests that monitor your liver function for two days after taking ALA and possibly after that if there are any abnormal liver function values found. If these tests show any abnormalities, you will continue to have these tests twice a week until the abnormal values disappear. Most people with these liver abnormalities do not feel unusual. The abnormal test result usually clears up in 3 days. For the first few days after surgery, these tests

will be taken at the same time as other necessary blood tests. So no additional blood will be drawn for this study and you will have no discomfort due to the most likely changes that will occur in your liver test results. If the liver tests need to be monitored for longer than 3 days post-operatively, the additional tests may result in some slight bruising on your arm where blood samples will be taken, as this can occur with any blood test.

These three effects have been seen in patients who were given higher doses of ALA, doses which are 3 to 30 times more than what you, as a participant in this study, will receive. The risks of sunburn, damage to your eyes, or liver problems are minimal if appropriate precautions are taken.

As a participant in this study you will receive instruction for the protection from light during the first 24 hours following your taking ALA. During your stay in the hospital immediately following surgery, precautions will be taken by your doctor, and nurses working with your doctor, to protect your skin and eyes from bright light. During this time you must avoid exposure to bright light. If bright light is unavoidable, then you must cover your skin with light blocking clothing and wear sunglasses and a hat. Sunscreen lotions have NOT been proven to be effective in protecting against this light sensitivity. You should avoid eye examinations, which utilize bright light during this period. If the guidelines in the information sheet are followed, no side effects are anticipated from the administration of ALA. After 24 hours have passed, and you have completed the test for photosensitivity as described in the information sheet that will be provided to you, it is recommended that you return to normal light exposure.

Other Risks: The risks of blood drawing include temporary discomfort from the needle stick, bruising, and, rarely, infection. As a participant in this study please understand that small tissue samples will be taken from the tissue surrounding your brain tumor. These tissue samples will only be taken when your surgeon can safely do so. The risk of taking these tissue samples is anticipated to be minimal.

As a participant in this study you must notify your doctor immediately should any adverse events or complications occur. You must understand that from the time you take ALA until you hear otherwise from your doctor or the nurse working with that doctor, that you should not take any drugs, including non-prescription drugs such as aspirin, without the approval of your doctor.

Please understand that adverse reactions are possible in any clinical research program despite the use of high standards of care and could occur through no fault of yours or the doctor involved. Because this study involves research, unforeseen reactions may also occur.

BENEFITS

As a participant in this study there is no direct benefit to you from taking the medication ALA because the operation itself will not be modified as a part of this study. However, your

participation in this study may aid in the testing of this new drug and may help other patients in the future.

ALTERNATIVES TO PARTICIPATION

Your decision to take part in this study is voluntary and if you refuse there will be no penalty or loss of benefits. In addition, you may withdraw from the study at any time without penalty or loss of benefits. If you decide to withdraw from the study, you are encouraged to contact the doctor conducting the study or clinic. They will explain the best way for you to stop taking part in the research study. You will be informed of any new findings that may affect your decision to remain in this study.

If you do not wish to participate in this study because it is adjuvant to (occur alongside) tumor resection, other available treatment options, such as radiation therapy or chemotherapy, will be made available to you. Your doctor will discuss with you the benefits and side effects of other treatment options.

FINANCIAL INFORMATION

As a participant in this study you are not responsible for the costs of the drug 5-aminolevulinic acid (ALA) you will receive. The drug will be provided free of charge. There will be no charge for blood tests, tumor biopsies or hospitalization done solely for research purposes. You will not be charged for the night you spend in the DCRU. However, you or your insurance company are responsible for the routine or standard of care (surgery, anesthesia, routine laboratory tests, urinalysis and images) for your disease. If you become ill or are physically injured as a result of participation in this study medical treatment will be provided. You will not receive reimbursement for taking part in this study.

U.S. NATIONAL INSTITUTES OF HEALTH (NIH) CLINICAL TRIAL DATABASE

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

HIPAA AUTHORIZATION SECTION

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

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Project Title: CASE 1305 Fluorescence-guided Detection of Malignant Gliomas: A Dose Ranging Study Using 5-Aminolevulinic Acid (ALA) Induced Protoporphyrin IX (PpIX) in a Phase II Clinical Trial

University Hospitals Cleveland Medical Center Principal Investigator: Andrew Sloan, MD

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Andrew Sloan, MD and the research study staff at University Hospitals for the purpose of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research includes:

- your name or initials, address, telephone number, fax number, email address, date of birth, and name of your physician(s);
- the history and diagnosis of your disease, including a family medical history;
- specific information about the treatment/therapy you received, including previous treatment/therapy you may have had, and previous surgery, hospitalizations and medications;
- information about other medical conditions that may affect your treatment, including information relating to Human Immunodeficiency Virus (HIV) status and prior treatment for Acquired Immunodeficiency Syndrome (AIDS);
- medical data, including physical exam findings, laboratory test results, tumor measurements, CT scans, MRIs, x-rays, ultrasounds and other radiologic scans, photographs of areas of disease and pathology results;
- information on side effects (adverse events) you may experience, and how these were treated;
- long-term information about your general health status and the status of your disease;
- data that may be related to tissue and/or blood samples that may be collected from you;
- numbers or codes that will identify you, such as your social security number, medical record number and study case number.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the University Hospitals Clinic Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Paul Muller, M.D., and his scientific colleagues in this multicenter clinical trial. Dr. Muller is at the Ontario Cancer Center at the University of Toronto/Princess Margaret Hospital (Canada).
- The University Hospitals Cleveland Medical Center Institutional Review Board, and any Institutional Review Board accrediting body;
- the Food and Drug Administration, the Department of Health and Human Services, Office of Human Research Protections, and other national and international governmental agencies and regulatory agencies;
- the National Committee for Quality Assurance and the Joint Commission for Accreditation of Healthcare Organizations; and
- laboratories that may be involved in testing a sample.

- your insurance company;
- Other staff from the Principal Investigator's medical practice group
- University Hospitals Cleveland Medical Center, including the Center for Clinical Research and the Law Department
- Government representatives or Federal agencies, when required by law.

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Andrew Sloan, MD
Department of Neurosurgery/Seidman Cancer Center
University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland OH 44106

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the University Hospitals Institutional Review Board assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

Voluntary Participation

Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or my willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Cleveland Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

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DISCLOSURE OF STUDY RECORDS

Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Cleveland Medical Center Institutional Review Board may review your study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records.. If your records are reviewed your identity could become known.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the University Hospitals Cleveland Medical Center's Research Subjects Rights Phone line at 216-983-4979.

You may call the National Cancer Institute's Cancer Information Services at:
1-800-4-CANCER (1-800-422-6237) or

You may also visit the NCI website at http://cancer.gov
- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo

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

US National Institutes of Health (NIH) Clinical Trial Database
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.

Emergency or after-hours contact information
If you have questions about this research study or develop a research-related problem, you should contact Dr. Andrew Sloan at (216) 844-6054. During non-business hours you should call the University Hospitals Cleveland Medical Center after-hours contact line at (216) 844-3591 and ask for the doctor from Neurological Surgery that is on call to contact the patient's study doctor.

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SIGNATURE

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about my participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____	_____	_____
Signature of Participant	Date	Printed Name of Participant

_____	_____	_____
Signature of Witness	Date	Printed Name of Witness

USE THIS WHEN A WITNESS IS USED IN THE CONSENTING PROCESS (Common examples include: Inclusion of illiterate individuals, blind individuals or individuals who cannot physically sign but are able to provide informed consent.)]

_____	_____
Signature of Person Obtaining Consent	Date

_____
Printed Name of Person Obtaining Consent