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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: **A Phase I Study of Convection-Enhanced Delivery (CED) of Liposomal-Irinotecan Using Real-time Imaging with Gadolinium in Patients with Recurrent High Grade Glioma**

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This is a clinical trial, a type of research study. Your study doctor, Dr. Nicholas Butowski, and his study team from the UCSF Department of Neurosurgery will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have a recurrent high grade brain tumor (glioma), which has grown or has recurred despite prior treatment.

Why is this study being done?

The study you are being asked to join uses a study drug called nano liposomal (NL) irinotecan delivered to your tumor using convection-enhanced delivery (CED). CED is a method of delivering the drug directly into the brain in order to improve the distribution of the drug throughout the brain. NL administration of study drug treatment is not approved by the Food and Drug Administration for use in brain tumors, but has granted Dr. Butowski permission to use it in this study. The primary purpose of this research study is to test the safety and tolerability of this drug delivered at different dose levels. We want to find out what effects, good and/or bad, it has on you and your brain cancer to help better understand your disease and to improve treatment for recurrent high grade gliomas. Dr. Butowski is receiving support from the National Institutes of Health and Ipsen Biopharmaceuticals, Inc to conduct this study. The study drug NL irinotecan will be provided by Ipsen Biopharmaceuticals, Inc

Patients with high grade gliomas that have recurred or grown despite having previous treatment may be eligible to participate in this study. If you participate in this study, NL irinotecan is given to you by CED infusion. NL irinotecan is mixed with a contrast agent called gadolinium and it is delivered directly into your tumor by 1-3 catheters surgically placed in your skull. You will undergo a magnetic resonance imaging scan (MRI) before insertion of the catheters and during the CED infusion to monitor the distribution of the drug.

How many people will take part in this study?

Approximately 24 patients will take part in this study at UCSF. There are two different drug concentration levels to this escalation study. At the beginning of the study, at least 3 patients will be treated with a lower concentration of the drug, with a total dose conformal to the shape and size of the tumor. If the rate of side effects is deemed acceptable, then subsequent patients will be enrolled at a second higher concentration. You can ask your study doctor what concentration and dose you will receive.

What will happen if I take part in this research study?

Before you begin the main part of the study...

You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated; this will be up to your study doctor.

The following screening procedures will be completed within 21 days of study drug infusion:

- **A history, physical examination, and neurological exam**: These exams will be similar to those done for your regular medical care. You will have vital signs taken, which will include measurements of your body temperature, blood pressure, heart rate, breathing rate, height and weight. Your complete medical history will also be recorded, including previous surgeries and any other prior treatments you have had, as well as any medications you are taking.
- **Karnofsky Performance status**: We will evaluate how well you are able to carry on with your usual activities.
- **Blood drawing (venipuncture):** You will be asked to give a blood sample for laboratory tests. Approximately 1-2 tablespoons of blood will be drawn by inserting a needle into a vein in your arm. These blood tests are used to evaluate the level of red blood cells, white blood cells and platelets, check how well your blood clots, and will check the function of your liver and kidneys as well as monitor your blood sugar levels.
- **Pregnancy Test:** If you are a woman of childbearing potential, you must have a negative pregnancy test done within 14 days prior to starting treatment
- **Brain MRI:** You will have a Magnetic Resonance Imaging (MRI) exam to assess your tumor For the MRI exam, you will lie down on a narrow bed that will then be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will need to lie there quietly for about one hour, during which time there will be a loud banging noise. You may feel warm during this procedure. Gadolinium (contrast material) will be injected into a vein in your arm. The dye makes tissue and organ more visible in the MRI.
- **UGT1A1 genotyping:** Can be acquired from an outside screening facility, and is not necessary for eligibility

During the main part of the study…

If the exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, you can continue on in the study. You will be placed in one of the following two concentration cohorts/groups. The total dose that you will receive will depend on the size of your tumor, which will be determined by your study doctor.

Tumor Diameter (cm)	Tumor Volume (cm^3)	Required volume of injection (ml)	cohort 1 (mg) 20mg/ml	cohort 2 (mg) 40mg/ml
1cm	~0.5cm^3	2-3	40 - 60	80 - 120
2cm	~4.1cm^3	3-4	60 - 80	120-160
3cm	~14cm^3	6-7	120-140	240-280
4cm	~34cm^3	Up to 17	Up to 340	Up to 680

Within 48 hours prior to CED Infusion

The following study procedures will be done within 48 hours of the CED infusion:

- Physical Examination
- Neurological Examination
- Karnofsky Performance Status
- Vital signs
- Review of your medical symptoms
- Review of your concomitant medications
- MRI with DTI brain for catheter placement planning by iPlan® Flow to determine the optimal positions for IT catheter placement with the intent to place 1-4 catheters into the tumor.
- Research Blood Test- approximately 1 teaspoon of blood to assess how your body affects the study drug

Day of CED Infusion

- Vital signs
- You will undergo general anesthesia. 1-4 catheters will be surgically placed in your brain tumor and checked by MRI or CT scan for accuracy.
- After recovery from anesthesia (0-24 hours after catheter placement) you will be transferred to an MRI suite where you will be put into the MRI machine. The CED infusion of NL irinotecan mixed with gadolinium will be started.
- A research blood test will be done approximately 1 hour post infusion
- Note, you will likely be admitted to hospital for 1-3 nights. Prior similar studies demonstrate that most patients can be discharged from hospital within this time frame barring unforeseen complications.

When you are finished receiving the CED infusion...

End of Infusion

- MRI following the completion of the study drug infusion
- Physical examination
- Neurological Examination

- Karnofsky Performance status
- Vital signs
- Review of your medical symptoms
- Review of your concomitant medications

1 Day after CED infusion

These procedures will be completed 1 day after CED infusion:

- Physical examination
- Neurological Examination
- Karnofsky Performance status
- Vital signs
- Review of your medical symptoms
- Review of your concomitant medications

7 days after CED infusion

- Research blood test

14 days after CED infusion

These procedures will be completed 14 days after CED infusion:

- Physical examination
- Neurological Examination
- Karnofsky Performance status
- Vital signs
- Review of your medical symptoms
- Review of your concomitant medications
- Blood drawing

30 days after CED infusion

These procedures will be completed 30 days (± 3days) after CED infusion:

- Physical examination
- Neurological Examination
- Karnofsky Performance status
- Vital signs
- Review of your medical symptoms
- Review of your concomitant medications
- Blood drawing
- Brain imaging (MRI)

Post-treatment/Follow-Up Visits

After your day 30 visit, you will be followed every 8 weeks for 12 months, and then per standard

of care after that, until your disease has progressed. The following procedures will be performed at the Follow-Up Visit(s):

- Physical examination
- Neurological Examination
- Karnofsky Performance Status
- Vital signs
- Review of your medical symptoms
- Review of your concomitant medications
- Blood drawing

Brain imaging (MRI)

End-of-Treatment Study Procedures

The following procedures will be performed within 30 days when 12 months have passed after the CED infusion or at progression:

- Physical examination
- Neurological Examination
- Karnofsky Performance Status
- Vital signs
- Review of your medical symptoms
- Review of your concomitant medications
- Blood drawing
- Brain imaging (MRI)

How long will I be in the study?

You will be clinically examined and have a scan 30 days after the CED procedure, then you will have clinical exams and scans performed every 8 weeks for 12 months, and then per standard of care, until your tumor grows or your study doctor has determined that it would be unsafe for you to continue in the study.

You will continue on the same schedule unless:

- Your tumor grows.
- You desire to stop treatment.
- The researcher may decide to take you off this study if your doctor thinks it will be in your best interest, your condition worsens, or new information becomes available.
- The Sponsor also has the right to terminate the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the

study drug and procedures can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the study drug infusion has stopped. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

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

Risks and side effects related to the CED infusion include those which are:

Likely

- Pain at the insertion sites for the catheters
- Headache
- Fatigue
- Light headed feeling that should pass in a day

Less Likely

- Moderate to severe headache which should be treatable with medication
- Nausea

Rare but serious

- Infection at the site of catheter placement
- Bleeding into the brain from the catheter placement
- Brain swelling with resulting severe headache requiring medication
- Neurological worsening affecting movement and sensation
- Potential blood vessel injury resulting in stroke

Risks and side effects related to NL irinotecan include those which are:

Likely

- Nausea
- Mild headache
- Fatigue
- Loss of appetite

Less Likely

- Stomach upset with Diarrhea
- Vomiting
- Dehydration

Rare but serious

- Decreased number of white blood cells
- Decreased number of platelets

Risks and side effects of commercial irinotecan

It is unknown whether or not the side effects for the commercial formulation of Irinotecan (CPT-11) will occur with this formulation (NL CPT-11), but as a precautionary measure, any additional risks for Irinotecan are listed below.

Likely

- Sleepiness
- Flushing
- Abnormal heart rate
- Runny nose
- Allergic reaction
- Rash

Rare

- Pneumonia
- Confusion
- Cracking and peeling of hands and feet
- Changes in color of finger and toe nails
- Colon inflammation or infection (which can cause blood in the stool)

Neutropenia (an abnormally low number of white blood cells in the blood) and/or late diarrhea (diarrhea generally occurring more than 24 hours after irinotecan administration) have been reported as side effects experienced by subjects in irinotecan studies that prevented treatment with irinotecan. Other common side effects include nausea and vomiting, loss of appetite, abdominal cramping, infection, alopecia (loss of hair), asthenia (weakness), lymphocytopenia (low white blood cell count in the blood), and anemia (low red blood cell count).

Dehydration has occurred as a result of diarrhea, particularly when associated with severe vomiting. There may also be an acute syndrome of lacrimation (secretion and discharge of tears), diaphoresis (profuse sweating), abdominal cramping, and early diarrhea (during or shortly after irinotecan administration).

Other risks that may occur because of participation in this study include the following:

- **The risks of catheter placement and CED infusion:** This procedure, like any neurological procedure, carries neurological and anesthetic risks (less than 10% of the time). Your Neurosurgeon and Anesthesiologist will discuss these procedures and risks with you. Risks include infection, bleeding in or around the brain, brain swelling with headache, vomiting, seizures, sleepiness, coma, weakness or changes in neurologic function (worsening of

symptoms or appearance of new symptoms). Side effects may also include spinal fluid leaking, paralysis, sensory loss, difficulty with language or intellect, pneumonia, air in the lungs, airway injury, low blood pressure, heart attack, stroke, liver or kidney damage, or death. Other side effects related to infusion of fluid into tumor include vomiting, seizures, coma, weakness, or other neurological symptoms depending on the location of the tumor. Spread of tumor along the catheter is possible though unlikely. Close monitoring for these symptoms will take place during infusion. Specific to this study, the combination of CED and the study agent, NL CPT-11, may result in blood vessel damage and resulting stroke; this was seen in one patient on his 30 day post-CED MRI. However, it is felt that the procedure itself may result in such an outcome.

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.

- **MRI risks:** Because the MRI machine acts like a large magnet, it could move iron- containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

  Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

  Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

- **Contrast agent (gadolinium) risks**: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than on in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

  Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

- **Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

- **Radiation Risks:** There are no radiation risks beyond routine clinical care. This study involves radiation exposure as part of routine clinical care. You will not receive additional radiation as a result of participating in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

- One patient, treated at the 40mg/ml experienced confusion for 1-2 days post study agent administration. This patient did recover back to baseline two days later.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that CED infusion of NL irinotecan will be more useful against cancer compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about CED infusion of NL irinotecan as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study.
- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before deciding if you will take part in this study.

How will my information be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality

assurance, and data analysis include:

- Governmental entities that have the right to see or review your health information, such as the Office of Human Research Protections, the Food and Drug Administration, and regulatory agencies in the U.S. and other countries, as well as the National Cancer Institute (NCI)
- Ipsen Biopharmaceuticals, Inc
- University of California

What are the costs of taking part in this study?

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer. Ipsen Biopharmaceuticals, Inc is supplying NL at no cost to you. Additionally, the following tests and procedures are covered by the study budget and there will be no charge to you:

- CED catheters, CED catheter placement, CED NL administration and the procedure, including MRI and anesthesia
- Hospitalization following the CED procedure for 1-3 days. In addition, all of the research blood tests will be paid for by the study sponsor. Any additional non-standard of care MD visits and clinical labs will be covered by the study

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call **1-800-4-CANCER (1-800-422-6237)** and ask them to send you a free copy.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor or Dr. Nicholas Butowski if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her [redacted].

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California or the Ipsen Biopharmaceuticals, Inc depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may

call the office of the Committee on Human Research at 415-476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor or Dr. Nicholas Butowski [redacted].

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

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.

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CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

_____	_____
Date	Participant's Signature for Consent
_____	_____
Date	Person Obtaining Consent
_____	_____
Date	Witness – Only required if the participant is a non-English speaker