PATIENT INFORMED CONSENT

STUDY TITLE: Phase I Clinical Trial of HSV G207 Alone or With a Single Radiation Dose in Children with Recurrent Supratentorial Brain Tumors (UAB 1472)

IRB PROTOCOL NUMBER: IRB-150319005

PRINCIPAL INVESTIGATOR:

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SPONSOR: U.S. Food and Drug Administration**,** Kaul Pediatric Research Institute and the UAB Department of Pediatrics, Division of Pediatric Hematology and Oncology

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

You are being asked to participate in a clinical trial (a type of a research study) of an investigational product called G207 that is being tested as a possible treatment for patients with brain tumors. G207 is currently in clinical development and has not been approved by health authorities. You are being invited to take part in this study because you (or your child) have a progressive or recurrent brain tumor despite radiotherapy and/or chemotherapy. During your participation in this study, some participants will also receive a single dose of radiation within 24 hours of receiving G207. We want to find out if giving you an experimental virus treatment alone or in addition to the radiation therapy is safe and of benefit.

It is important that you understand the study, including the possible benefits and risks, before you decide to participate. This form gives you detailed information about the study. Please take your time to read it carefully and discuss it with your physician. Ask your physician if there is anything that is unclear or if you would like to receive further information. In addition you may take home a copy of this information and discuss it with your relatives and friends. You will receive a signed copy of this form, should you decide to participate.

WHY IS THIS STUDY BEING DONE?

This is a Phase 1 study of an investigational new drug called HSV G207. It is considered investigational because it has not been proven to work in recurrent or progressive brain tumors in children. We are using HSV G207 because it has been shown to be safe in Phase I trials in adults with brain tumors and some adults responded to the treatment. The goal of this study is to determine the highest safe dose (maximum tolerated dose) without causing severe side effects. We also want to learn what kind of side effects can be caused by G207 and what side effects can be caused by G207 when given in combination with a single dose of radiation therapy.

The study is planned to enroll three patients in each of 4 groups (cohorts). The first three patients will receive G207 at a starting dose of 1×10^7 plaque-forming units (infectious virus particles). If no severe adverse events occur, groups 2 will receive a higher dose of G207 (1×10^8). If no dose-limiting severe adverse events are seen, group 3 will receive the same dose of G207 as group 1 plus a single dose of radiation therapy. If no severe adverse events occur, group 4 will receive the same dose of G207 as group 2 plus a single dose of radiation therapy

G207 is an experimental herpes simplex virus (HSV). HSV causes cold sores and, rarely, causes a severe brain infection. G207 has been genetically changed and

weakened, in the hope that only cancer cells will be infected and killed by the virus, without harming normal brain tissue. A dose of radiation combined with G207 may increase the virus' ability to kill cancer cells. The purpose of this study is to test the human safety of G207 alone or combined with a single dose of radiation and see what effects (good or bad) it has on you (or your child) and your (their) brain tumor.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

It is anticipated that 12 patients will take part in the study. If significant side effects require changes in the dose, then between 4 and 24 patients will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you volunteer for this study, you will first have tests to see if you are suitable to be injected with G207. These include a medical history and a physical exam. Your vital signs (temperature, heart rate, breathing rate and blood pressure) will be measured. Your urine will be checked to make sure your kidneys are working. About 3-4 tablespoons of your blood will be collected by putting a needle into your vein or port, and that blood will be tested to check your general state of health, to make sure that you are not pregnant (if applicable), and to see if you have any unknown infections (including HIV infection). Some of that blood will also be used to see if you have ever had a herpes virus infection before. A small sample of your saliva and conjunctiva (mucous membrane (white surface of the eye) that lines the eyelid) will be collected by brushing a sterile cotton-tipped swab in your mouth and along the eyelid to see if you have a herpes virus infection right now. Lastly, a magnetic resonance image (MRI) of your head will be done to see how big your brain tumor is right now and its precise location. During part of the MRI procedure, a dye will be injected into your vein so that the tumor can be better seen. By the time the study is over, you will have up to 10 different MRI procedures done.

If you qualify for this study, you will be taken to the operating room and put to sleep for anesthesia. After you are asleep, you will have a metal frame placed around your head to help determine the exact site for virus infusion. The neurosurgeon will make a small opening in the skin over your skull and will cut a hole about the size of a dime in your skull. The hole will be needed to take a few pieces of tumor (each about the size of a grain of rice) so that the neuropathologist can determine if the tumor is growing back. If the tumor is growing back, the neurosurgeon will place one to four catheters (flexible tube) into the tumor which will come outside the scalp through the surgical opening and the skin will be closed around it. Most often one hole (the same hole made to take tumor pieces) will be used for the catheters but based on the location of the tumor and depending on the number of catheters placed, up to 4 holes may be made in the skull. A postoperative CT scan will be obtained to confirm the location of each catheter within the tumor. If needed, the

surgeon will adjust the position of the catheter tip by withdrawing it to a more desirable location. The catheter(s) will be hooked up to a syringe pump and the virus will be pumped in during a 6 hour infusion. After the infusion, the catheters will be removed. Once the virus given alone is shown to be safe, patients will receive a single dose of radiation at the UAB Hazelrig-Salter Radiation Oncology Center within 24 hours of the virus infusion. The radiation will be directed to the tumor area by a trained Radiation Oncologist. The radiation treatment is expected to take 10-30 minutes. If there are no complications after you recover, you will remain in a regular hospital room for an estimated 2-3 days to be watched, in case you have any side effects.

After leaving the hospital, you must call the clinic immediately if there are any problems. After the treatment, you will be required to return to the clinic for evaluation at 7, 14, and 28 days; 3, 5, 7, 9, 12, 18 and 24 months; and yearly thereafter for up to 15 years. Each time, you will have many exams and tests repeated, including a physical exam, blood tests and MRI scans, and your doctor will ask about side effects and about medications you may be taking. Patients who are unable to follow-up in person will be contacted by telephone on a yearly basis to monitor for delayed events.

During this study blood samples will be taken at each visit to check your general blood count, test your immunity and general state of health. About 1-2 tablespoons of blood will be taken each time. If you consent, blood in excess of what is needed for the tests and an additional teaspoon of blood will be banked for future studies. Swabs of your saliva and conjunctiva will also be collected at each visit. These will all be used to see whether you are able to infect others with the G207 you received. Additionally, if you consent, tumor tissue taken at the time of the biopsy or at a later time point if tumor is removed will be used to study features of the tumor which may help us predict in the future which patients are most likely to respond to HSV therapy. If you consent, any tissue not used will be banked for future studies.

Quality of Life and Parental Stress Assessments: We would like to learn more about the quality of life (physical, emotional, and social well-being) of children that are receiving G207 therapy and the quality of life of their parent(s). If you agree to take part in these optional assessments, you and/or your child will be asked to complete up to 5 surveys. These are expected to take less than 30 minutes and can be completed during a routine clinic visit. You will be asked to complete these surveys prior to receiving G207 therapy, and then 1, 3, 5, and 12 months after completing therapy. You do not have to do these optional research surveys if you do not want to, and you can still be in the study if you do not want to do these surveys. At the end of this consent there are questions for you to indicate if you want to take part in these optional research assessments.

If you stop the study early, we will also keep track of how you are doing from time to

time, for as long as possible. Therefore, we will keep your current address on file and you should be sure to tell us if you change your address. Should you die, no matter what the cause, permission from your family for an autopsy (after death medical examination) will be requested, unless you tell us that you would not want an autopsy done.

HOW LONG WILL I BE IN THE STUDY?

The main period of follow-up for this study is two years; however we would like to continue evaluations for up to 15 years. You may leave the study at any time, for any reason. However, if you consider stopping, we encourage you to talk to your doctor first. Your doctor may take you out of the study (even if you do not want to stop) if he or she feels that it is not safe for you to continue.

WHAT ARE THE RISKS OF THE STUDY?

G207 has been tested on very few people (less than 40), and little is known about side effects in humans. You may have some of the side effects mentioned below and you should discuss these with the study doctor and/or your regular doctor. There may also be side effects that we cannot predict. Many side effects will be of short duration, but in some cases side effects can be serious or long lasting or permanent.

Possible side effects from the infusion procedure, and from taking blood for special tests include:

- Bleeding or bruising
- Discomfort or pain
- Rarely infection or thrombosis (clotting)
- Lowered blood pressure resulting in lightheadedness, dizziness or fainting
- Allergic reactions to the contrast dye, other chemicals or band aids
- Damage to blood vessels

Potential side effects from the tumor biopsy and catheter(s) placement include:

- Allergic reaction to the anesthesia
- Bleeding into the tumor
- Discomfort or pain after the procedure
- Infection at the surgical site

Potential side effects from the removal of the catheter(s) include:

- Bleeding

Side effects that have been seen in patients shortly after experimental treatment

with G207 so far include:

- Headache
- Nausea
- Vomiting
- Diarrhea
- Decreased appetite
- Weakness
- Drowsiness
- Seizure
- Low red blood cell count
- Low platelet count
- Low white blood count
- Fever
- Fatigue
- Confusion
- Increased liver enzymes
- Skin infection
- Varicella zoster infection
- Pseudoprogression (transient enlargement of tumor on MRI)

Although not reported, side effects could include more severe reactions such as:

- Viral infections with flu-like symptoms and allergic reactions to G207, ranging from itching and hives to difficulty breathing
- Development of irritation or swelling of the brain including swelling due to HSV infection (encephalitis) and/or hepatitis. If there is concern for encephalitis, a CT scan or MRI scan will be performed and the antivirus drug acyclovir started. Surgical biopsy may be necessary. If there is concern for significant swelling at the tumor site due to pseudoprogression that cannot be controlled with medications, a CT scan or MRI scan may be performed and surgery may be recommended to remove dead tumor tissue and any residual tumor.

Potential side effects following radiation therapy include:

- Headache and nausea
- post-radiation swelling causing weakness, numbness, difficulty walking, seizures

Boys and girls that are able to have babies must take special care:

- Mothers may not breast-feed during the study

- Patients and partners of patients must practice an effective double-barrier (condom plus a second type of contraception prevention) method of birth control for a minimum of 2-months after G207 administration. There could be unknown risks to an unborn child or to the patient should pregnancy occur. If you are pregnant, you may not participate in this study.
- Patients may not donate sperm or eggs for 2 months following the G207 administration
- Patients should avoid intimate contact (including kissing, body fluid exchange, and sexual activity) for 2 weeks following infusion with G207. Close contact with pregnant women, infants and young children, elderly people, and those with weak immune systems (for example, those with HIV or AIDS), should also be avoided during this time period.

Potential side effects from CT scan:

You will receive a head CT scan to confirm placement of the catheters and if you are receiving radiation therapy, before radiation therapy. The radiation from each CT scan is approximately equal to 1 year of exposure to natural background radiation, and is much less than the radiation used in the radiation therapy. Background radiation is radiation normally received from sources such as cosmic rays and natural radioactivity in building materials and the ground. There is a small risk that the radiation may cause cancer or other radiation effects in several years.

To prepare you for your CT scan prior to radiation therapy, a liquid called a "contrast dye" will be injected into your veins to improve the quality of the image. There is a small possibility that you could have a severe allergic reaction to this dye that could cause injury or death. If you have any kidney problems, the dye may cause other medical problems.

• If you have any kidney problems or have ever had an allergic reaction to contrast dye, you must let the study physician know as soon as possible.

• If you are taking the drug metformin for diabetes, you should not take it on a day you are injected with contrast dye, or for two or three days after.

Potential side effects from MRI scans:

MRI has negligible risks for most people; however, if you have any metal objects in your body MRI may not be safe for you and you will not be allowed to take part in this study. During the exam, you will be in a small, enclosed space. If you suffer from a fear of enclosed spaces, or experience extreme anxiety during the exam,

please let the research staff know immediately.

To prepare you for your MRI exam, a liquid called a “contrast dye” will be injected into your veins to improve the quality of the image. There is a small possibility that you could have a severe allergic reaction to this dye that could cause injury or death. If you have any kidney problems, the dye may cause other medical problems. If you have any kidney problems or have ever had allergic reactions to contrast dye, you must let the study physician know as soon as possible.

Potential side effect from radiation therapy:
If you receive radiation therapy, the amount of radiation is much less than what is normally used to kill tumors. However, it can still damage normal tissue. To prevent this, the doctors will design the radiation therapy to avoid the most sensitive parts of the brain.

Common side effects include:

- Fatigue
- Hair loss
- Skin changes
- Swelling/edema
- Nausea
- Sexual effects (reduced desire)
- Blood clots

Less common but more serious side effects include:

- Neurologic deficits (this usually depends on the area of the brain being treated)
- Cognitive problems
- Seizures
- Headaches
- Additional cancers later in life

For more information about risks and side effects, speak with your doctor or ask the doctor in charge of the study: Dr. Gregory Friedman at 205-638-9285.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Your participation in this study may not be of any direct medical benefit to you. If you respond to this therapy, your tumor may shrink and your symptoms from the tumor may

improve. We hope that information learned from this study may help patients with brain tumors in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- Other research studies that your doctor may be aware of for the treatment of your type of cancer
- Treatment with therapies such as surgery, chemotherapy, or radiation (not part of a research study).
- Treatment to make you comfortable without any anti-cancer therapy. The investigator will discuss these options with you.

WHAT ABOUT CONFIDENTIALITY?

Information obtained about you for this study will be kept confidential to the extent allowed by law. We will do our best to keep your identity confidential and protect your privacy.

Organizations or individuals that have the right to inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Staff or agents of Aettis, Inc. (the company that owns the virus)
- The U.S. Food and Drug Administration (FDA)
- The National Institutes of Health (NIH)
- UAB's Institutional Review Board (IRB)

You will not be identified by name in any reports or publications resulting from this study. A copy of this consent document will be placed in your medical record at Children's of Alabama. Your medical record will indicate that you are on a clinical trial and will provide the name and contact information for the principal investigator.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of UAB and UAB Health System affiliated entities, along with Children's of Alabama and its billing agents so that the costs for clinical services can be appropriately paid for by either the study account or by the patient/patient's insurance.

Positive test results for HIV will be reported to the county health department as required by state law.

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.

WHAT ARE THE COSTS?

We will cover the costs of all evaluations and scans required by the study that are not part of your routine treatment and disease management. We will cover the costs of the placement and removal of the catheters, the virus and the infusion of the virus. Either you or your insurance company will be billed in the usual manner for routine medical care, tests, and for problems that are unrelated to your being in this study. This includes routine blood tests, x-rays, scans, medications you currently take or are prescribed and physician charges. The cost to you should not be more than it would be if you were not in this study. Financial assistance may be available, and we have a social worker who can work with you if needed.

WILL I RECEIVE PAYMENT FOR RESEARCH RELATED INJURIES?

UAB and Children's of Alabama have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge. Your doctor will arrange for the proper care and treatment for any injury resulting directly from being in this study.

Will I RECEIVE COMPENSATION FOR PARTICIPATION IN RESEARCH?

There is no compensation for participation.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Being in this study is voluntary. You may choose not to be in this study or you may leave this study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

You will be informed about any new information that may affect your health, welfare, or willingness to stay in this study.

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll, or withdraw after enrolling at any time before the study is over, with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

WHOM DO I CALL IF I HAVE PROBLEMS OR QUESTIONS?

If you have questions about this study, if you want more information about this study, or if you feel that you have been injured as a result of being in this study, you may call the doctor in charge of this study: Dr. Gregory Friedman at 205-638-9285. Dr. Friedman may also be reached after hours by paging him at 205-638-9100.

If you have questions about your rights as a research participant, or concerns or

complaints about the research, you may contact the UAB Office of IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at
1--800--4-CANCER (1-800--422-6237)
or TTY: 1-800-332-8615

Visit the National Cancer Institute Web sites:

Cancer Trials: comprehensive clinical trials information
http://cancertrials. nci.nih.gov.

CancerNet™: accurate cancer information
http://cancernet.nci.nih.gov.

SIGNATURE PAGES

I agree to participate in the quality of life assessments

Yes_____ No_____ Initials_____ Date_____

I agree to have any excess blood not needed for routine studies and an extra teaspoon of blood taken at the time of blood draws banked for use by researchers for future studies related to brain cancer or virus therapy

Yes_____ No_____ Initials_____ Date_____

I agree to have tumor tissue taken at biopsy or at a later time point if tumor is removed studied for features that may predict a response to HSV therapy

Yes_____ No_____ Initials_____ Date_____

I agree to have tumor tissue taken at biopsy or at a later time point if tumor is removed banked for use by researchers for future studies related to brain cancer or virus therapy

Yes_____ No_____ Initials_____ Date_____

Signatures for Participants Age 18

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Signature of Participant Date

I have carefully explained the purpose and procedures of this study to the patient. I certify by my signature that, to the best of my knowledge, the patient understands the nature, demands, risks and benefits involved by their participation in this study.

_____

Signature of Principal Investigator Date

_____

Signature of Person Obtaining Consent Date

Signatures for Research Involving Children

You are making a decision whether or not to have your child participate in this study. Your signature indicates that you have read (or been read) the information provided above and decided to allow your child to participate. You will receive a copy of this signed consent form.

_____

Signature of Participant 14-17 Years of Age Date

_____

Signature of Parent or Guardian of Participants 3-17 Years of Age Date

I have carefully explained the purpose and procedures of this study to the patient. I certify by my signature that, to the best of my knowledge, the patient understands the nature, demands, risks and benefits involved by their participation in this study.

_____

Signature of Principal Investigator Date

_____

Signature of Person Obtaining Consent Date

Waiver of Assent

_____

The assent of _____ (name of child/minor) was waived because of:

Age_____ Maturity_____ Psychological state of the child_____

University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF
PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____
Research Protocol: Phase I Clinical Trial of HSV G207 Alone or With a Single Radiation Dose in Children with Recurrent Supratentorial Brain Tumors

UAB IRB Protocol Number: IRB-150319005
Principal Investigator: Gregory K Friedman, MD
Sponsor: U.S. Food and Drug Administration, Kaul Pediatric Research Institute and the UAB Department of Pediatrics, Division of Pediatric Hematology and Oncology

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____