

COG-ACNS1931: A Phase 3 Study of Selumetinib (NSC# 748727, IND# 77782) 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

FAST FACTS

Eligibility Reviewed and Verified By _____

MD/DO/RN/LPN/CRA Date _____

MD/DO/RN/LPN/CRA Date _____

Consent Version Dated _____

PATIENT ELIGIBILITY:

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

- ___ 1. **Pre-Enrollment Eligibility Screening (Step 0)**
Patients must be consented and enrolled on APEC14B1, the COG Project:EveryChild Registry, Eligibility Screening, Biology, and Outcome Study, followed by same day enrollment on the ACNS1931 Pre-Enrollment Eligibility Screening (Step 0) to complete the RAPID CENTRAL PATHOLOGY and RAPID CENTRAL MOLECULAR REVIEWS. The APEC14B1 consent will cover the Pre-Enrollment Eligibility Screening (including pathology and molecular central reviews) for ACNS1931. See [Appendix XIII, Section 3.1.1, Section 13.0, and Section 14.0](#).
Please note that a reservation is required prior to Step 0 enrollment. See [Section 3.1.6](#).
- ___ 2. **Pre-Enrollment Eligibility Screening Criteria**
The following criteria must be met prior to initiating the Pre-Enrollment Eligibility Screening on ACNS1931 (Step 0).
- ___ 3. **Age**
Patients must be ≥ 2 years and ≤ 25 years of age at the time of enrollment on Step 0.
 - All patients > 21 years of age at the time of enrollment must have had initial diagnosis of low-grade glioma by 21 years of age.
- ___ 4. **Diagnosis**
 - Patient is suspected of having progressive or recurrent low-grade glioma (LGG).
 - Patient does not have a known diagnosis of neurofibromatosis type 1 (NF1) or tuberous sclerosis complex (TSC).
- ___ 5. **Consent**
Patient and/or their parents or legal guardians have signed informed consent for eligibility screening on APEC14B1 Part A.
- ___ 6. **Timing**
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.**
- ___ 7. **Patient Eligibility Criteria**

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

Laboratory Studies

All laboratory studies to determine eligibility must be performed within 7 days prior to *enrollment* unless otherwise indicated.

The following laboratory studies must be repeated prior to the *start of protocol therapy* if >7 days have elapsed from their most recent prior assessment: CBC with bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment. If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to

initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Clinical Studies

For all patients, ECHO/EKG must be done within 4 weeks prior to enrollment with values that meet eligibility as per [Section 3.3.5.3](#). For all patients, ophthalmology toxicity assessments must be done within 4 weeks (28 days) prior to enrollment (see [Section 17.1](#)). For OPG patients, ophthalmology functional assessments must be done following biopsy and within 33 days prior to treatment (see [Section 17.2](#)).

Disease/Staging Imaging

Disease/staging imaging studies, if applicable, must be obtained within 4 weeks (28 days) prior to enrollment and start of protocol therapy (repeat if necessary).

8. Age
 - Feasibility Phase: Patients must be ≥ 2 years and ≤ 21 years of age at the time of enrollment.
 - Efficacy Phase: Patients must be ≥ 2 years and ≤ 25 years of age at the time of enrollment.
 - All patients > 21 years of age at the time of enrollment must have had initial diagnosis of low-grade glioma by 21 years of age.
9. Body Surface Area

Patients must have a body surface area (BSA) of ≥ 0.5 m² at enrollment.
10. Diagnosis
 - Patients must have **eligibility confirmed by rapid central pathology and central molecular screening reviews performed on APEC14B1 (see [Section 3.1](#))**:
 - Non-neurofibromatosis type 1 (non-NF1), non-tuberous sclerosis complex (non-TSC) low-grade glioma (LGG) without a *BRAF*^{V600E} or *IDH1* mutation
 - Patients must have progressive or recurrent LGG. **Note**: Biopsy may be at either initial diagnosis or recurrence.
 - Patients must have measurable disease, defined as having a two-dimensional measurable tumor volume of ≥ 1 cm².
 - Tumor size will be measured to include both solid and cystic components of the tumor (whether or not tumor is enhancing) + FLAIR signal.
 - Eligible histologies will include all tumors considered low-grade glioma or low-grade astrocytoma (WHO Grade 1 and II) by the WHO Classification of Tumors of the Central Nervous System – 4th Edition Revised, with the exception of subependymal giant cell astrocytoma.
 - Patients with metastatic disease or multiple independent primary LGGs are eligible.
11. Prior Therapy
 - Patients must be progressive or recurrent after having been treated with at least one prior tumor-directed therapy before enrollment.
 - Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.
 - Myelosuppressive chemotherapy: Must not have received within 2 weeks of entry onto this study (4 weeks if prior nitrosourea).
 - Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent.
 - Radiation therapy (RT): ≥ 2 wks for local palliative RT (small port); ≥ 6 months must have elapsed if prior craniospinal RT or if $\geq 50\%$ radiation of pelvis; ≥ 6 wks must have elapsed if other substantial BM radiation.
 - Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to \leq Grade 1.
 - MEK inhibitor or vinblastine: Must not have received treatment with a MEK inhibitor or vinblastine within 6 months of study enrollment.
12. Organ Function Requirements
 - Adequate renal function defined as:
 - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m² or
 - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

- Adequate liver function defined as:
 - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age (children with a diagnosis of Gilbert’s syndrome will be allowed on study regardless of their total and indirect [unconjugated] bilirubin levels as long as their direct [conjugated] bilirubin is < 3.1 mg/dL)
 - SGPT (ALT) ≤ 135 U/L*
 - Albumin ≥ 2 g/dL

**Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*
- Adequate cardiac function defined as:
 - LVEF $\geq 53\%$ (or institutional normal; if the LVEF result is given as a range of values, then the upper value of the range will be used) by echocardiogram
 - QTc interval ≤ 450 msec by EKG
- Adequate bone marrow function defined as:
 - Absolute neutrophil count $\geq 1,000/\mu\text{L}$ (unsupported)
 - Platelets $\geq 100,000/\mu\text{L}$ (unsupported)
 - Hemoglobin ≥ 8 g/dL (may be supported)
- Adequate central nervous system function defined as:
 - Patients with a known seizure disorder should be stable and should not have experienced a significant increase in seizure frequency within 2 weeks prior to enrollment.
 - Stable neurological examination for > 1 week

13. Study Specific Requirements

- a. Hypertension
Patients 2–17 years of age must have a blood pressure that is ≤ 95 th percentile for age, height, and gender (see [Appendix X](#)) at the time of enrollment (with or without the use of anti-hypertensive medications). Patients ≥ 18 years of age must have a blood pressure $\leq 130/80$ mmHg at the time of enrollment (with or without the use of anti-hypertensive medications).
Note for patients of all ages: Adequate blood pressure can be achieved using medication for the treatment of hypertension. See [Section 4.3.2](#).
- b. Ophthalmology Toxicity Assessments
All patients must have ophthalmology toxicity assessments performed within 4 weeks prior to enrollment. See [Section 17.1](#) for details.
- c. Imaging
For all patients, an MRI of the brain (with orbital cuts for optic pathway tumors) and/or spine (depending on the site(s) of primary disease) with and without contrast must be performed within 4 weeks prior to enrollment.
Note: If surgical resection or biopsy is performed at the time of progression or recurrence, a post-operative MRI is required.
- d. Performance Level
Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See https://www.cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials under Standard Sections for Protocols.
- e. Patients must have the ability to swallow whole capsules.

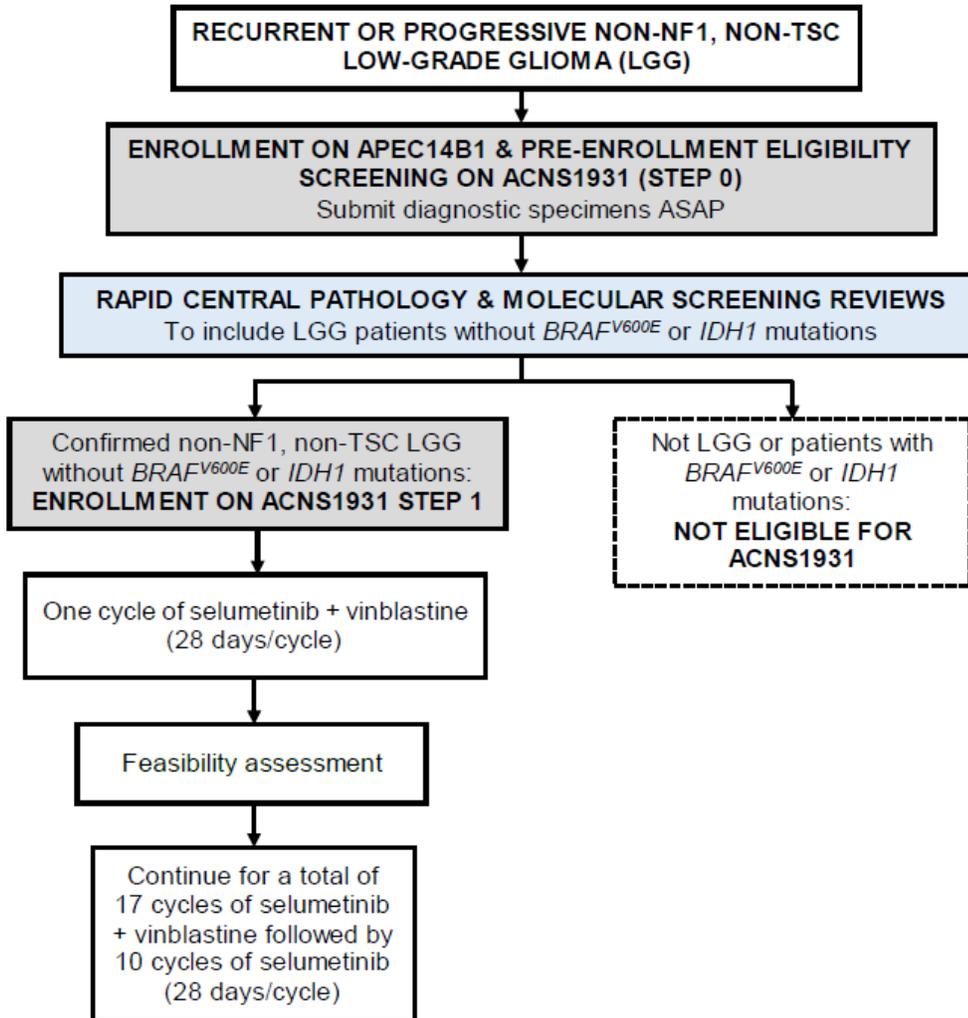
Assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA:

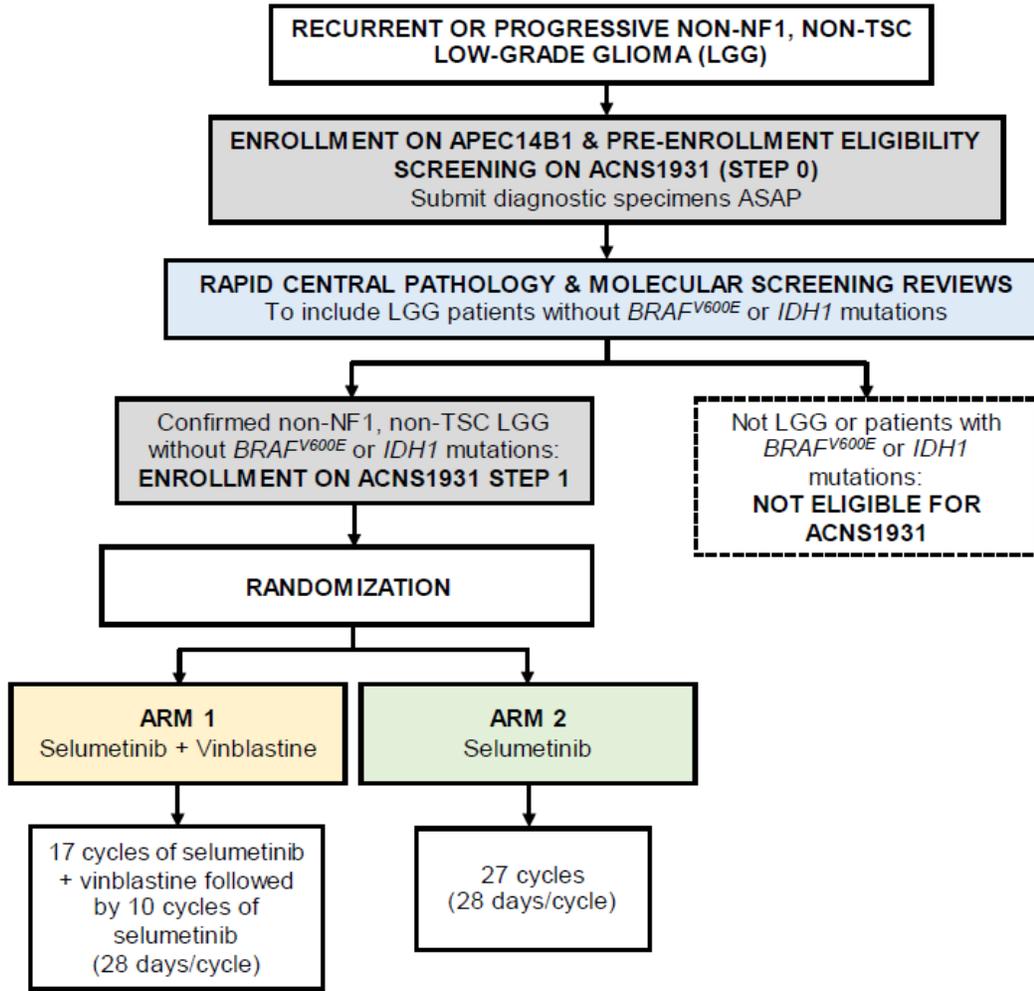
- ___ 1. Prior Therapy
 - Prior therapy with vinblastine and/or a MEK inhibitor is permitted, with the following exceptions:
 - Patients must not have had progressive disease while on therapy with vinblastine or a MEK inhibitor.
 - Patients must not have discontinued vinblastine or selumetinib due to toxicity.
Note: See [Section 3.3.4.2](#) for additional restrictions regarding prior therapy with vinblastine and/or a MEK inhibitor.
 - Patients with a concurrent malignancy or history of treatment (other than surgery) for another tumor within the last year are ineligible.
- ___ 2. Patients with diffuse intrinsic pontine tumors as seen on MRI (> 2/3 of pons involvement on imaging) are not eligible even if biopsy reveals Grade I/II histology.
- ___ 3. Patients may not be receiving any other investigational agents.
- ___ 4. Patients must not have known hypersensitivity to selumetinib, vinblastine, or similar compounds.
- ___ 5. CYP3A4 Agents: Patients must not have received fluconazole or drugs that are strong inducers or inhibitors of CYP3A4 within 7 days prior to study enrollment. See [Appendix VI](#) for a list of agents.
Please see [Section 4.3](#) for the concomitant therapy restrictions for patients during treatment.
- ___ 6. Patients with any serious medical or psychiatric illness/condition, including substance use disorders or ophthalmological conditions, likely in the judgment of the investigator to interfere or limit compliance with study requirements/treatment.
- ___ 7. Patients who, in the opinion of the investigator, are not able to comply with the study procedures are not eligible.
- ___ 8. Pre-existing Conditions
 - Cardiac Conditions
 - Known genetic disorder that increases risk for coronary artery disease. Note: The presence of dyslipidemia in a family with a history of myocardial infarction is not in itself an exclusion unless there is a known genetic disorder documented.
 - Symptomatic heart failure
 - NYHA Class II-IV prior or current cardiomyopathy
 - Severe valvular heart disease
 - History of atrial fibrillation
 - Ophthalmologic Conditions
 - Current or past history of central serous retinopathy
 - Current or past history of retinal vein occlusion or retinal detachment
 - Patients with uncontrolled glaucoma o If checking pressure is clinically indicated, patients with IOP > 22 mmHg or ULN adjusted by age are not eligible.
- ___ 9. Supplementation with vitamin E: Any multivitamin containing vitamin E must be stopped prior to study enrollment even if it contains less than 100% of the daily recommended dosing for vitamin E.
- ___ 10. Surgery within 2 weeks prior to enrollment, with the exception of a surgical biopsy, placement of a vascular access device or CSF diverting procedure such as endoscopic third ventriculostomy (ETV) and ventriculoperitoneal (VP) shunt.
Note: Patients must have healed from any prior surgery.
- ___ 11. Patients who have an uncontrolled infection are not eligible.
- ___ 12. Pregnancy and Breastfeeding
 - Female patients who are pregnant are not eligible since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
 - Lactating females who plan to breastfeed their infants.
 - Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for 12 weeks after stopping study therapy are not eligible.
Note: Women of child-bearing potential and males with sexual partners who are pregnant or who could become pregnant (i.e., women of child-bearing potential) should use effective methods of contraception for the duration of the study and for 12 weeks after stopping study therapy to avoid pregnancy and/or potential adverse effects on the developing embryo.

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA: FEASIBILITY PHASE



EXPERIMENTAL DESIGN SCHEMA: EFFICACY PHASE



REQUIRED OBSERVATIONS:

Note: No starter supplies will be provided. Drug orders of selumetinib (AZD6244 hydrogen sulfate) should be placed with CTEP after enrollment and treatment assignment to ACNS1931 with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy.

Required Observations – Arm 1: Selumetinib and VBL – Cycles 1-17

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

- a. Medical history and physical exam: Perform at baseline, on Day 15 (for Cycle 1 only).
- b. Neurologic exam: Perform at baseline.
- c. Height, weight: Perform at baseline.
- d. Vital signs: Perform at baseline.
- e. Performance status: Perform at baseline.
- f. CBC with diff/platelets: Perform at baseline and weekly thereafter.
- g. Creatinine/bilirubin: Perform at baseline.
- h. Electrolytes, BUN, Ca⁺⁺, PO₄, Mg⁺⁺: Perform at baseline.
- i. AST, ALT, urinalysis, albumin: Perform at baseline.
- j. ECG: Perform at baseline. May be omitted if treatment starts within 4 weeks of the ECG used to determine eligibility.
- k. ECHO: Perform at baseline.
- l. CPK: Perform at baseline.
- m. Pulse oximetry: Perform at baseline before Cycle 1.
- n. Brain and/or spine MRI (as clinically indicated to monitor disease): Perform at baseline and every 12 weeks (after Cycles 3, 6, 9, 12, and 15).
- o. Ophthalmology toxicity assessment: Perform after Cycle 3, after Cycle 12, and as clinically indicated with any new visual complaints while on therapy. See [Section 17.0](#).
- p. Ophthalmology functional assessment (*in all patients with hypothalamic/OPG*): Evaluation includes TAC in all patients, and HOTV in patients developmentally able to perform. Perform at baseline (following biopsy and within 33 days prior to treatment) See [Section 17.0](#).
- q. Pregnancy test (*urine or serum*): Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Perform at baseline.
- r. PedsQL Generic and Brain Tumor Module: Perform at study entry (± 2 weeks) and Cycle 7 Day 1 (± 2 weeks). See [Section 18.0](#).
- s. Medication Diary (see [Appendix VIII](#)): Medication diaries should be reviewed after Week 2 of Cycle 1 and after completion of each treatment cycle, and uploaded into RAVE.

SPECIMEN REQUIREMENTS:

Per APEC14B1 CNS requirements.

Note: This trial has a protocol supplied drug information handout and wallet card that is required to be provided to the patient. See Appendix IX.

BIOLOGY REQUIREMENTS:

See Section 14.2 for optional studies. If patient has consented to optional banking on APEC14B1, these samples do not need to be duplicated for the optional specimen banking on ACNS1931.