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May 15, 2025

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #2 to protocol **ACNS1931**, *A Phase 3 Study of Selumetinib (NSC# 748727, IND#* [redacted] *or Selumetinib in Combination with Vinblastine for non-NF1, non-TSC Patients with Recurrent or Progressive Low-Grade Gliomas (LGGs) Lacking BRAF^{V600E} or IDH1 Mutations*

Amendment #2 to ACNS1931 is being submitted in response to a Request for Rapid Amendment (RRA) from Dr. Lorraine Pelosof (lorraine.pelosof@nih.gov), dated May 01, 2025. In this amendment, the revised CAEPR for Selumetinib (Version 2.11, dated February 25, 2025) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised. Revisions to both the protocol and consent documents are detailed in the pages below.

Administrative changes have been made; specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please let me know if you have any questions or need additional information.

Sincerely,

Natasha Mirt, Protocol Coordinator (for)

Daniel Bowers, MD, ACNS1931 Study Co-Chair,
Daphne Haas-Kogan, MD, ACNS1931 Study Co-Chair,
Maryam Fouladi, MD, CNS Committee Chair, and
Douglas S. Hawkins, MD, COG Group Chair

SUMMARY OF CHANGES: INFORMED CONSENT PART A

In accordance with the above discussion, the following specific revisions have been made to the consent. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	All	Updated version date of consent to match the current version of the protocol.
2.	Risks of Study	8-9	In response to a Request for Rapid Amendment (RRA) from Dr. Lorraine Pelosof, Dated May 1, 2025, the Selumetinib risk profile has been updated.

3.	Attachment 2	18-19	In response to a Request for Rapid Amendment (RRA) from Dr. Lorraine Pelosof, Dated May 1, 2025, the Selumetinib risk insert has been updated as follows:
			• Added New Risk:
			  • Occasional: Liver damage which may cause yellowing of eyes and skin, swelling; Swollen or broken skin around the nail which may cause redness (paronychia); Potential liver damage (Alanine aminotransferase increased and Aspartate aminotransferase increased); Muscle pain/muscle breakdown (CPK increased)
			  • Rare: Cloudiness of the eye, visual disturbances; Glaucoma; Blockage of internal organs which may cause inability to pass stool; Blood infection; Bleeding (increased risk of bleeding given the vitamin E levels in the capsules)
			• Increase in Risk Attribution:
			  • Changed to Occasional from Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Change in hair color
			  • Changed to Rare from Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Seeing spots before eyes; Discomfort from light, visual loss; Damage to muscle which may cause muscle pain, dark red urine; Redness, pain or peeling of palms and soles
			• Decrease in Risk Attribution:
			  • Changed to Occasional from Common: Rash
			  • Changed to Also Reported on Selumetinib Trials But With Insufficient Evidence for Attribution from Rare (i.e., removed from the Risk Profile): Damage to lungs which may cause shortness of breath

			• Deleted Risk:
			  • Rare: Damage to eye causing blurred vision or blindness; Vision changes; Blood clot in the eye which may cause blurred vision or blindness
			
			• Provided Further Clarification:
			  • Belly pain (under Common) is now reported as Pain (under Common)

4.	Attachment 2	19	Deleted: • "~~some patients may develop a nail disease (also known as paronychia) that is an often-tender infection of the hand or foot where the nail and skin meet at the side or the base of a finger or toenail~~". These risks are now included in the risk insert tables.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions must use the sections of this document that are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ACNS1931: A Phase 3 Study of Selumetinib (NSC# 748727, IND# [redacted] or Selumetinib in Combination with Vinblastine for non-NF1, non-TSC Patients with Recurrent or Progressive Low-Grade Gliomas (LGGs) Lacking BRAFV600E or IDH1 Mutations

Study Title for Study Participants:

A Study to Compare Treatment with the Drug Selumetinib Alone vs. Selumetinib and Vinblastine in Patients with Recurrent or Progressive Low-Grade Glioma

CONSENT 1: FOR SUBJECTS IN PART A (SAFETY PHASE) ONLY

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.

Overview

You are being asked to take part in this research study because you have been diagnosed with a cancer called low-grade glioma (LGG). You have previously been treated for your LGG and it is considered recurrent or progressive because the tumor has not responded to the treatment or has returned after treatment.

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

The overall goals of this study are:

1) To find the highest dose of vinblastine that can be given safely in combination with selumetinib. This is Part A of the study.
2) To see if selumetinib and vinblastine together work better than selumetinib alone for subjects with recurrent or progressive LGG. This is Part B of the study.

This consent form describes treatment in Part A of the study. The treatment involves cancer fighting medicine called chemotherapy with the drugs selumetinib and vinblastine. The treatment on this study takes about 27 months. You will receive 17 cycles of selumetinib and vinblastine together and then you will receive a further 10 cycles of selumetinib alone.

Subjects are people who agree to take part in this study. All subjects will receive selumetinib at the same dose but the dose of vinblastine will vary. The dose of vinblastine given with selumetinib for the first subjects enrolled on the study will be one dose level below the recommended dose for vinblastine when given alone. If the side effects are not too severe, the next group of subjects will receive a higher dose of vinblastine. If side effects are too severe, the next group of subjects will receive a lower dose of vinblastine. Dosing is done this way because we do not yet know the best dose of vinblastine to use when given with selumetinib.

If you are enrolled early in this study you may receive a lower or higher dose of vinblastine than those who are enrolled later. A lower dose may be less likely to have any effect on your tumor. Whatever dose you start at, your dose will not be increased. If you are assigned to a higher dose level you may be more likely to have side effects. If you have bad side effects, your dose may be decreased. Up to 3 different doses of vinblastine in combination with selumetinib may be studied.

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished.

This study uses the investigational drug selumetinib. Common side effects of this drug are diarrhea, nausea, swelling of the body, tiredness, acne, and rash. Some less common but notable side effects are constipation, vomiting, dry mouth, sores in the mouth, and loss of appetite. The full list of risks for selumetinib are available in Attachment 2.

You can ask your study doctor questions about side effects at any time.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the section Are there benefits to taking part in the study?

You have a choice between another treatment for LGG and this clinical trial.

The rest of this form provides detailed information about the study and what to expect should you decide to participate.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you have been diagnosed with low-grade glioma (LGG). Your LGG is considered recurrent or progressive because the tumor has not responded to treatment or has returned after prior treatment.

A glioma is a type of cancer that occurs in the brain or spine. Glioma is considered low-risk (or low-grade) when it is growing slowly and not spreading quickly to other parts of your brain or body. The term, risk, refers to the chance of the cancer coming back after treatment.

You previously had pre-screening tests done on another study called APEC14B1 which you consented to. Those tests looked for genetic changes (called mutations) in your cancer cells including *BRAF*^{V600E} and *IDH1*. The pre-screening tests confirmed that you have an LGG without a *BRAF*^{V600E} or *IDH1* mutation. Because of this, the study doctors have determined that you are eligible for this study, ACNS1931.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients.

This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between another treatment for LGG and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?

We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point. Treatment options for LGGs that come back after initial treatment may include different chemotherapy drugs (cancer fighting medicine) such as vinblastine.

Why is this study being done?

The best treatment option for LGGs that come back after initial treatment is uncertain and doctors want to improve treatment by reducing short-term and long-term side effects and improving patients' quality of life during treatment. The pre-screening tests that you had done on APEC14B1 showed that you have an LGG that does not have a *BRAF*^{V600E} or *IDH1* mutation. Previous studies have shown that patients with LGG may benefit from a new type of treatment like the one we will test on this study.

This study looks at how well selumetinib and vinblastine work when given together to children and young adults with recurrent or progressive LGGs. Vinblastine is often given to children with progressive or recurrent LGGs. Selumetinib is a drug that works by blocking a protein (a basic building block of the human body) that lets cancer cells grow without stopping. Early studies with selumetinib have had some success in treating patients with LGG that came back after a first attempt at treatment. However, the use of selumetinib in children and young adults with recurrent or progressive LGG is considered experimental because selumetinib has not yet been FDA approved for this type of cancer.

The study doctors want to find out what the highest combined dose of selumetinib and vinblastine is that will be well-tolerated in children and young adults with recurrent or progressive LGGs. We also want to see if selumetinib in combination with vinblastine works better than selumetinib alone for getting rid of or shrinking LGGs and stopping them from coming back. In addition, study doctors want to see if treatment affects quality of life or will lessen long-term side effects from the disease, such as problems with vision.

The overall goals of this study are to:

- **Find the highest dose of the combination treatment of selumetinib and vinblastine that we can give safely.**
- **Compare the effects, good and/or bad, of selumetinib alone versus selumetinib with vinblastine in subjects with progressive or recurrent LGG to find out which is better.**

What will happen on this study that is research?

The treatment involves cancer fighting medicine called chemotherapy. Subjects in Part A will receive both selumetinib and vinblastine. The treatment on this study takes about 27 months. The combination treatment of selumetinib and vinblastine will be given for 17 months and selumetinib alone will be given for an additional 10 months.

There are 2 parts to this study. <u>You are being asked to participate in Part A.</u> Subjects that participate in Part A of this study will not be able to participate in Part B.

<u>Part A, Dose Confirmation</u>
In Part A of this study we will find out the highest dose of vinblastine that can be given in combination with selumetinib without causing side effects that are too severe. All subjects will receive selumetinib at the same dose but the dose of vinblastine will vary.

The dose of vinblastine given with selumetinib for the first subjects enrolled on the study will be one dose level below the recommended dose for vinblastine when given alone. Between 2 and 6 subjects will receive selumetinib and vinblastine at each dose. If the side effects are not too severe, the next group of subjects will receive a higher dose of vinblastine. If side effects are too severe, the next group of subjects will receive a lower dose of vinblastine. Dosing is done this way because we do not yet know the best dose of vinblastine to use when given with selumetinib.

If you are enrolled early in this study you may receive a lower or higher dose of vinblastine than those who are enrolled later. A lower dose may be less likely to have any effect on your tumor. Whatever dose you start at, your dose will not be increased. If you are assigned to a higher dose level you may be more likely to have side effects. If you have bad side effects, your dose may be decreased. Up to 3 different doses of vinblastine in combination with selumetinib may be studied to find the highest dose that will be well-tolerated. Once that dose is determined, we will treat 6 more subjects at that dose so as to better understand the side effects of the combination therapy.

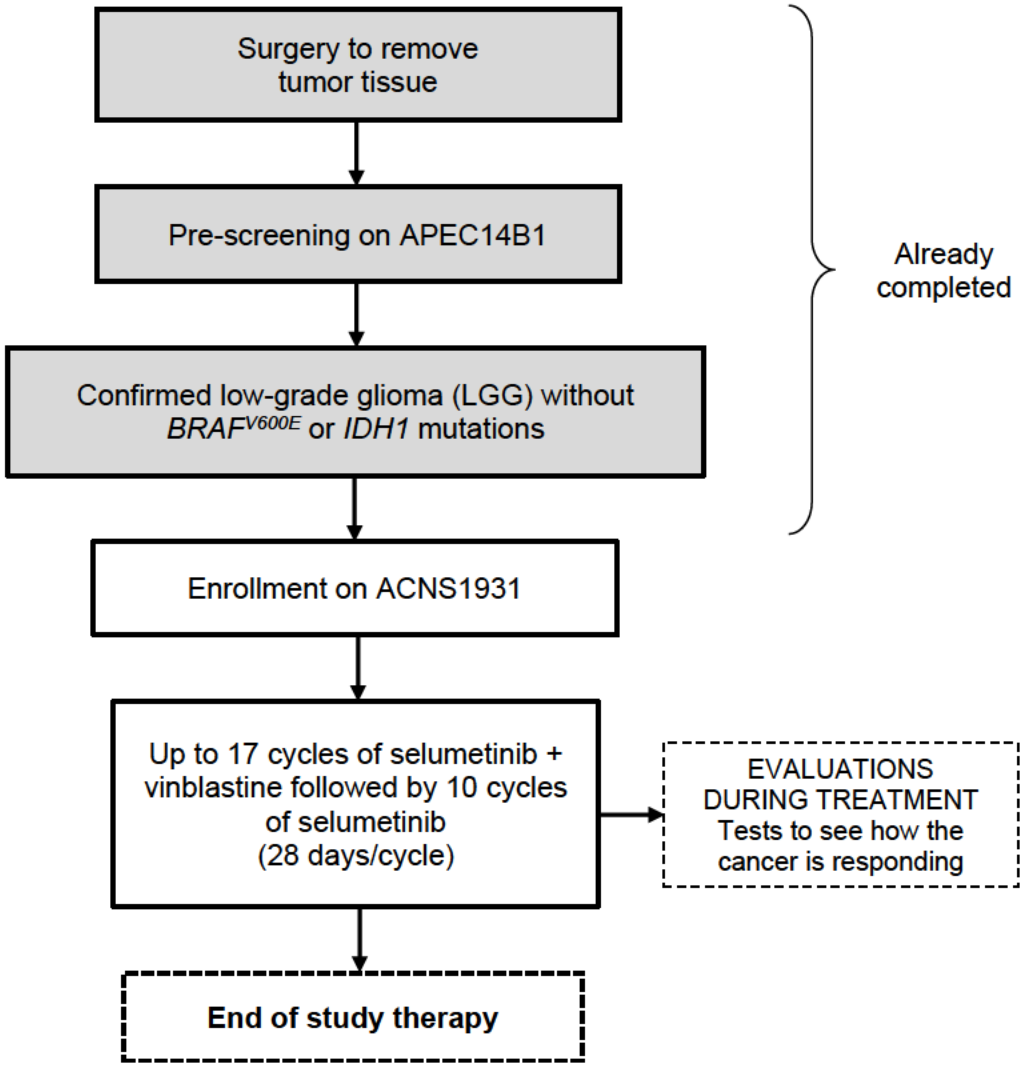
Once we have determined the highest dose of vinblastine to give with selumetinib, we will move on to Part B of this study.

Part B

In Part B, subjects will receive either selumetinib and vinblastine or selumetinib alone. Subjects in Part B who are assigned to receive the combination treatment of selumetinib and vinblastine will be given the dose of vinblastine found in Part A. We will treat more subjects with recurrent or progressive LGG in order to examine and compare the effects of the combination treatment with selumetinib alone.

Diagram of Treatment

This chart shows the treatment on Part A of this study.



Note: If your tumor gets bigger at any time during treatment or if side effects are too severe, you will stop study therapy and your doctor will discuss other options with you.

Experimental parts of treatment

The selumetinib treatment being given on this study is considered experimental because it has not yet been approved for the treatment of recurrent or progressive LGG. It is being given along with the commonly used drug vinblastine.

Detailed study treatment tables are found in Attachment 1.

Additional Required Research Study Tests

The following tests will be done because you are part of this study. If you were not in the study you may not have all these tests done. The results of these tests will not be returned to you unless otherwise stated below.

Copies of the scans used to diagnose the cancer will be sent to a central review center to help confirm findings.

Procedures that are common to all patients with LGG are described in Attachment 1.

Quality of Life (QOL): (for patients able to complete testing in English or Spanish)
This testing is required if you take part in this study but may be done even if you do not participate in this study. The study doctors would like to learn more about the effects of treatment for subjects on this study. Brain tumors and cancer treatment can affect quality of life. Your participation in these tests will help us better understand how these therapies affect quality of life.

We will ask you and your parent/guardian to fill out questionnaires that measure your quality of life. You and your parent/guardian will complete these questionnaires during your clinic visits at 3 different times while you are on this study: (1) study entry, (2) 6 months after starting treatment, and (3) 17 months after starting treatment. These sessions will take about 8 minutes to fill out the questionnaires.

While rare in our experience, parents filling out the questionnaires about their child's everyday thinking and learning can feel worry. If any questions make you feel uncomfortable, please speak with a psychologist or other study team member.

Additional Optional Research Study Tests

Biobanking
We would like to take some samples for future research. This is called "specimen banking" or "tissue banking." A tissue bank is a lab where specimens (such as tumor, blood or bone marrow) are kept for use in future research studies.

As part of your regular care, your doctor may have removed some tumor tissue. If any of this tissue is left over and no longer need for your medical care, we would like to keep some of this tissue. Obtaining this sample will not require extra surgery.

We would also like to collect about 1-2 teaspoons of blood (5-10 mL) before you start treatment. The blood would be taken when blood is drawn for other standard tests and would not require any extra needle sticks.

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

Treatment Risks
All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

The risks of the individual drugs given are listed in **Attachment 2**.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished.

Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. Parents will be taught more about caring for their child when his or her blood counts are low.

Risks of Study
The use of experimental treatment (selumetinib in combination with vinblastine) instead of other available treatments may cause more complications.

The experimental treatment that is being studied could be less effective than other available treatments.

You may lose time at school, work or home and spend more time in the hospital or doctor's office than usual. You may be asked sensitive or private questions which you normally do not discuss.

The chemotherapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

If you choose to take part in this study, there is a risk that the selumetinib (AZD6244 hydrogen sulfate) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The selumetinib (AZD6244 hydrogen sulfate) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables in Attachment 2 show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Reproductive risks

Women should not become pregnant and men should not father a baby while on this study and for 12 weeks after stopping study therapy because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex 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 birth control methods might not be approved for use in this study. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include:

- getting rid of your cancer for a long time or for the rest of your life
- fewer side effects,
- fewer long term side effects (for example, being less likely to develop problems with the heart, lungs, kidneys; being less likely to have learning problems, or, less risk of getting another cancer later as a result of treatment),
- better vision or less vision loss for patients with optic pathway tumors.

With any cancer treatment, sometimes treatment does not make the cancer go away. Or, sometimes treatment makes the cancer go away for a while but the cancer comes back later.

Information learned from this study may benefit other patients in the future.

What other options are there?

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

- **Getting treatment for your cancer without being in a study.**
- **Taking part in another study.**

Please talk to your doctor about these and other options.

How many people will take part in the study?

Up to 40 people will take part in Part A of this study and up to 260 people will take part in Part B of this study.

The total number of people enrolled on this study is expected to be 300.

How long is the study?

People in this clinical trial may receive treatment on this study for about 2 years. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health for about 10 years after you enter this study. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you
- if you become pregnant
- if you begin breastfeeding

What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Children's Oncology Group has a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the Children's Oncology Group will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in **Attachment 3**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group and research partners**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research.**
- **The Institutional Review Board of this hospital**
- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The study sponsor and any drug company supporting the study or their designated reviewers.**

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate

you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The NCI will supply the selumetinib at no charge while you take part in this study. The NCI does not cover the cost of getting the selumetinib ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the selumetinib to the NCI for some reason. If this does happen, other possible options are:

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

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing specimens to the researcher, there are no plans for you to profit from any new product developed from research done on your specimens.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/).* To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all people on the study is completed, and not only when you complete treatment.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* Institutional Review Board (IRB) Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

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

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Specimens for Optional Biobanking

If you agree to Biobanking, your sample will be stored in the *Biopathology Center at Nationwide Children's Hospital, in a locked location*. The Biopathology Center is supported by the NCI. The samples will be kept until they are used up, unless you request that they be destroyed. Some information from your medical record will also be kept in secure databases at the Biobank and updated from time to time. The information and samples will be kept under a code, not your name.

This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. Qualified researchers can submit a request to use the materials stored in the Biobank. The research may be about your type of cancer, about other cancers, or even about conditions unrelated to cancer. A science committee at the Children's Oncology Group, and/or the National Cancer Institute, will review each request. The goal of this is to make more research possible that may improve people's health. Researchers will not be given your name or any other information that could directly identify you. Your sample will not be sold to third parties. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples, unless something is discovered that could directly affect your health. If that happens your study doctor will be notified and will decide whether and how to contact you.

Right now, we don't know what research may be done in the future using your samples. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

Some of your genetic and health information may be placed in central databases that may be made available to qualified researchers, along with information from many other people. Information that could directly identify you will not be included.

Even without your name or other identifiers, your genetic information is unique to you. If you agree to Biobanking, there is a risk of a data security breach and that someone could trace the genetic information in a central database back to you. Although this has never happened in real life and we have many safeguards in place to prevent it from happening, the risk may change in the future as people come up with new ways of tracing information. There are laws against the

misuse of genetic information, but they may not give full protection. In some cases, misuse of the information could be used to make it harder for you to get or keep a job or insurance.

There can also be risks in learning about your own genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. Sometimes this is upsetting to families or they wish they didn't know the information. We encourage you to discuss this study with your relatives before you decide whether to participate in the Biobanking part.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: https://www.cancer.gov/publications/patient-education/providing-tissue.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

1) Check YES if you agree to have samples kept (banked) for use in research to learn about, prevent, or treat cancer or other health problems (for example: diabetes, Alzheimer's disease, or heart disease). Check NO if you do not want samples banked.

Yes _____ No _____ _____ / _____
Initials Date

Signature

I have been given a copy of all _____ pages of this form. The form includes 2 attachments.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

Attachment 1

Treatment and Procedures Common to all Patients with LGG

Methods for Giving Drugs

Various methods will be used to give drugs:

- **PO** - Drug is given by tablet or liquid swallowed through the mouth.
- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").

Central Line

Your doctor may recommend that you get a special kind of IV called a "central line." This is a kind of IV placed into a big vein in your body, usually in the chest, that can stay in for a long time. The risks connected with central lines will be explained to you and all of your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign for this procedure. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

Treatment Tables

The treatment described below is the full study treatment for patients with recurrent or progressive LGG.

You will receive 17 cycles of selumetinib and vinblastine together, and then you will receive a further 10 cycles of selumetinib alone. You will receive up to 27 cycles of therapy in total. Each cycle lasts 28 days (4 weeks).

Drug	How the drug will be given	Days	Cycles
Selumetinib	PO (by mouth) twice daily	1-28	1-27
Vinblastine	IV over 1 minute*	1, 8, 15, and 22	1-17

* Or may be given as a short IV infusion by some institutions

Selumetinib capsules must be swallowed whole. Selumetinib should be taken on an empty stomach 1 hour before or 2 hours after food. If you vomit within 15 minutes after taking the medication, you may repeat the dose once.

You will be given instructions on how to take selumetinib. You will also be given a medication diary to fill out at home each time selumetinib is taken. Use the diary to record the date and time you take the drug, the number of capsules taken, and any side effects you experience. Also record in the diary other medications and/or supplements you are taking and whether you vomited or missed a dose. This diary should be returned to the clinic, along with the medication bottle (even if it is empty) at your next scheduled clinic visit. This will help us know how much of the drug you take and how it made you feel.

During treatment, you will have regular tests to see how the cancer is responding to therapy, and to monitor for side effects. You will stop treatment on this study if the tumor gets larger or if side effects from the treatment are too severe. If that happens, your doctor will discuss other treatment options with you.

Standard Tests and Procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- Frequent labs to monitor your blood counts and blood chemistries.
- Frequent physical exams.
- Pregnancy test for females of childbearing age before treatment begins.
- MRI scans to monitor your response to treatment.
- Tests to monitor your heart and lung function.
- Tests to monitor your hearing.
- Tests to monitor your vision (if you have a tumor in the optic pathway).

Attachment 2

Risks of Drugs Used to Treat Recurrent or Progressive Low-Grade Glioma

Possible Side Effects of Selumetinib (AZD6244 hydrogen sulfate)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Selumetinib (AZD6244 hydrogen sulfate), more than 20 and up to 100 may have:
• **Diarrhea, nausea** • **Swelling of the body** • **Tiredness** • **Acne**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Selumetinib (AZD6244 hydrogen sulfate), from 4 to 20 may have:
• **Anemia which may require blood transfusion** • **Blurred vision** • **Swelling of the eye** • **Pain** • **Constipation, vomiting** • **Dry mouth, skin** • **Sores in the mouth which may cause difficulty swallowing** • **Fever** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Swollen or broken skin around the nail which may cause redness (paronychia)** • **Potential liver damage (Alanine aminotransferase increased and Aspartate aminotransferase increased)** • **Muscle pain/muscle breakdown (CPK increased)** • **Infection, especially when white blood cell count is low** • **Loss of appetite** • **Dizziness, headache** • **Cough, shortness of breath** • **Change in hair color** • **Itching, rash** • **High blood pressure which may cause headaches, dizziness, blurred vision**

RARE, AND SERIOUS In 100 people receiving Selumetinib (AZD6244 hydrogen sulfate), 3 or fewer may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Cloudiness of the eye, visual disturbances** • **Glaucoma** • **Seeing spots before eyes** • **Discomfort from light, visual loss** • **Blockage of internal organs which may cause inability to pass stool** • **Blood infection** • **Change in heart function**

- **In children and adolescents: decreased height**
- **Damage to muscle which may cause muscle pain, dark red urine**
- **Redness, pain or peeling of palms and soles**
- **Bleeding (increased risk of bleeding given the vitamin E levels in the capsules)**

Possible Side Effects of Vinblastine

COMMON, SOME MAY BE SERIOUS In 100 people receiving vinblastine, more than 20 and up to 100 may have:
• **High blood pressure which may cause headaches, dizziness, blurred vision** • **Tiredness** • **Pain** • **Mouth sores** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving vinblastine, from 4 to 20 may have:
• **Stroke, which may cause paralysis, weakness** • **Damage to the lungs which may cause shortness of breath** • **Hair loss** • **Confusion** • **Nausea, vomiting, loss of appetite, constipation** • **Pain or redness at site of infusion** • **Numbness and tingling in fingers and toes** • **Abnormal menstrual period**

RARE, AND SERIOUS In 100 people receiving vinblastine, 3 or fewer may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Headache** • **Damage to hearing which may be permanent**

Attachment 3

Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.