CLINICAL STUDY PROTOCOL AG881-C-004

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-Controlled Study of AG-881 in Subjects With Residual or Recurrent Grade 2 Glioma With an IDH1 or IDH2 Mutation

Study Sponsor:	Institut de Recherches Internationales Servier (I.R.I.S.) 50, rue Carnot 92284 Suresnes cedex - France
Responsible Medical Officer:	[redacted]
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This study will be conducted according to the protocol and in compliance with Good Clinical Practices (GCP), the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines, applicable local regulatory requirements, and the spirit of the ethical principles stated in the Declaration of Helsinki.

Contractual signatories	
I, the undersigned, have read the foregoing protocol for the study and agree to conduct the study in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. **MEDICAL DIRECTOR**	
NAME	[redacted]
DATE	[redacted]
SIGNATURE	[redacted]

Contractual signatories	
I, the undersigned, have read the foregoing protocol for the study and agree to conduct the study in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. **BIOSTATISTICS PROGRAM HEAD OR DESIGNEE**	
NAME	[redacted]
DATE	[redacted]
SIGNATURE	[redacted]

Contractual signatories	
I, the undersigned, have read the foregoing protocol for the study and agree to conduct the study in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. **INVESTIGATOR**	
NAME	
SITE NUMBER	
DATE	
SIGNATURE	

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Assessment of Amendment 3 (Version 4.0)

This amendment is considered substantial because it changes the Sponsor for the study.

The rationale for the protocol amendment is described in the following section.

Purpose and Rationale for the Protocol Amendment

The primary purpose of this protocol amendment was to change the Sponsor for the study.

Several nonsubstantial changes were also made as part of this amendment; a detailed summary of the amendment changes is provided in a separate document.

SYNOPSIS

Name of Sponsor/Company:
I.R.I.S.

Name of Investigational Product:
Vorasidenib (AG-881)

Study Title:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-Controlled Study of AG-881 in Subjects With Residual or Recurrent Grade 2 Glioma With an IDH1 or IDH2 Mutation

Study Center(s):
This multicenter study will be conducted internationally at approximately 80 study centers.

Phase of Development:
3

Objectives:

Primary:

- The primary objective of the study is to demonstrate the efficacy of vorasidenib based on radiographic progression-free survival (PFS) per blinded independent review committee (BIRC) compared with placebo in subjects with residual or recurrent Grade 2 oligodendroglioma and astrocytoma with an isocitrate dehydrogenase (IDH)1 or IDH2 mutation who have undergone surgery as their only treatment.

Key Secondary:

- To demonstrate the efficacy of vorasidenib based on time to next intervention (TTNI) compared with placebo.

Other Secondary:

- To evaluate the safety and tolerability of vorasidenib.
- To evaluate vorasidenib and placebo with respect to tumor growth rate (TGR) as assessed by volume per the BIRC.
- To evaluate the efficacy of vorasidenib and placebo based on objective response, complete response (CR) + partial response (PR), time to response, time to CR+PR, duration of response, and duration of CR+PR, with response assessed per the BIRC and the Investigator.
- To evaluate vorasidenib and placebo with respect to overall survival (OS).
- To evaluate vorasidenib and placebo with respect to health-related quality of life (HRQoL) as assessed by the Functional Assessment of Cancer Therapy – Brain (FACT-Br) questionnaire.
- To evaluate vorasidenib and placebo with respect to PFS per the Investigator assessment.
- To evaluate the pharmacokinetics (PK) of vorasidenib and its circulating metabolite AGI-69460 in plasma.

Exploratory:

- To evaluate, for subjects who cross over from placebo to vorasidenib, the time from first dose of vorasidenib to documented progression on vorasidenib, as assessed by the Investigator, or death due to any cause, whichever occurs first.
- To evaluate TGR before and after treatment with vorasidenib among subjects who cross over from placebo to vorasidenib.

- To evaluate HRQoL with vorasidenib and placebo as assessed by the EuroQol 5 Dimensions, 5-Level (EQ-5D-5L) questionnaire and Patient Global Impression (PGI) questions.
- To evaluate neurocognitive function in subjects receiving vorasidenib and placebo as assessed by a validated battery of cognitive performance instruments.
- To evaluate seizure activity in subjects receiving vorasidenib and placebo.
- To evaluate the molecular and cellular markers that may be predictive of response and/or resistance, where feasible, in blood and archival tumor tissue.
- To evaluate TGR before and after treatment with vorasidenib and placebo.
- To evaluate time to malignant transformation and radiographic changes associated with histopathology-proven malignant transformation in subjects who have surgery or biopsy as an intervention.

Methodology:

Subject eligibility will be determined during a Prescreening period, which will occur up to 84 days before randomization (central confirmation of tumor isocitrate dehydrogenase [IDH] mutation status only), and a Screening period, which will occur within 28 days before randomization (all other eligibility requirements, including central confirmation of non-enhancing disease by imaging). Subjects are required to have a histologically confirmed diagnosis of IDH1 or IDH2 gene–mutated Grade 2 oligodendroglioma or astrocytoma (per World Health Organization [WHO] 2016 classification) with residual or recurrent disease. Subjects must have had at least 1 prior surgery (biopsy, sub-total resection, or gross-total resection), with the most recent surgery occurring at least 1 year (-1 month) and no more than 5 years (+3 months) before the date of randomization, with no other treatment, including systemic chemotherapy or radiotherapy, and not be in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator. Central confirmation of IDH1 or IDH2 mutation status in the tumor sample (archived [preferably from most recent surgery] or fresh biopsy) and presence of measurable non-enhancing disease based on imaging review by the BIRC are required before randomization.

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive vorasidenib orally at a dose of 40 mg once daily (QD) or vorasidenib–matched oral placebo QD. Randomization will be stratified by local 1p19q status (co-deleted or not co-deleted) and baseline tumor size per local assessment (longest diameter of ≥2 cm or <2 cm). Starting with Cycle 1 Day 1 (C1D1), dosing is continuous; there are no planned intercycle rest periods.

A BIRC will assess radiographic eligibility for study entry, the primary efficacy endpoint of radiographic PFS per modified Response Assessment for Neuro-Oncology for Low-Grade Gliomas (RANO-LGG) criteria, and the secondary efficacy endpoint of TGR as assessed by tumor volume. The BIRC will also be used to confirm radiographic disease progression (PD) by the Investigator to permit unblinding and crossover. Radiographic disease assessment (by magnetic resonance imaging [MRI]) for evaluation of disease response will be conducted at specified time points throughout the study or at any time PD is suspected. Target lesion selection and tumor response per RANO-LGG criteria will be performed by the institutional radiologist/Investigator. Scan acquisition parameters required per protocol will be detailed in a separate site-specific imaging core manual. All MRI scans will be sent to the BIRC as detailed in the site-specific Imaging Core Manual.

Subjects who discontinue study treatment for reasons other than centrally confirmed radiographic PD by the BIRC or withdrawal of consent from treatment and overall study participation (and not just study treatment) will enter PFS Follow-up with the same schedule of assessments as before study treatment discontinuation until radiographic PD is documented by the BIRC. Overall Survival Follow-up assessments will occur approximately 6 months (±4 weeks) after End of Treatment (EOT). For subjects in PFS Follow-up, OS Follow-up will begin once PFS Follow-up has ended. Overall Survival Follow-up will continue for up to 5 years after the last subject is randomized or until all subjects have

died, withdrawn consent from overall study participation, or are lost to follow-up or the Sponsor ends the study, whichever occurs first.

Number of Subjects Planned:

Approximately 340 subjects are planned to be randomized 1:1 to receive vorasidenib or vorasidenib-matched placebo.

Eligibility Criteria:

Inclusion Criteria:

Subjects must meet all of the following criteria to be enrolled in the study:

1. Be at least 12 years of age and weigh at least 40 kg.
2. Be able to understand and willing to sign informed consent or assent as determined by local requirements and willing to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling and urine sampling, during the study. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's institutional review board/independent ethics committee. A parent or legal guardian must sign informed consent for adolescent subjects who sign assent. (Note: Subjects who do not read and/or speak one of the languages in which the HRQoL instruments are provided will be permitted to enroll and not complete these HRQoL outcome instruments, assuming all other eligibility criteria are met.)
3. Have Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria.
4. Have had at least 1 prior surgery for glioma (biopsy, sub-total resection, gross-total resection), with the most recent surgery having occurred at least 1 year (-1 month) and not more than 5 years (+3 months) before the date of randomization, and no other prior anticancer therapy, including chemotherapy and radiotherapy, and not be in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator. (Note: Subjects undergoing biopsy solely to obtain tissue for central confirmation of IDH mutation status [eg, tissue from previous surgery was exhausted or not available] will be considered an exception and will not need to wait an additional year from biopsy to be eligible.)
5. Have confirmed IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status disease by central laboratory testing during the Prescreening period and available 1p19q status by local testing (eg, fluorescence in situ hybridization, comparative genomic hybridization array, sequencing) using an accredited laboratory.
6. Have MRI-evaluable, measurable, non-enhancing disease, as confirmed by the BIRC, assessed at Screening on 2D T2-weighted or 2D T2-weighted fluid-attenuated inversion recovery MRI with ≤4 mm slice thickness and no interslice gap. Measurable non-enhancing disease is defined as a least 1 target lesion measuring ≥1 cm × ≥1 cm (bidimensional). Enhancement that is centrally confirmed by the BIRC to be minimal, non-nodular, and non-measurable and that has not changed between the 2 most recent scans (including screening scan) will be permitted.
7. Have a Karnofsky Performance Scale (KPS) score (for subjects ≥16 years of age) or Lansky Play Performance Scale (LPPS) score (for subjects <16 years of age) of ≥80%.
8. Have expected survival of ≥12 months.
9. Have adequate bone marrow function as evidenced by:
   a. Absolute neutrophil count ≥1,500 mm^3 or ≥1.5 × 10^9/L
   b. Hemoglobin ≥9 g/dL
   c. Platelets ≥100,000 mm^3 or ≥100 × 10^9/L.

10. Have adequate hepatic function as evidenced by:
    a. Serum total bilirubin ≤1.5 × upper limit of normal (ULN) unless considered due to Gilbert's disease after approval by the Medical Monitor, and
    b. Aspartate aminotransferase at or below ULN and alanine aminotransferase at or below ULN, and
    c. Alkaline phosphatase ≤2.5 × ULN.
11. Have adequate renal function as evidenced by:
    a. Serum creatinine ≤2.0 × ULN, OR
    b. Creatinine clearance >40 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation: (140 − Age) × (Weight in kg) × (0.85 if female) / 72 × Serum Creatinine (for subjects ≥18 years of age). For subjects <18 years of age, the Bedside Schwartz method is to be used: 0.413 × (Height in cm / Serum Creatinine in mg/dL).
12. Have recovered from any clinically relevant toxicities associated with any prior surgery for the treatment of glioma unless stabilized under medical management.
13. Female subjects of childbearing potential must have a negative serum pregnancy test before the start of therapy. Women of childbearing potential are defined as having had onset of their first menstrual period and have not undergone a hysterectomy or bilateral oophorectomy or are not naturally postmenopausal (ie, have not menstruated at all in the preceding 24 consecutive months). Women of childbearing potential as well as fertile men with partners who are women of childbearing potential must agree to abstain from sexual intercourse or to use 2 highly effective forms of contraception, at least one of which must be a barrier method, from the time of giving informed consent or assent, throughout the study, and for 90 days after the last dose of vorasidenib. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject; periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Highly effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone release systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

Exclusion Criteria:

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Have had any prior anticancer therapy other than surgery (biopsy, sub-total resection, gross-total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, laser ablation, etc.
2. Have features assessed as high-risk by the Investigator, including brainstem involvement either as primary location or by tumor extension, clinically relevant functional or neurocognitive deficits due to the tumor in the opinion of the Investigator (deficits resulting from surgery are allowed), or uncontrolled seizures (defined as persistent seizures interfering with activities of daily life AND failed 3 lines of antiepileptic drug regimens including at least 1 combination regimen).
3. Concurrent active malignancy except for a) curatively resected nonmelanoma skin cancer or b) curatively treated carcinoma in situ. Subjects with previously treated malignancies are eligible provided they have been disease-free for 3 years at Screening.
4. Are pregnant or breastfeeding.
5. Have an active infection that requires systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of C1D1.
6. Have a known hypersensitivity to any of the components of vorasidenib.

7. Have significant active cardiac disease within 6 months before the start of study treatment, including New York Heart Association Class III or IV congestive heart failure, myocardial infarction, unstable angina, and/or stroke.
8. Have left ventricular ejection fraction (LVEF) <40% by echocardiogram (or by other methods according to institutional practice) obtained within 28 days before the start of study treatment.
9. Have a heart-rate corrected QT interval using Fridericia's formula (QTcF) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with bundle branch block and prolonged QTcF are permitted with approval of the Medical Monitor.
10. Are taking therapeutic doses of steroids for signs/symptoms of glioma. Subjects taking physiologic doses (defined as equivalent of ≤10 mg prednisone daily) for medical conditions not related to glioma will be permitted.
11. Exclusion Criterion 11 removed in Protocol Amendment 1 (v2.0).
12. Are taking any medications that are cytochrome P450 (CYP) 2C8, CYP2C9, CYP2C19, or CYP3A substrates with a narrow therapeutic index. (Subjects should be transferred to other medications before receiving the first dose of study drug.)
13. Have known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, known positive human immunodeficiency virus antibody results, or AIDS-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed by institutional practice will be permitted.
14. Have known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other condition that limits the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).
15. Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of C1D1) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

Investigational Product, Dosage, and Mode of Administration:

Vorasidenib 40 mg QD will be taken orally by the subject on Days 1 to 28 in 28-day cycles. Dosing is continuous; there are no planned intercycle rest periods.

Reference Therapy, Dosage, and Mode of Administration:

Vorasidenib–matched placebo 40 mg QD will be taken orally by the subject on Days 1 to 28 in 28-day cycles. Dosing is continuous; there are no planned intercycle rest periods.

Duration of Treatment and End of Study:

Subjects will receive vorasidenib or vorasidenib–matched placebo in continuous 28-day cycles until centrally confirmed radiographic PD by the BIRC; development of unacceptable toxicity; need for initiation of chemotherapy, radiotherapy, or other anticancer therapy in the opinion of the Investigator in the absence of centrally confirmed radiographic PD by the BIRC; confirmed pregnancy; death; withdrawal of consent from treatment; lost to follow-up; or Sponsor ending the study, whichever occurs first. Subjects who are determined to be receiving placebo upon unblinding after centrally confirmed radiographic PD, and who are not in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator, will have the option to cross over to receive vorasidenib, in consultation with the Medical Monitor, provided the following eligibility criteria are met based on the EOT

assessments: all initial screening eligibility criteria except Inclusion Criteria numbers 1, 3, 4, 5, 6, and 12 and Exclusion Criteria numbers 1, 6, and 8. Subjects who cross over to vorasidenib will restart the schedule of assessments at C1D1 and follow the same schedule of assessments as in the blinded treatment phase. Subjects who cross over to vorasidenib may continue to receive vorasidenib until PD according to the Investigator, development of unacceptable toxicity, start of subsequent anticancer therapy, confirmed pregnancy, death, withdrawal of consent from treatment, lost to follow-up, or Sponsor ending the study, whichever occurs first. Subjects who are determined to be receiving vorasidenib upon unblinding after centrally confirmed radiographic PD will not be permitted to continue vorasidenib.

The study will end and the final OS analysis will be performed approximately 5 years after the last subject has been randomized to the study or all subjects have died, withdrawn consent from overall study participation, are lost to follow-up, or the Sponsor ends the study, whichever occurs first. The subject enrollment period is estimated to be approximately 42 months, and the total duration of the study is estimated to be 8 years.

Statistical Methods:

Summaries will be produced for subject disposition, demographic and baseline disease characteristics, efficacy, safety, PK, and pharmacodynamics, as appropriate. Categorical data will be summarized by frequency distributions (number and percentages of subjects). Continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Time-to-event endpoints will be estimated using the Kaplan-Meier method. Point estimates and 95% CIs will be provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates), will be produced.

All data will be provided in by-subject listings.

The following analysis sets will be evaluated and used for presentation of the data:

- Full Analysis Set: all subjects who are randomized. Subjects will be classified according to the randomized treatment arm as per the intent-to-treat principle. The FAS will be the default analysis set for all efficacy analyses including analysis of primary endpoint, unless otherwise specified.
- Per-Protocol Set (PPS): a subset of the FAS. Subjects who do not receive at least 1 dose of the randomized treatment will be excluded from the PPS. Other criteria leading to exclusion of subjects will be prespecified in the Statistical Analysis Plan. The PPS will be used to perform sensitivity analyses for the primary endpoint.
- Safety Analysis Set: all subjects who receive at least 1 dose of the study treatment. Subjects will be classified according to the treatment received. The Safety Analysis Set will be the primary analysis set for all safety analyses, unless otherwise specified.
- Pharmacokinetic Analysis Set: a subset of the safety analysis set and includes all subjects who have at least 1 postdose blood sample providing evaluable PK data for vorasidenib or its metabolite AGI-69460.

Primary endpoint:

The primary endpoint is PFS, defined as the time from date of randomization to date of the first occurrence of radiographic PD by modified RANO-LGG assessed by the BIRC or death from any cause, whichever occurs earlier. Progression-free survival for subjects without centrally confirmed radiographic PD by RANO-LGG by the BIRC or death will be censored at the date of the last disease assessment. Censoring reasons also include start of a subsequent anticancer therapy, withdrawal of consent from overall study participation, and loss to follow-up.

The primary efficacy analysis will compare the PFS time between the 2 treatment arms using a 1-sided stratified log-rank test. The test will be stratified by 1p19q status and baseline tumor size. A Cox

proportional hazards (PH) model stratified by randomization stratification factors will be used to estimate the hazard ratio of PFS, along with its 95% CI.

Assuming a median PFS of 18 months for the placebo arm and a median PFS of 30 months for the vorasidenib arm, a total of 164 PFS events are required to provide at least 90% power to detect a hazard ratio of 0.6 at a 1-sided alpha of 0.025 level of significance using a log-rank test stratified by the randomization stratification factors, and a 3-look group sequential design with a Gamma family (-24) α-spending function to determine the efficacy boundaries and a Gamma family (-5) β-spending function to determine the nonbinding futility boundaries. Assuming a recruitment period of approximately 42 months, and a 10% dropout rate in PFS at 12 months, approximately 340 subjects will need to be randomized to the 2 treatment arms in a 1:1 ratio.

There are 3 planned analyses for PFS: an interim analysis for futility, an interim analysis for superiority, and a final analysis. A small alpha will be allocated to the PFS futility analysis based on the selected α-spending function. The interim analyses for PFS will be performed based on FAS and will take place after the target number of events has occurred as described below.

- Interim analysis 1 (IA1, futility only): will be conducted when approximately 55 PFS events (33.5% of the expected 164 events) have occurred
- Interim analysis 2 (IA2, superiority and futility): will be conducted when all subjects are randomized and approximately 123 PFS events (75% of the expected 164 events) have occurred.
- Final analysis (FA): will be conducted when all subjects are randomized and 164 PFS events have occurred.

Key secondary endpoint:

The key secondary endpoint is TTNI, defined as the time from randomization to the initiation of the first subsequent anticancer therapy (including vorasidenib, for subjects randomized to placebo who subsequently cross over) or death due to any cause.

The secondary efficacy analysis will compare the TTNI between the 2 treatment arms using a 1-sided stratified log-rank test. The test will be stratified by 1p19q status and baseline tumor size. A Cox PH model stratified by randomization stratification factors will be used to estimate the hazard ratio of TTNI, along with its 95% CI.

The sample size of 340 subjects will also allow an assessment for TTNI assuming a 10% dropout rate for TTNI at 12 months. With an assumed median TTNI of 21 months for the placebo arm, a total of 152 TTNI events are required to provide approximately 80% power to detect a hazard ratio of 0.636 at a 1-sided alpha of 0.025 level of significance using a log-rank test stratified by the randomization stratification factors, and a 2-look group sequential design with a Gamma family (-22) α-spending function to determine the efficacy boundaries. To control the overall type I error rate at the 1-sided 2.5% level, the fixed sequence testing procedure will be used to adjust for multiple statistical testing of the primary endpoint and key secondary efficacy endpoint TTNI. These endpoints will be tested in the following order:

- PFS per BIRC
- TTNI.

Other secondary endpoints:

Other secondary efficacy endpoints are TGR, objective response, CR+PR, time to response, time to CR+PR, duration of response, duration of CR+PR, OS, FACT-Br scores, and PFS by investigator.

Safety:

Safety will be evaluated by the incidence, severity, and type of adverse events, and by evaluation of vital signs, KPS/LPPS, clinical laboratory results, electrocardiograms, and LVEF data (as clinically

indicated). All data will be provided in by-subject listings. All safety data will be listed by subject and summarized by treatment arm based on the Safety Analysis Set.

Pharmacokinetics:

Descriptive statistics of plasma concentrations (arithmetic and geometric means, standard deviation, coefficient of variation [CV%], CV% geometric mean, minimum, median and maximum) of vorasidenib and its metabolite AGI-69460 will be summarized.

Table 1: Schedule of Assessments

Visit	**Pre-screen-ing[1]**	**Screen-ing**	**Cycle 1**		**Cycle 2**		**Cycle 3**	**Cycles 4-12**	**Cycle 13-36[2]**	**Cycle 37+ (Odd Cycles Only)[2]**	**End of Treat-ment[3]**	**Safety Follow-up**	**PFS Follow-up[4]**	**OS Follow-up[5]**
Study Day	**D -84 to D -1**	**D -28 to D -1**	**D1**	**D15 ±2 Days**	**D1 ±2 Days**	**D15 ±2 Days**	**D1 ±2 Days**	**D1 ±2 Days**	**D1 ±5 Days**	**D1 ±5 Days**	**Within 7 Days After Last Dose**	**28 (+5) Days After Last Dose**		
Prescreening informed consent or assent	X													
Banked tumor tissue or fresh tumor biopsy for central confirmation of IDH mutation and exploratory biomarkers[1]	X[1]	X[1]												
Main study informed consent or assent		X												
Inclusion/exclusion criteria		X												
Demographics		X												
Disease history		X												
1p19q status testing (if previous results are not available)[6]		X												
Medical and surgical history		X												
Complete physical exam including neurological exam		X									X			
Limited physical exam including neurological exam[7]			X		X		X	X	X	X		X		
Tanner staging of sexual maturity (if applicable)[8]			X					X[8]	X[8]	X[8]	X[8]			
Height[9]		X	X[9]					X[9]	X[9]	X[9]	X			
Weight		X	X		X		X	X	X	X	X			

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Study Day	**D -84 to D -1**	**D -28 to D -1**	**D1**	**D15 ±2 Days**	**D1 ±2 Days**	**D15 ±2 Days**	**D1 ±2 Days**	**D1 ±2 Days**	**D1 ±5 Days**	**D1 ±5 Days**	**Within 7 Days After Last Dose**	**28 (+5) Days After Last Dose**		
KPS/LPPS		X	X[10]		X		X	X	X	X	X	X		
Vital signs[11]		X	X	X	X	X	X	X	X	X	X	X		
ECHO (or other methods according to institutional practice) for LVEF		X									X			
ECG	See Table 2 for ECG schedule.													
Laboratory Evaluations														
Hematology[12,13]		X	X	X	X	X	X	X	X	X	X			
Serum chemistry[12,14]		X	X	X	X	X	X	X	X	X	X			
Coagulation studies[15]		X									X			
Urinalysis[16]		X												
Pregnancy test[17]		X	X		X		X	X	X	X	X	X		
Tumor Assessments														
Central confirmation of measurable non-enhancing disease[18]		X												
Evaluate extent of disease and response to treatment[19]		X						X[19]	X[19]	X	X[19]		X[19]	
Randomization and Study Treatment														

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Visit	**Pre-screen-ing[1]**	**Screen-ing**	**Cycle 1**		**Cycle 2**		**Cycle 3**	**Cycles 4-12**	**Cycle 13-36[2]**	**Cycle 37+ (Odd Cycles Only)[2]**	**End of Treat-ment[3]**	**Safety Follow-up**	**PFS Follow-up[4]**	**OS Follow-up[5]**
Study Day	**D -84 to D -1**	**D -28 to D -1**	**D1**	**D15 ±2 Days**	**D1 ±2 Days**	**D15 ±2 Days**	**D1 ±2 Days**	**D1 ±2 Days**	**D1 ±5 Days**	**D1 ±5 Days**	**Within 7 Days After Last Dose**	**28 (+5) Days After Last Dose**		
Randomization[20]			X											
Study drug administration[21]			X (continuous)											
Study drug compliance and seizure diary assessments[22]			X	X	X	X	X	X	X	X	X			
Other Clinical Assessments														
HRQoL FACT-Br[23]			X		X		X	X[23]	X[23]	X	X			
HRQoL EQ-5D-5L[23]			X					X[23]	X[23]	X	X			
PGI-S, PGI-F questions[23]			X					X[23]	X[23]	X	X			
PGI-C[23]								X[23]	X[23]	X	X			
Neurocognitive assessments[23]			X					X[23]	X[23]	X	X			
In-clinic seizure assessment[24]			X		X		X	X	X	X	X			
Blood for exploratory biomarkers[25]			X	X				X[25]	X[25]	X	X[25]			
Buccal swab for germline mutation analyses (optional)[26]			X											
Tumor biopsy[27]											X			
CSF sample (crossover subjects only)[28]			X								X			
Blood for PK sampling	See Table 2 for blood sampling schedule.													

Table 1: Schedule of Assessments

Visit	Pre-screening[1]	Screening	Cycle 1		Cycle 2		Cycle 3	Cycles 4-12	Cycle 13-36[2]	Cycle 37+ (Odd Cycles Only)[2]	End of Treatment[3]	Safety Follow-up	PFS Follow-up[4]	OS Follow-up[5]
Study Day	**D -84 to D -1**	**D -28 to D -1**	**D1**	**D15 ±2 Days**	**D1 ±2 Days**	**D15 ±2 Days**	**D1 ±2 Days**	**D1 ±2 Days**	**D1 ±5 Days**	**D1 ±5 Days**	**Within 7 Days After Last Dose**	**28 (+5) Days After Last Dose**		
Adverse events[29]	X[29]	X[29]	X	X	X	X	X	X	X	X	X	X		
Prior and concomitant medications/ procedures[30]		X	X	X	X	X	X	X	X	X	X	X		
Survival status and subsequent anticancer therapy check														X

Abbreviations: CSF = cerebrospinal fluid; CXDY = Cycle X Day Y; ECG = electrocardiogram; ECHO = echocardiogram; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; FACT-Br = Functional Assessment of Cancer Therapy – Brain Tumor; HRQoL = health-related quality of life; IDH = isocitrate dehydrogenase; KPS = Karnofsky Performance Scale; LPPS = Lansky Play-Performance Scale; LVEF = left ventricular ejection fraction; OS = overall survival; PFS = progression-free survival; PGI-C = Patient Global Impression of Change; PGI-F = Patient Global Impression of Frequency; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics.

[1] Subjects will sign prescreening consent or assent to allow for central testing of IDH mutation status using banked tumor sample (preferably from the most recent surgery) or fresh tumor biopsy (if no banked tissue is available). Prescreening can be initiated up to 84 days before randomization, and slides may be submitted during the Pre-screening or Screening (up to 28 days before randomization) period; however, testing results must be available as part of subject eligibility review before randomization. Ten freshly cut, unstained slides (4-5 micron each) of formalin-fixed paraffin-embedded (FFPE) tissue and 1 hematoxylin and eosin (H&E) –stained slide, along with the corresponding pathology report, will be shipped to a central laboratory designated by the Sponsor for central confirmation of IDH mutation status to determine eligibility. Any slides remaining after the IDH mutation status testing may also be used for additional exploratory biomarker analysis. After confirmation of eligibility, additional slides are requested for exploratory biomarker analysis. An additional at least 10 additional freshly cut, unstained slides (4-5 micron each) of FFPE tissue or a tumor tissue block, with corresponding pathology report, are to be shipped to a central laboratory designated by the Sponsor. Details regarding sample processing and shipment will be detailed in a separate laboratory manual.

[2] Beginning at Cycle 13, the window for study visits will increase to (±5 days). Beginning at Cycle 37, subjects on-treatment with vorasidenib/placebo will have clinic visits every other cycle (eg, Cycle 39, 41, etc) through End of Treatment (EOT). For subjects requiring more frequent laboratory monitoring for ongoing adverse events (AEs) per the dose modification guidelines (eg, elevated transaminases), additional labs may be performed on the off cycles using central or local labs and recorded as unscheduled assessments.

[3] All subjects will have an EOT visit within 7 days after their last dose. For subjects who cross over from the placebo arm to vorasidenib after centrally confirmed radiographic disease progression (PD) by the blinded independent review committee (BIRC), EOT procedures will be used to confirm eligibility for crossover. EOT assessments performed within 3 days of the Crossover C1D1 visit do not need to be repeated at the Crossover C1D1 visit.

[4] Subjects who discontinue study treatment for reasons other than centrally confirmed radiographic PD by the BIRC or withdrawal of consent from overall study participation (not just study treatment) will have response assessments conducted at the EOT visit. These subjects will enter PFS Follow-up with the same schedule of assessments as before study treatment discontinuation, unless the subject withdraws consent from overall study participation (and not just study treatment) or death occurs.

[5] Subjects will be contacted by phone every 6 months (±4 weeks) beginning at the EOT visit for OS Follow-up. For subjects in PFS Follow-up, OS Follow-up will begin once PFS Follow-up has ended. Subjects will be followed for survival for up to 5 years after the last subject is randomized or until death, withdrawal of consent from overall study

participation, lost to follow-up, or Sponsor ending the study, whichever occurs first. Information regarding subsequent anticancer therapy (including surgery) will also be collected.

[6] Assessment of 1p19q status by local testing (eg, fluorescence in situ hybridization, comparative genomic hybridization array, sequencing) from an accredited laboratory must be available during the Screening period and submitted as part of eligibility review. Previous testing results may be used. If no prior testing was performed, or results are not available, testing must be repeated during the Screening period (preferably from the most recent surgery, and preferably from the same tumor specimen used for central IDH mutation status testing).

[7] Limited physical exam to include respiratory, cardiovascular, abdominal, and neurologic body systems. Additional targeted assessments may be performed as clinically indicated.

[8] All subjects who are 12-17 years of age at the C1D1 visit will also be assessed to determine Tanner stage. Subjects who are less than Stage V (ie, Stage I-IV) at C1D1 will be assessed to determine Tanner stage every 3 months (ie, Day 1 of Cycle 4, 7, etc) through Cycle 37, every 6 months thereafter, and at EOT or until they reach Stage V. Subjects who are assessed as Stage V at C1D1 will not need to be assessed at subsequent visits. Any abnormal or unexpected findings should be recorded as AEs, and consultation with an endocrinologist should be considered.

[9] Height is to be collected at Screening and EOT from all subjects. Subjects who are 12-17 years of age and who are being assessed to determine Tanner stage will also have height collected at the same visits as the Tanner stage assessment: C1D1, every 3 months (ie, Day 1 of Cycle 4, 7, etc) through Cycle 37, and every 6 months thereafter until they reach Tanner Stage V.

[10] On C1D1 and Crossover C1D1, assessment should be conducted predose.

[11] Vital sign measurements to include diastolic and systolic blood pressure, heartrate, respiratory rate, and body temperature. Assessments should be conducted while the subject is seated or supine.

[12] Screening assessments performed within 3 days before C1D1 do not need to be repeated at the C1D1 visit. Hematology and serum chemistry assessments are required at EOT and Crossover C1D1. If assessments for hematology and serum chemistry at EOT were performed within 3 days before Crossover C1D1, these do not need to be repeated at the Crossover C1D1 visit. On C1D1 and Crossover C1D1, assessments should be conducted predose. Safety lab assessments at all visits will be conducted using a central laboratory. Instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

[13] Hematology includes hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, and platelet count. Safety laboratory assessments at all visits will be conducted using a central laboratory. Instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

[14] Serum chemistry includes sodium, potassium, chloride, calcium, magnesium, phosphorus, carbon dioxide, albumin, glucose, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, total bilirubin, and direct bilirubin. Safety laboratory assessments at all visits will be conducted using a central laboratory. Screening eligibility is to be determined based on central laboratory results. Instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

[15] Coagulation includes activated partial thromboplastin time and either prothrombin time or international normalized ratio. Safety lab assessments will be conducted using a central laboratory. Screening eligibility is to be determined based on central laboratory results. Instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

[16] Urinalysis includes color, appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic inspection of sediment. Safety lab assessments will be conducted using a central laboratory. Screening eligibility is to be determined based on central laboratory results. Instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual.

[17] For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a serum or urine pregnancy test will be collected on C1D1 and confirmed negative before dosing, and on Day 1 of all subsequent cycles, and at EOT. A local serum or urine pregnancy test is also to be collected at the 28-day Safety Follow-up visit. On C1D1 and Crossover C1D1, test should be conducted predose. Safety lab assessments will be conducted using a central laboratory. Instructions for the collection, processing, and shipment of samples will be provided in a separate laboratory manual. Central laboratory serum pregnancy test results should be used to determine eligibility at Screening; however, if a central serum pregnancy test is missed or needs to be repeated, a local serum pregnancy test may be used for eligibility.

[18] During Screening, at minimum 2D T1-weighted magnetic resonance imaging (MRI) pre- and postcontrast enhancement, 2D T2-weighted MRI, and 2D fluid-attenuated inversion recovery scans will be collected and submitted to a central imaging facility for central confirmation of eligibility by the BIRC. This includes presence of measurable non-enhancing disease (at least 1 lesion ≥1 cm × ≥1 cm), and that any enhancement is minimal, non-nodular, and non-measurable. If the most recent scan is collected as part of standard of care within 28 days (+7 days) before randomization, it may be used as the screening scan, provided it was acquired using the exact parameters as described in the site-specific imaging core manual. In addition, if available, up to 3 pretreatment (historical) MRI scans, collected as part of standard of care before Screening (do not need to meet exact parameters required for on-study scans), are requested to be submitted; of these, at least 1 submitted should be at least 3 months before Screening.

[19] Response assessment per Response Assessment for Neuro-oncology for Low-Grade Gliomas will be conducted every 12 weeks (84 ±7 days) beginning at C4D1. Beginning at Cycle 37, response assessment will be conducted every 6 months (eg, Cycle 43, Cycle 49) for the next 2 years, and annually after that. All scans collected during the study will be submitted to a central imaging vendor as detailed in a separate site-specific imaging core manual. When radiographic PD is determined by the Investigator, all scans will be reviewed by the BIRC for confirmation of radiographic PD to permit unblinding and determine eligibility for crossover. In the case of radiographic PD assessed by the Investigator that is not confirmed by BIRC, a confirmatory scan may be collected before the next scheduled response assessment (but at least 4 weeks after the previous scan) and submitted for BIRC review. Subjects who discontinue treatment for reasons other than centrally confirmed radiographic PD by the BIRC or withdrawal of consent from treatment and overall study participation (and not just study treatment) will enter PFS Follow-up with the same schedule of assessments as before study treatment discontinuation until radiographic PD is documented by the BIRC. Subjects who cross over to receive vorasidenib will follow the same schedule of response assessments starting at C1D1; during the Crossover period, response, including progression, will be documented according to the Investigator.

[20] Randomization may occur up to 3 days before C1D1.

[21] Vorasidenib and/or matched placebo will be administered orally daily starting on C1D1 in continuous 28-day cycles.

[22] Subject study medication compliance will be assessed using a subject dosing diary. This same diary will be used by the subject to record daily seizure activity including frequency, seizure severity, and loss of consciousness due to seizures. This diary is to be reviewed for compliance (eg, dosing occurred in accordance with the dosing instructions per the Pharmacy Manual and dosing diary) at each clinic visit. Treatment compliance will be assessed using the dosing diary and/or return of unused drug.

[23] HRQoL will be assessed using the FACT-Br and EQ-5D-5L questionnaires, and the PGI-C for overall health; PGI-S for glioma symptoms, neurocognitive function, and seizures; and PGI-F for seizures. Neurocognitive status will be assessed using a validated battery of tests measuring verbal learning, psychomotor function, working memory, attention, and executive function. Questionnaires and tests will be conducted sequentially and, whenever possible, should be the first assessment of the clinic visit. The FACT-Br will be administered at C1D1, C2D1, C3D1, and C4D1 and then every 3 months thereafter (eg, C4D1, C7D1, C10D1) and at EOT. The EQ-5D-5L, PGI-S, and PGI-F questions, and neurocognitive tests will be administered at C1D1 and then every 3 months thereafter (eg, C4D1, C7D1, C10D1) and at EOT; the PGI-C will not be collected at C1D1 and will be administered every 3 months beginning at C4D1 (eg, C4D1, C7D1, C10D1) and at EOT. Beginning with Cycle 37, all assessments will be performed every 6 months (eg, C43D1, C49D1). These assessments should take approximately 30 minutes total to complete.

[24] Seizure frequency, seizure severity, and loss of consciousness due to seizures will be assessed using a subject diary. At the clinic visit on Day 1 of each cycle, the seizure activity information recorded in the diary will be reviewed. In addition, the Investigator, in consultation with the subject, will determine the types of seizures experienced by the subject, including the type of the most severe seizure for the period captured by the diary (eg previous cycle[s]). At C1D1, seizure activity in the previous 30 days is to be discussed with the subject to determine subject's seizure history, including frequency, severity of the most severe seizure (scale of 1 [not bad] to 10 [as bad as you can imagine]), loss of consciousness due to seizures, and types of seizures experienced by the subject, including the type of the most severe seizure.

[25] Blood sample for exploratory biomarkers is to be collected predose on C1D1, C1D15, C4D1, and every third cycle (C7D1, C10D1, etc) thereafter, and at any time during the EOT visit. Beginning with Cycle 37, blood sample for exploratory biomarkers will be collected every 6 months (eg, C37D1, C43D1, C49D1, etc). Sample processing instructions will be provided in a separate sample processing laboratory manual.

[26] For subjects who provide consent, a buccal swab for germline mutation analysis will be collected predose at C1D1. Buccal swab does not need to be repeated at Crossover C1D1 in subjects who cross over to vorasidenib open-label.

[27] For any subject who discontinues treatment and proceeds to have a biopsy or surgery as an intervention, a tumor sample from that surgery is requested if available. Sample processing instructions will be provided in a separate sample processing laboratory manual.

[28] For subjects who cross over to receive unblinded vorasidenib, a CSF sample is requested at Crossover C1D1 predose and at EOT.

[29] After the Screening informed consent or assent has been signed, but before first dose, only serious adverse events (SAEs) that are caused by a protocol-mandated intervention (eg, SAEs related to invasive study procedures such as biopsies) will be recorded. All AEs and SAEs will be recorded starting at first dose through 28 days after the last dose of study drug for all subjects. After the 28-day follow-up period, only SAEs that are considered to be related to study drug should be reported in the safety database. SAEs that occur during the Prescreening period that are related to protocol-mandated intervention (ie, fresh tumor biopsy) will be reported in the safety database.

[30] For all subjects, all medications and procedures occurring within 28 days of first dose through 28 days after the last dose of study drug will be collected.

Table 2: Pharmacokinetic and Electrocardiogram Schedule

Visit	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3+**		**End of Treatment[1]**		**Safety Follow-up**
Study Day	**D -28 to D -1**	**D1**		**D15 ±2 Days**		**D1 ±2 Days**		**D1 ±2 Days**		**Within 7 Days After Last Dose**		**28 (+5) Days After Last Dose**
Assessment	**ECG**	**ECG**	**Blood**	**ECG**	**Blood**	**ECG**	**Blood**	**ECG**	**Blood**	**ECG**	**Blood**	**ECG**
Predose[2, 3]	X	X[2]	X[3]			X[2]	X[3]	X[2]	X[3]			
Postdose												
0.5 hr postdose[4, 5]			X				X					
2 hr postdose[4, 5]		X[4]	X[5]	X[4]	X[5]	X[4]	X[5]					
4 hr postdose[5]			X[5]				X[5]					
Anytime postdose										X	X[5]	X

Abbreviations: CXDY = Cycle X Day Y; ECG = electrocardiogram.

Note: All ECGs should be obtained after 3 minutes of recumbency or semirecumbency. The same schedule should be used for placebo subjects who cross over to vorasidenib after centrally confirmed radiographic disease progression. For all subjects, unscheduled ECGs may be collected at any time during study treatment if clinically indicated.

[1] Assessments to be conducted at End of Treatment (EOT) within 7 days of last dose of study drug may be collected at any time during the visit.

[2] Predose 12-lead ECGs are to be obtained within 30 minutes before dose on C1D1, C2D1, C3D1, and Day 1 of every cycle thereafter. On days where pharmacokinetic (PK) blood sampling is also performed, ECG should be done before PK sampling.

[3] Predose blood samples are to be collected from all subjects within 30 minutes before dose on C1D1, C2D1, C3D1, and Day 1 of every cycle thereafter until EOT.

[4] ECG to be obtained within ±15 minutes of specified time.

[5] Blood samples to be collected within ±10 minutes of the specified time and within 10 minutes after completion of the ECG, if applicable.

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Abbreviation	Definition
2-HG	2-hydroxyglutarate
α-KG	alpha-ketoglutarate
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
$AUC_{0\text{-}24hr}$	area under the concentration × time curve from time 0 to 24 hours
BCRP	breast cancer resistance protein
BIRC	blinded independent review committee
C1D1	Cycle 1 Day 1
CGH	comparative genomic hybridization
CL_p	plasma clearance
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRO	clinical research organization
CSF	cerebrospinal fluid
CV%	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DoR	duration of response
EANO	European Association of Neuro-Oncology
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels

Abbreviation	Definition
EQ-VAS	EQ-visual analog scale
FA	final analysis
FACT-Br	Functional Assessment of Cancer Therapy – Brain Tumor
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	Full Analysis Set
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
FLAIR	fluid-attenuated inversion recovery
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMR	geometric mean ratio
H&E	hematoxylin and eosin
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HRQoL	health-related quality of life
IA	interim analysis
IC_{50}	half-maximal inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IDH	isocitrate dehydrogenase
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
IWRS	interactive web response system
KPS	Karnofsky Performance Scale
LGG	low-grade glioma
LPPS	Lansky Play-Performance Scale
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response

Abbreviation	Definition
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OATP	organic anion transporting polypeptide
OS	overall survival
PD	disease progression
PFS	progression-free survival
PGI-C	Patient Global Impression of Change
PGI-F	Patient Global Impression of Frequency
PGI-S	Patient Global Impression of Severity
P-gp	P-glycoprotein
PH	proportional hazards
PK	pharmacokinetics
PPS	Per-Protocol Analysis Set
PR	partial response
PRO	patient-reported outcome
QD	once daily
QTc	corrected QT interval
QTcF	corrected QT interval using Fridericia's formula
RANO-LGG	Response Assessment for Neuro-Oncology for Low-Grade Gliomas
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TGR	tumor growth rate
TTNI	time to next intervention
TTR	time to response
UGT	uridine 5′-diphospho-glucuronosyltransferase
ULN	upper limit of normal
WHO	World Health Organization
WT	wild type

1. INTRODUCTION

1.1. Cellular Metabolism and Cancer

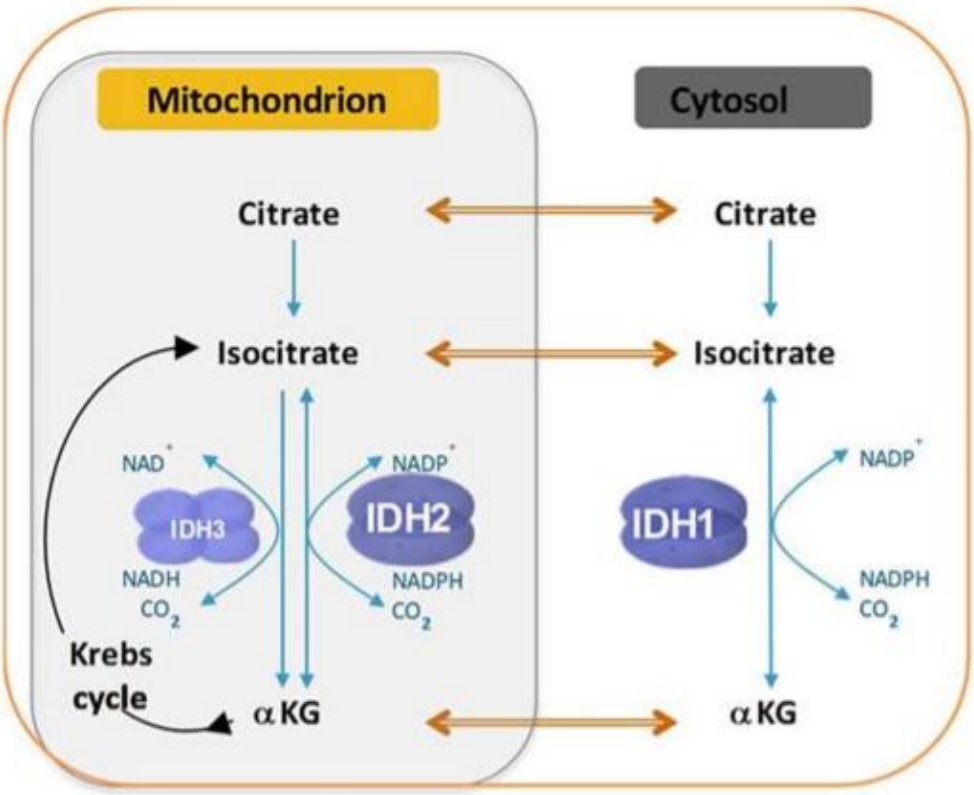
1.1.1. The Role of Isocitrate Dehydrogenase

The isocitrate dehydrogenase (IDH) proteins are critical metabolic enzymes that exist as 3 isoforms: IDH1, IDH2, and IDH3 (Figure 1). All 3 catalyze the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO_2) and alpha-ketoglutarate (α-KG). IDH1 and IDH2 produce nicotinamide adenine dinucleotide phosphate, whereas IDH3 produces only nicotinamide adenine dinucleotide.

Cancer-associated mutations have been identified in IDH1 and IDH2; however, to date, no mutations have been described in IDH3 (Yen et al, 2010). One fundamental difference between IDH1 and IDH2 is the subcellular localization of the 2 proteins. IDH1 is localized in both peroxisomes and cytosol (Geisbrecht and Gould, 1999; Yoshihara et al, 2001). IDH2 is a mitochondrial isoform of IDH (Wang et al, 2013; Yoshihara et al, 2001).

The genes encoding IDH1 and IDH2 are located on chromosomes 2q33.3 and 15q26.1, respectively. Mutations in these IDH proteins most commonly lead to alterations affecting arginine-132 (R132H or R132C) in IDH1 and the analogous arginine residue (R172K) or arginine-140 (R140Q) in IDH2.

Figure 1: The Citric Acid Cycle



Abbreviations: CO_2 = carbon dioxide; IDH = isocitrate dehydrogenase; NADH = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate; αKG = alpha-ketoglutarate.

1.1.2. Tumorigenesis Hypothesis

Mutant IDH1 and IDH2 are not catalytically inactive enzymes but rather possess novel enzymatic activities, consistent with a gain-of-function activity, reconciling the heterozygous nature of the point mutations (Dang et al, 2009). The mutated proteins themselves have a gain-of-function, neomorphic activity, catalyzing the reduction of α-KG to 2-hydroxyglutarate (2-HG) (Dang et al, 2009). The Sponsor's studies established that purified mutant protein efficiently catalyzes the proposed reduction of α-KG to 2-HG while being unable to synthesize isocitrate (Dang et al, 2009). Mutations in IDH1 and IDH2 are almost always mutually exclusive and occur at very early stages of tumor development, suggesting that they promote formation and progression of tumors (Welch et al, 2012).

Evidence supports that cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal production of 2-HG, a potential oncometabolite. High levels of 2-HG have been shown to inhibit α-KG–dependent dioxygenases including histone and deoxyribonucleotide demethylases, which play a key role in regulating the epigenetic state of cells (Chowdhury et al, 2011; Koivunen et al, 2012; Xu et al, 2011). Consistent with 2-HG promoting tumorigenesis via an effect on chromatin structure, patients with IDH mutations display a cytosine-preceding guanine dinucleotide island methylator phenotype, and several studies have shown that overexpression of IDH mutant enzymes can induce histone and DNA hypermethylation as well as impair normal cellular differentiation (Figueroa et al, 2010; Lu et al, 2012; Turcan et al, 2012).

Clinical studies in several tumor types including gliomas and acute myelogenous leukemia have found elevated levels of 2-HG in cells with mutant IDH1 and IDH2 as compared with cells with wild-type (WT) alleles (Gross et al, 2010; Ward et al, 2010). In normal cells, 2-HG is present in low levels. However, IDH1/IDH2 mutations in cancer cells result in the excess accumulation of 2-HG to extremely high levels, which can alter a number of downstream cellular activities. The elevated levels of 2-HG also are present in the sera and urine of some affected patients.

1.1.3. IDH Mutations in Gliomas and Other Solid Tumors

IDH1 and IDH2 mutations have been identified in a variety of solid tumor subtypes, including gliomas, chondrosarcomas, and intrahepatic cholangiocarcinomas. Mutations in IDH1 have been found in approximately 70% of Grade 2 to 3 gliomas and secondary glioblastomas (Yan et al, 2009), 50% of chondrosarcomas (Amary et al, 2011), 20% of intrahepatic cholangiocarcinoma (Borger et al, 2012), and a smaller percentage of extrahepatic cholangiocarcinomas (Kipp et al, 2012). IDH2 mutations occur less frequently, in approximately 4% of Grade 2 to 3 gliomas (Hartmann et al, 2009).

IDH mutations are driver mutations and occur early in gliomagenesis. IDH mutations confer neomorphic activity of the enzyme leading to the production of 2-HG, which is considered an oncometabolite. These mutations are associated with a hypermethylation phenotype, changes in cellular metabolism, and altered response to hypoxic and oxidative stress (Cohen et al, 2013; Dang et al, 2009). Inhibition of the IDH mutant enzyme leading to reduction of 2-HG could potentially affect the biology of the disease and improve clinical outcome through the differentiation of the malignant cells. Given the prevalence of IDH mutations in low-grade

gliomas (LGGs) and the role of 2-HG as an oncometabolite, targeting these IDH mutations and restoring normal function is an active area of research.

1.1.4. Overview of Glioma

In 2019, approximately 26,170 new cases of primary malignant brain tumors will be diagnosed in the United States (NBTS, 2019). In 2008, approximately 133,905 new cases of primary glial brain tumors of the central nervous system (CNS) were diagnosed in the European Union (RARECARE). Grade 2 diffuse gliomas, otherwise known as LGGs, are among the less frequent subtypes (about 3,500 new cases), whereas glioblastomas account for more than 50% (approximately 13,000 new cases) (Ostrom et al, 2017). Based on the World Health Organization (WHO) 2016 classification, gliomas are now classified based on molecular features in addition to histology. IDH mutations and the molecular 1p19q status of tumors differentiate the oligodendroglioma variant in which 1p19q is co-deleted from the astrocytomas that are 1p19q intact (not co-deleted). The mean age of diagnosis for IDH wild-type LGGs is 50 years, while the mean age of diagnosis is 38 years for IDH-mutated 1p19q co-deleted patients, and 42 years for IDH-mutated 1p19q intact patients and includes a range of adolescents in their late teens (14 to 17 years) (Cancer Genome Atlas Research Network et al, 2015). The outcomes associated with these molecularly defined gliomas are under active evaluation; thus far, it appears that the IDH-mutated 1p19q co-deleted population has the most favorable outcome with median survival extending beyond a decade. However, regardless of molecular subtypes, LGGs are incurable and most transform into high-grade gliomas, which are characterized by an aggressive clinical course and shortened survival (Louis et al, 2016).

The optimal management and timing of treatments in patients with IDH-mutated LGG is an area of active clinical investigation considering these tumors typically present during the late adolescent and younger adult age ranges in patients who are otherwise healthy. In general, the management of LGG at the time of initial diagnosis includes maximal safe resection of the tumor followed by active observation with serial imaging (ie, watch and wait) or adjuvant radiotherapy in combination with chemotherapy (NCCN, 2018; Weller et al, 2017). Decision-making to initiate adjuvant chemotherapy or radiotherapy is often based on a risk assessment of various features including age, residual disease, symptoms, and histologic grade or genetic features associated with the disease. Low-risk patients are typically defined as age <40 and/or with gross total resection. Temozolomide and multidrug regimens are the common chemotherapies delivered either with radiotherapy in the adjuvant setting or without in the recurrent setting and have resulted in prolonged progression-free survival (PFS) and overall survival (OS) in glioma patients (Buckner et al, 2016; van den Bent et al, 2005; van den Bent et al, 2017). At the time of progression or recurrence, treatment varies depending on the initial treatment and can include additional resection, radiotherapy, or chemotherapy (Nahed et al, 2015).

Despite available treatment, LGGs are incurable and eventually progress or recur, and there are currently no targeted therapies approved specifically for this disease. Further, available treatments such as radiotherapy are associated with comorbidities including neurocognitive decline, highlighting the unmet need for additional treatment options in this population (McAleer and Brown, 2015). Finally, the transformation into high-grade glioma is common, leading to a more aggressive clinical course that generally leads to death. Because IDH mutations are an

early genetic lesion in the molecular evolution of LGG, targeting this mutant protein early in the disease setting could have the greatest impact on the natural history and may reduce the need for more intensive, noncurative chemoradiation treatments.

1.2. Vorasidenib

Vorasidenib (AG-881) is an orally available, brain-penetrant, potent inhibitor of IDH1 and IDH2 mutant proteins. The compound has been demonstrated to reduce tumor 2-HG levels in mouse xenograft models, including an orthotopic glioma mouse model, by >96%; to reverse growth factor–independent growth in vitro; and to induce cellular differentiation in leukemia cell models.

1.2.1. Summary of Nonclinical Information

Details of the nonclinical development program for vorasidenib are provided in the Investigator's Brochure. A summary of the key information is provided below.

1.2.1.1. Biochemical and Cellular Pharmacology

Initial studies sought to identify IDH1 and IDH2 mutant inhibitors that can suppress 2-HG production in cancer cells. Based on the concentration of drug that achieved half-maximal inhibition (IC_{50}), vorasidenib exhibited low nanomolar potency inhibition against IDH1R132 (H, C, G, L, and S), IDH2R140Q, and IDH2R172K homodimer enzymes and against IDH1 WT/R132H, IDH2 WT/R140Q, and IDH2 WT/R172K heterodimer enzymes. Vorasidenib is a rapid equilibrium inhibitor of IDH1R132H and IDH2R172K homodimer enzymes and a slow-binding inhibitor of IDH2R140Q homodimer and IDH1 WT/R132H, IDH2 WT/R140Q, and IDH2 WT/R172K heterodimers. Vorasidenib also exhibited low nanomolar potency inhibition against IDH1 and IDH2 WT enzymes and is a slow-binding inhibitor these enzymes.

The potency against IDH1 and IDH2 mutant enzymes has also been shown in cell-based assays engineered to express IDH mutations. Each of these cell lines produced high levels of 2-HG as a result of the expression of the mutant IDH proteins. The IC_{50} range for 2-HG inhibition by vorasidenib was 0.04 to 22 nM in cells expressing IDH1R132C, IDH1R132G, IDH1R132H, or IDH1R132S mutations and was 7 to 14 nM and 130 nM in cells expressing IDH2R140Q and IDH2R172K mutations, respectively.

1.2.1.2. Summary of Nonclinical Pharmacology

A series of in vivo pharmacology studies was conducted with vorasidenib in mouse xenograft models, including a human chondrosarcoma/fibrosarcoma (HT1080) model with an endogenous IDH1R132C mutation, a U87 glioblastoma astrocytoma model that over expresses IDH2R140Q, and an orthotopic TS603 glioma model with an endogenous IDH1R132H mutation, confirmed the potency of vorasidenib in suppressing 2-HG levels in tumor tissue. In these studies, tumor concentrations of 2-HG decreased rapidly after administration of vorasidenib, and the inhibition was dose and drug exposure dependent. Administration of repeated doses (every 12 hours) of vorasidenib in the HT1080 and U87 mouse models (IDH1R132C) reduced tumor 2-HG levels by >96% at doses ≥30 mg/kg. In the orthotopic glioma model (IDH1R132H), brain tumor 2-HG levels were reduced by >97% at doses ≥0.1 mg/kg.

Based on in vivo exposure-response analyses, vorasidenib area under the concentration × time curve (AUC) from time 0 to 24 hours ($AUC_{0\text{-}24hr}$) values of 402 hr•ng/mL and 45,200 hr•ng/mL are projected to result in sustained 97% reduction in tumor 2-HG in the glioma indication and the solid and liquid tumor indications, respectively.

1.2.1.3. Absorption, Distribution, Metabolism, and Excretion

Studies to evaluate the absorption, distribution, metabolism, and excretion of vorasidenib were conducted in mice, rats, dogs, and monkeys. In vitro metabolism and transporter studies also were conducted.

The pharmacokinetics (PK) of vorasidenib is characterized by rapid oral absorption, low total body plasma clearance (CL_p) in mice (<0.41 L/hr/kg), rats (0.289 L/hr/kg), and monkeys (0.506 L/hr/kg), and high CL_p in dogs (1.85 L/hr/kg); the volume of distribution at steady state was high in mice (>7.9 L/kg), rats (8.27 L/kg), dogs (13.7 L/kg), and monkeys (12.3 L/kg). The apparent terminal elimination half-life was long except in dogs and ranged from 6.4 hours (dog) to 24 hours (monkey) after intravenous dosing. Oral bioavailability ranged from 6% (dog) to 109% (monkey) across species. The oral bioavailability in the monkey for the 5-, 25-, and 100-mg vorasidenib citrate salt tablets under fasted conditions was estimated to be in the range of 27% to 73%; bioavailability of the 100-mg tablet under fed conditions was 57%. Dosing with food increased exposure to vorasidenib (~2-fold increase in area under the concentration × time curve from time 0 to infinity).

Vorasidenib showed penetration into the brain with brain-to-plasma ratios ranging from 0.62 to 0.720 in mice and 1.11 to 1.48 in rats, based on $AUC_{0\text{-}24hr}$, and from 1.25 to 3.01 in monkeys based on the concentration at 24 hours after the last dose.

The plasma protein binding of vorasidenib is high (>94%) in human, monkey, dog, rat, and mouse, and it was concentration independent.

Metabolism is the major elimination pathway for vorasidenib. Excretion of unchanged vorasidenib in the urine of the rat, dog, and monkey was negligible.

Vorasidenib has a low turnover rate in liver microsomes and hepatocytes from multiple species, including humans. The metabolic profiles were broadly similar among all species tested, and the metabolites observed in vivo were consistent with those seen in vitro. Overall, all human in vitro metabolites were observed either in vitro or in vivo in animal species used for safety testing.

1.2.1.4. Pharmacokinetic Drug Interactions

Vorasidenib was not found to directly inhibit cytochrome P450 (CYP) 1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5; IC_{50} values were >10 μM, which was the solubility limit of vorasidenib in the test system. There was little or no evidence of time-dependent or metabolism-dependent inhibition by vorasidenib of any of the CYP enzymes evaluated, suggesting that formation of reactive metabolites is unlikely. The likelihood of a serious drug-drug interaction (DDI) caused by competitive or mechanism-based inhibition is therefore extremely low.

Vorasidenib induced CYP2B6, CYP2C8, CYP2C9, CYP3A4/5, and uridine 5′-diphospho-glucuronosyltransferase (UGT)1A4 messenger RNA expression in cultured human hepatocytes. Vorasidenib increased CYP2C19 enzyme activity but not CYP2C19 messenger RNA expression

and, therefore, may also induce CYP2C19. Drug-drug interactions with the substrates of these enzymes are possible (except for UGTA14; the likelihood of clinically relevant DDIs upon coadministration of vorasidenib with UGT1A4 substrates is low [Section 1.2.2.4]).

Autoinduction of vorasidenib metabolism was not observed in human hepatocytes in in vitro studies.

Vorasidenib was not a substrate for P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transporter pumps. While no inhibition of P-gp was seen, vorasidenib showed inhibition of BCRP. A literature review revealed no instances of compounds eliminated solely via BCRP. Therefore, it is unlikely that inhibition of BCRP by vorasidenib will result in a DDI. Vorasidenib appears to be an inhibitor of MATE1 and MATE2-K with IC_{50} values of >25 µM. Vorasidenib was neither a substrate nor an inhibitor for organic anion transporting polypeptide (OATP)1B1 or OATP1B3.

1.2.1.5. Safety Pharmacology and Toxicology

The toxicity profile of vorasidenib has been evaluated in vitro in bacterial reverse mutation assays and human peripheral blood lymphocyte micronucleus assays and in vivo in Sprague-Dawley rats and cynomolgus monkeys. The compound was not mutagenic and was well tolerated at estimated human efficacious exposures.

Safety Pharmacology

Multiple studies were conducted to address the potential cardiovascular effects of vorasidenib. These studies demonstrated that vorasidenib does not inhibit the rapidly activating delayed rectifier potassium current at the highest concentration tested (IC_{50}>12.3 µM). A marginal prolongation of the corrected QT interval (QTc) of 32 msec was identified in 1 male monkey administered the nontolerable dose of 40 mg/kg/day in the repeated-dose toxicology study. A modified Irwin assay was conducted to address the potential behavioral effects of vorasidenib on Sprague-Dawley rats; there were no vorasidenib–related effects on endpoints assessed in this assay.

Toxicology

In Good Laboratory Practice (GLP) 28-day and 13-week, repeated-dose toxicology studies, oral doses of vorasidenib at the projected mean steady state $AUC_{0\text{-}24hr}$ at the recommended human dose (50 mg QD; $AUC_{0\text{-}24hr}$ value of 2,766 hr•ng/mL) were well tolerated by both rats and monkeys.

In the GLP rat 28-day study, the lowest dose tested (3 mg/kg/day) was associated with $AUC_{0\text{-}24hr}$ values 8.6-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose. Significant findings at this dose level were reversible and limited to middle ear neutrophil infiltration and increases in liver weight correlating with hepatocellular enzyme induction. The next highest dose level tested (10 mg/kg/day) was associated with $AUC_{0\text{-}24hr}$ values 30-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose. Significant findings at this dose level were reversible and limited to middle ear neutrophil infiltration, gastrointestinal ulceration and erosion consistent with drug irritation, and liver findings that correlated with hepatocellular enzyme induction (increased weights and hepatocellular hypertrophy). Dose-limiting toxicity (DLT) in the 28-day rat study occurred at the highest dose tested (100 mg/kg/day) and was associated with Day 27 $AUC_{0\text{-}24hr}$ values 197-fold the projected

mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose. The cause of DLT was body weight loss/inanition secondary to test article administration. An underlying cause for reduced food consumption was not definitively determined but may have been related to stomach and duodenal lesions.

In the GLP rat 13-week study, the lowest dose tested (5 mg/kg/day) was associated with $AUC_{0\text{-}24hr}$ values 30-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose. Test article-related effects were observed in the liver (increased weight, hepatocellular hypertrophy, hepatocellular vacuolation), kidney (tubular degeneration, tubular epithelial pigment), skeletal muscle (atrophy), testis (seminiferous tubule degeneration/atrophy), prostate and seminal vesicles (atrophy, decreased prostate weight), ovaries (decreased/absent corpora lutea, increased atretic follicles, interstitial cell vacuolation), female tubular reproductive tract (persistent estrus), and mammary gland (atrophy). Hematologic effects were limited to increased lymphocyte counts. Serum chemistry effects suggested decreased food consumption, and other serum chemistry and urinalysis changes were limited to minimal increases in serum phosphorus and fractional excretion of potassium. Most test article-related findings, including all significant histologic findings, were partially to fully reversible over the 4-week recovery period. DLT in the 13-week rat study was observed the highest dose tested (50 mg/kg/day) and was associated with Day 91 $AUC_{0\text{-}24hr}$ values 182-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose. A definitive cause of moribundity was not determined; however, vorasidenib-related marked body weight loss, skeletal muscle atrophy, and/or renal tubular degeneration were considered to have contributed to the deteriorating condition of the animals.

In the monkey 28-day study, the lowest dose tested (3 mg/kg/day) was associated with $AUC_{0\text{-}24hr}$ values 3.4-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose and did not result in any test article-related effects. The next highest dose level (10 mg/kg/day) was associated with $AUC_{0\text{-}24hr}$ values 14-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose. Significant findings at this dose level were limited to effects secondary to hepatocellular enzyme induction (increased weights, hepatocellular hypertrophy, and minimal clinical pathology changes of increased gamma-glutamyl transferase [GGT], alanine aminotransferase [ALT], and sorbitol dehydrogenase) and stress (decrease in zona fasciculata vacuolation in the adrenal cortex). All significant effects in the monkey were reversible except for elevated levels of GGT, which partially resolved after the 14-day recovery period. DLT occurred at a dose of 40 mg/kg/day, resulting in a Day 27 $AUC_{0\text{-}24hr}$ 33-fold the projected efficacious AUC value. The causes of DLT were tremors, ataxia, impaired equilibrium, and head tilt requiring that the animals be euthanized in extremis. Additional vorasidenib–related findings at this dose level were reduced body weight and effects that correlated with hepatocellular enzyme induction, stress, and desquamation of the skin. The predominant clinical observation noted at this dose level was tremors, with the earliest time of onset occurring on Day 7. Tremors were reversible although signs of stress persisted. A marginal QTc prolongation was noted in 1 male monkey at the 40 mg/kg/day dose level on Day 25.

In the monkey 13-week study, the lowest dose tested (2 mg/kg/day) was associated with $AUC_{0\text{-}24hr}$ values 2.5-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose and did not result in any test article-related effects. The next highest dose level (6 mg/kg/day) was associated with $AUC_{0\text{-}24hr}$ values 10-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose. Significant findings at this dose level were

increased liver organ weights with microscopic correlates of hepatocellular hypertrophy, increased mixed cell infiltrate, and Kupffer cell hyperplasia, with recovery observed with hepatocellular hypertrophy and mixed cell infiltrates and partial recovery observed with liver organ weights. Key changes in clinical pathology parameters were limited to those associated with hepatocellular hypertrophy. One male dosed with vorasidenib at the highest dose level (20 mg/kg/day) was euthanized early on Day 51 due to declined clinical condition related to the dilated cardiomyopathy and secondary congestive heart failure. It was, however, unknown if the dilated cardiomyopathy was associated with vorasidenib administration, but a relationship with the test article could not be ruled out. For the animals dosed at the high dose level that survived until scheduled euthanasia, the Day 91 $AUC_{0\text{-}24hr}$ value was 75-fold the projected mean steady state $AUC_{0\text{-}24hr}$ value at the recommended human dose.

Vorasidenib was nonmutagenic in the Ames assay both in the absence and presence of Aroclor-induced rat liver microsomes. Vorasidenib was negative for the induction of micronuclei in human peripheral blood lymphocytes both in the absence and presence of Aroclor-induced rat liver S9 fractions.

1.2.2. Summary of Emerging Clinical Data

The vorasidenib clinical development program was initiated in June 2015. As of 29 April 2020, a total of 8 studies have been completed or are ongoing, including 2 Phase 1 studies designed to evaluate single-agent vorasidenib in subjects with advanced hematologic malignancies (Study AG881-C-001) or advanced solid tumors including gliomas (Study AG881-C-002), and a Phase 1 perioperative study designed to evaluate CNS penetrance and tumor 2-HG suppression of ivosidenib or vorasidenib (Study AG120-881-C-001). Clinical data from these studies are summarized below. Please refer to the Investigator's Brochure for further details on the completed and ongoing studies.

As of 29 April 2020, a total of 226 subjects (63 healthy volunteers and 163 subjects in a patient population) have received at least 1 dose of vorasidenib at a total daily dose ranging from 10 to 1,100 mg, including 46 subjects in Study AG881-C-001, 93 subjects (52 glioma subjects and 41 nonglioma subjects) in Study AG881-C-002, and 24 subjects in Study AG120-881-C-001.

1.2.2.1. AG881-C-002

Study AG881-C-002 is evaluating the safety, PK, pharmacodynamics, and clinical activity of vorasidenib in subjects with solid tumors, including gliomas, harboring an IDH1 or IDH2 mutation. Enrollment in the study is complete and analysis remains ongoing. A total of 93 subjects, including 41 subjects with nonglioma solid tumors and 52 subjects with glioma, were enrolled, and as of 29 April 2020, 9 glioma subjects and none of the nonglioma solid tumor subjects remained on treatment. Five initial dose levels were tested ranging from 25 mg QD to 400 mg QD. Five subjects with glioma experienced adverse events (AEs) of elevated liver transaminases without bilirubin increase at doses of 100 mg and above that were designated as DLTs by the Sponsor. After identification of this safety signal, the 50 mg QD dose level was expanded to include an additional 6 subjects (total n=11) and a 10 mg QD dose level was enrolled (n=6). Although the maximum tolerated dose was not reached in Study AG881-C-002 by the Bayesian logistic regression model used for dose escalation, further dose escalations

above 300 mg QD were not implemented in glioma subjects, and the clinical study team recommended exploration of doses of less than 100 mg QD in glioma.

As of 29 April 2020, all 52 (100.0%) glioma subjects in Study AG881-C-002 have reported at least 1 AE. The most commonly reported AEs (≥10%) among glioma subjects were Headache (24 [46.2%] subjects; ALT increased (23 [44.2%] subjects); Aspartate aminotransferase (AST) increased (21 [40.4%] subjects); Fatigue and Nausea (17 [32.7%] subjects each); Seizure (15 [28.8%] subjects); Hyperglycaemia and Vomiting (10 [19.2%] subjects each); Constipation, Dizziness, and Neutrophil count decreased (9 [17.3%] subjects each); Cough and Diarrhoea (8 [15.4%] subjects each); White blood cell (WBC) count decreased (7 [13.5%] subjects); and Aphasia and Hypoglycaemia (6 [11.5%] subjects each).

Preliminary response data are available as of 03 March 2020 for all 52 glioma subjects treated with vorasidenib in Study AG881-C-002. The evaluable population includes subjects who were enrolled and received at least 1 dose of vorasidenib. The objective response rate in subjects with non-enhancing glioma (n=22) was 18.2%, with 1 subject (4.5%) having a partial response (PR) and 3 subjects (13.6%) having a minor response (MR). Most (16 of 22, 72.7%) subjects with non-enhancing disease showed prolonged stable disease as best response. Across subjects with enhancing disease (n=30), most (17 [56.7%]) subjects had a best response of stable disease. As of 03 March 2020, the median treatment duration was 25.8 months for subjects with non-enhancing disease and 3.25 months for subjects with enhancing disease. Across all subjects with glioma, the median PFS was 7.5 months (95% CI 3.7, 12.9) with 75% of events reported. In non-enhancing glioma subjects, the median PFS was 31.4 months (95% CI 11.2, 40.8) with 59.1% of events reported; 55% of these subjects were alive and progression-free at 24 months ((Mellinghoff et al, 2020) for non-enhancing glioma). In glioma subjects who received at least 1 dose of 50 mg QD (n=20), 17 received at least one cycle of 50 mg QD, with 1 PR (6%), 11 stable disease (65%), and 5 PD (29%) at this dose level as of 03 March 2020.

1.2.2.2. AG120-881-C-001

Study AG120-881-C-001 is evaluating the concentration of 2-HG in resected tumors after treatment with vorasidenib or ivosidenib compared with untreated controls, safety, PK, pharmacodynamics, and clinical activity in subjects with Grade 2 or 3 non-enhancing gliomas with an IDH1 R132H mutation. As of 29 April 2020, 24 subjects had received vorasidenib at either 50 mg QD (n=14) or 10 mg QD (n=10). This includes subjects who were randomized to vorasidenib preoperatively (n=22) and control subjects who were re-randomized to vorasidenib postoperatively (n=2). In this study, subjects received vorasidenib for approximately 4 weeks before surgery and were allowed to receive vorasidenib postoperatively until PD. All subjects proceeded to surgery as planned without delays, and all subjects continued treatment postoperatively. As of 29 April 2020, 7 subjects had discontinued treatment postoperatively, 6 because of PD and 1 because of Investigator decision.

As of 29 April 2020, all 24 subjects treated with vorasidenib in Study AG120-881-C-001 have reported at least 1 AE. The most commonly reported AEs (≥10%) were Nausea (10 [41.7%]); Headache (9 [37.5%]); Diarrhoea and Fatigue (7 [29.2%] each); Constipation (5 [20.8%]); ALT increased, Abdominal pain, Anaemia, and Insomnia (4 ([16.7%] each); AST increased, Hypophosphataemia, Hyperglycaemia, Weight decreased, Dyspepsia, Hypocalcaemia, Upper respiratory infection, and Memory impairment (3 [12.5%] each). Preliminary tumor 2-HG and

PK data from Study AG120-881-C-001 are available as of 26 July 2019. These data demonstrate brain penetrance by vorasidenib 50 mg QD and 10 mg QD. Vorasidenib 50 mg QD showed a brain-to-plasma ratio of 1.74 and >90% suppression of 2-HG in resected tumors from subjects following vorasidenib treatment compared with untreated control tumors (Mellinghoff et al, 2019).

Among the 14 subjects receiving 50 mg QD, an objective response rate of 30.8% was observed with 2 subjects achieving a PR and 2 subjects achieving an MR; an additional 7 (53.8%) subjects had a best response of stable disease (Mellinghoff et al, 2019).

For additional information, please refer to the current version of the vorasidenib Investigator's Brochure.

1.2.2.3. AG881-C-005

Study AG881-C-005 evaluated the absorption, distribution, metabolism, and excretion and the absolute bioavailability of vorasidenib in 5 healthy subjects after administration of a single 50-mg oral dose of [^{14}C]vorasidenib and a concomitant single 0.1-mg intravenous dose of [$^{13}C_6$,$^{15}N_3$]vorasidenib. The total (mean ± standard deviation) recovery of administered radioactive dose over a period of 44 days was 89.2 ±4.54%, with 4.52 ±2.36% in the urine and 84.7 ±5.62% in the feces. Most (78.8%) of the administered radioactivity was recovered in the first 168 hours postdose. The geometric mean absolute oral bioavailability after a single oral dose of 50 mg vorasidenib was 29.1%. Most of the radioactivity recovered in feces was associated with unchanged vorasidenib (55.5% of the dose), while no unchanged vorasidenib was detected in urine. In plasma, vorasidenib accounted for 66.24% and 29.47% of the total radioactivity in the pooled $AUC_{0\text{-}72hr}$ and $AUC_{96\text{-}336hr}$ plasma, respectively. Most of the remaining circulating radioactivity was accounted for by 1 downstream metabolite (M458, AGI-69460, deschloro-methyl sulfone vorasidenib), which represented ~9.10% and 43.92% of the total radioactivity for pooled $AUC_{0\text{-}72hr}$ and $AUC_{96\text{-}336hr}$ plasma, respectively.

1.2.2.4. AG881-C-006

Vorasidenib is considered an inducer of CYP3A4 based on in vitro studies; strong or moderate inducers of the CYP3A4 enzyme, which are also known to induce UGTs, the enzymes responsible for the metabolism of lamotrigine, may also enhance the metabolism of lamotrigine. Because lamotrigine is commonly used as an anti-seizure medication in subjects with glioma, the present study initially excluded use of lamotrigine during study treatment. Study AG881-C-006 evaluated the effect of vorasidenib on the PK of a single dose of lamotrigine in healthy adult subjects. The plasma exposures of single-dose lamotrigine when given after multiple-dose administration of vorasidenib versus given alone were similar (AUC ratios of 92-95% and C_{max} ratio of 95%), suggesting that vorasidenib did not significantly affect the PK of lamotrigine. Overall, the data suggest that coadministration of vorasidenib and lamotrigine appears to be generally safe and well tolerated and is unlikely to lead to clinically relevant decreases in lamotrigine exposures.

Based on the results of Study AG881-C-006, treatment with lamotrigine will be permitted in the present study.

1.2.2.5. AG881-C-007

Study AG881-C-007 evaluated the relative bioavailability, effect of food, and effect of omeprazole on the pharmacokinetics of vorasidenib. In the relative bioavailability portion of the study, 2 formulations of vorasidenib were evaluated. To date, vorasidenib Formulation 1 (herein referred to as vorasidenib uncoated tablet) has been utilized in all clinical studies, including the present study. Formulation 2 (herein referred to as vorasidenib film-coated tablets) is the intended commercial formulation and was introduced in the present study. Both formulations are comprised of common compendial-grade pharmaceutical excipients intended for immediate release and utilize standard solid oral dosage form manufacturing processes. The drug load was changed for vorasidenib film-coated tablets to better accommodate the dose strength range of interest and simplify the manufacturing process for commercial readiness. After single-dose administration, there was an increase in systemic exposure to vorasidenib for the film-coated tablet formulation compared with the uncoated tablet formulation (AUC ratio of 138% and C_{max} ratio of 164%). Based on these results, the dose of 40 mg QD of the vorasidenib film-coated tablets has been selected for this study, which is the dose strength that achieves plasma AUC exposures comparable to the exposures observed at the recommended 50 mg QD of the uncoated tablets (Section 1.3.3).

Study AG881-C-007 also examined the effect of food and effect of multiple doses of omeprazole on the PK of a single dose of vorasidenib in healthy subjects. A high-fat, high-calorie diet increased plasma exposure of vorasidenib (AUC ratio of 137% and C_{max} ratio of 313%). Multiple-dose administration of omeprazole (40 mg QD) did not significantly impact plasma AUC of vorasidenib and slightly lowered vorasidenib C_{max} (28%). Based on these results, the current dose administration guidelines indicating that vorasidenib is to be taken after at least 2 hours of fasting (water is allowed) and that food intake should be avoided for at least 1 hour after study drug will remain in the present study. In addition, multiple-dose administration of omeprazole (40 mg QD) did not significantly impact plasma AUC of vorasidenib and slightly lowered vorasidenib C_{max} (28%).

1.3. Study Rationale

1.3.1. Purpose of the Study

Low-grade IDH-mutated gliomas are generally incurable with a clinical course characterized by progression of disease requiring surgery (sometimes multiple), radiotherapy, chemotherapy, and other supportive therapies. Because of the relentless disease course of IDH-mutated LGG and potential acute and chronic toxicities associated with chemotherapy and radiotherapy, patients classified as low risk often pursue a watch and wait strategy after surgery consisting of active observation with serial imaging and clinical assessments. IDH mutations are considered driver mutations in the genetic evolution of LGG; therefore, inhibiting these mutant proteins early in the disease course in low-risk patients who have undergone surgery only may suppress the growth and transformation of the disease. Vorasidenib is a novel compound targeted to inhibit the mutated IDH1 and IDH2 proteins. Vorasidenib has been extensively evaluated in nonclinical studies and has been shown in vitro and in vivo to effectively inhibit the gain-of-function activity of the mutated IDH protein, leading to >96% reduction of 2--HG in tumor xenograft models. In addition, vorasidenib is brain penetrant, leading to >97% reduction of 2-HG in an orthotopic

glioma xenograft model (TS603) and >90% 2-HG suppression in human tumor samples obtained from an ongoing perioperative study (AG120-881-C-001).

Preliminary clinical data from the first-in-human Phase 1 Study AG881-C-002 show vorasidenib to have a favorable safety profile at doses of less than 100 mg QD, with evidence of clinical activity in subjects with glioma, including 4 objective responses (1 PR, 3 MRs) and most subjects with prolonged stable disease. Additionally, preliminary data from the ongoing perioperative study in subjects with Grade 2 to 3 non-enhancing glioma show a similar safety profile at both the 50 mg QD and 10 mg QD doses and confirm CNS penetrance and tumor 2-HG suppression by vorasidenib. Based on the observed safety and efficacy data in subjects with glioma, vorasidenib may serve as a novel molecularly targeted agent for the treatment of patients with residual or recurrent Grade 2 glioma who have had surgery as their only treatment and are considered to be under active observation, potentially delaying the need for more aggressive chemoradiation therapy.

1.3.2. Justification of the Study Design

Study AG881-C-004 is a randomized, double-blind, placebo-controlled study designed to demonstrate the efficacy and safety of vorasidenib in subjects with a histologically confirmed diagnosis of IDH1 or IDH2 gene-mutated Grade 2 oligodendroglioma or astrocytoma compared with placebo. Subjects eligible for the study are those who have Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria who have had surgery (biopsy, subtotal resection, gross total resection) as their only treatment, are at least 1 year (-1 month) but no more than 5 years (+3 months) from the most recent surgery at the time of randomization, and do not have an immediate need for chemotherapy or radiotherapy in the opinion of the Investigator. In addition, subjects must be considered clinically stable without high-risk clinical, histologic, or radiologic features.

The primary objective of the study is to demonstrate the efficacy of vorasidenib compared with placebo based on radiographic PFS per a blinded independent review committee (BIRC) in subjects with residual or recurrent Grade 2 oligodendroglioma and astrocytoma with an IDH1 or IDH2 mutation who have undergone surgery as their only treatment. The key secondary objective of the study is to demonstrate the efficacy of vorasidenib based on time to next intervention (TTNI) compared with placebo. Eligible subjects will be randomly assigned in a 1:1 ratio to receive vorasidenib or vorasidenib–matched placebo. Randomization will be stratified by local 1p19q status and baseline tumor size based on local assessment. Random assignment of subjects avoids bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment groups. The study includes a matched placebo arm with blinding of all site personnel involved in the evaluation of subjects' response to treatment (eg, Investigators, study coordinators, study pharmacists); this design allows for control of potential influences of the natural course of the disease other than those related to the pharmacologic action of the test drug, and reduces bias in subjective assessments, including both efficacy and safety evaluations. Eligible subjects will continue to receive best supportive care throughout the duration of the study.

The prognosis of IDH-mutated glioma varies by 1p19q status, with the 1p19q co-deleted subtype showing increased sensitivity to alkylator therapy and a favorable outcome, with median survival beyond a decade. Stratification by this molecular feature (co-deleted versus not co-deleted) will

help to maintain balance in both arms. Baseline tumor size has been shown to correlate with long-term outcome among glioma patients and may affect tumor growth kinetics (Shaw et al, 2008; Wijnenga et al, 2018); therefore, stratification by longest diameter (≥2 cm versus <2 cm) will help to maintain balance in both arms.

The study permits the option for subjects in the placebo arm to cross over to the vorasidenib arm upon centrally confirmed radiographic PD documented by the BIRC, provided the subject does not need immediate chemotherapy, radiotherapy, or other treatment in the opinion of the Investigator, and as long as they meet certain eligibility criteria determined at the End-of-Treatment (EOT) visit. Subjects who cross over will follow the same assessment schedule as from Cycle 1 Day 1 (C1D1).

IDH-mutated LGGs are biologically distinct diseases and are more commonly diagnosed in younger patients compared with IDH WT LGGs. Because the timing of adjuvant chemoradiation therapy for LGG has not been established and because both chemotherapy and radiotherapy are associated with short-term and long-term toxicities that can affect a patient's quality of life, the timing of adjuvant chemoradiation in LGG patients remains debatable, and the NCCN and EANO guidelines also endorse careful observation as a management option.

Importantly, these guidelines have yet to incorporate IDH as a molecularly prognostic variable to guide treatment decision-making, as IDH mutation–positive LGG may be the ideal setting to employ a less intensive treatment strategy. Given the relatively slower growth associated with IDH-mutated LGG and that patients with IDH-mutated LGG have a longer disease course than patients with IDH WT or higher-grade disease, they are more susceptible to the long-term toxicities of chemotherapy and radiotherapy that can manifest several years after therapy. Therefore, an opportunity exists to develop a novel targeted therapeutic option for IDH-mutated LGG where an otherwise active observation approach is considered.

Rationale for Inclusion of Adolescents

Pediatric LGG includes different types of tumors constituting clinical entities that vary in their molecular characteristics and prognosis. In general, pilocytic astrocytoma is the most common pediatric LGG, occurring almost exclusively at a young age and comprising approximately 90% of pediatric LGG (Gnekow et al, 2012; Sturm et al, 2017). Pilocytic astrocytomas are almost exclusively IDH wildtype and have a characteristic cystic appearance with a mural enhancing nodule on magnetic resonance imaging (MRI) (Jones et al, 2018; Packer et al, 2017). Other histopathological types of pediatric LGG include, but are not limited to, diffuse astrocytoma, diffuse oligodendrogliomas, and ganglioglioma (Gnekow et al, 2012; Sturm et al, 2017). This subset of pediatric LGG constitutes approximately 10% of pediatric LGG and does not usually harbor the IDH1/2 mutation seen in adults (Jones et al, 2018). However, oligodendroglial and astrocytic pediatric tumors that harbor IDH1/2 mutations tend to occur in older adolescents (≥16 years old) and show resemblance to adult counterparts, following a similar clinical path with an indolent growth and a favorable prognosis (Packer et al, 2017; Ryall et al, 2017; Sturm et al, 2017). These tumors are mostly treated with maximal surgical resection followed by chemotherapy and radiotherapy, although the concerns regarding radiotherapy-associated toxicity in younger patients have limited its use (Ater et al, 2012; de Blank et al, 2019).

Given the epidemiology of LGG, as well as data that support similar drug exposures in adolescent and adult patients (Momper et al, 2013), subjects at least 12 years of age will be

permitted in this study. In addition, the eligibility criteria were designed to allow adolescent subjects to enroll consistent with the *FDA Guidance for Industry Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials (March 2019)*, given that IDH is included on the FDA pediatric molecular target list as substantially relevant to the growth or progression of pediatric cancer.

1.3.3. Rationale for the Dose Selected

1.3.3.1. Dose Justification for 50 mg QD Uncoated Tablet Formulation

An uncoated tablet formulation has been used in all clinical studies to date, including this study. The selection of 50 mg QD as the starting dose for subjects in this study was based on preliminary safety, PK, pharmacodynamic, and efficacy data from 2 ongoing Phase 1 studies (Study AG881-C-002, a first-in-human dose escalation study in solid tumors including gliomas, and Study AG120-881-C-001, a Phase 1 perioperative study in non-enhancing Grade 2/3 gliomas).

Study AG881-C-002 (First-in-Human Dose-Escalation Study)

Data from the ongoing first-in-human Study AG881-C-002 show vorasidenib to have a manageable safety profile in subjects with glioma at doses of less than 100 mg QD. Dose-dependent elevated transaminases without elevated bilirubin were observed in glioma subjects receiving vorasidenib. Five subjects had elevated liver transaminases of Grade ≥2 at dose levels of 100 mg QD and higher, which were designated as DLTs by the study team. These events resolved with dose modification or discontinuation. Exposure safety analysis indicated a trend of increased probability of elevated transaminase with increased plasma exposure; no apparent concomitant drug interaction or underlying etiology was associated with the elevated transaminases. Although the maximum tolerated dose was not reached per protocol by the Bayesian logistic regression model in Study AG881-C-002, due to the occurrence of dose-dependent transaminase elevations occurring at doses of 100 mg QD and higher, the clinical study team recommended that doses of 100 mg QD and higher would no longer be explored in subjects with glioma. Of the 52 subjects with gliomas, 11 subjects received 50 mg QD vorasidenib as their initial dose and an additional 9 subjects received at least 1 dose of 50 mg QD as a result of either intrapatient dose escalation or dose reduction. No Grade 2 or higher liver transaminase AEs were observed in subjects receiving vorasidenib 50 mg QD in that study. As of 03 March 2020, preliminary clinical activity in this study showed 4 subjects with an objective response, including a subject with a confirmed PR while receiving 50 mg QD vorasidenib, and most subjects with best response of prolonged stable disease.

Study AG120-881-C-001 (Perioperative Study)

Preliminary safety data from the perioperative study show a similar safety profile as Study AG881-C-002. As of 26 July 2019, preliminary tumor 2-HG and PK data from the study confirmed CNS penetrance of 50 mg QD vorasidenib with measurable drug concentration in the tumor and >90% suppression of tumor 2-HG.

1.3.3.2. Dose Justification for 40 mg QD Film-Coated Tablet Formulation

A relative bioavailability study was conducted to compare the 2 formulations of vorasidenib (uncoated tablet formulation and film-coated tablet formulation; Section 1.2.2.5). The

film-coated tablet formulation is the intended commercial formulation and was introduced in this study. Based on the results from the bioavailability study, population PK simulations, and available clinical PK data from the vorasidenib Phase 1 studies, steady-state AUCs of 40 mg QD of the film-coated tablet formulation are projected to be comparable to those of 50 mg QD of the uncoated tablet formulation because the 90% CI of the geometric mean AUC ratio (GMR) falls within the accepted 0.8-1.25 bioequivalence interval (GMR of 1.12 [90% CI= 1.07-1.18]) (EMA, 2010; FDA, 2002). These data justify selection of 40 mg QD of the film-coated formulation as the dose for the present study, which is the dose that achieves plasma AUC exposures comparable to the exposures observed at the recommended 50 mg QD dose of the uncoated tablet formulation (Section 1.3.3.1).

1.3.3.3. Dosing Considerations for Adolescents

The dosing recommendation in adolescent subjects was based on preliminary population PK analysis for vorasidenib in adult subjects and extrapolation to adolescent subjects. Preliminary population PK analysis has been conducted in 67 adult subjects with glioma in 2 Phase 1 studies (Study AG881-C-002 and Study AG120-881-C-001). The age distribution for those studies ranges from 16-75 years old. Extrapolation to the adolescent population age group (12 to <18 years old) was made from the adult data with allometric principles with an assumption that an exposure range in pediatrics that matches the exposure range in adults will be efficacious and tolerable and that exposure-efficacy relationships in adults can be extrapolated to adolescents. It was demonstrated that clearance of vorasidenib was consistent with standard allometric relationships to body weight (ie, clearance is proportional to body weight raised to a power of 0.75).

To be eligible for Study AG881-C-004, subjects must be at least 12 years of age and weigh at least 40 kg. A weight of 40 kg was chosen for eligibility because it is the approximate median body weight of a 12-year-old and is generally the lower end of the body weight range that has no clinically relevant effect on drug PK or safety (US FDA, 2019). Adolescents 12 to <18 years of age enrolled in the study will receive the same fixed dose administered in adults (40 mg QD of the film-coated tablet formulation) because this dose is within a 53% difference of the body surface area–adjusted dose. Furthermore, the difference in population PK model–predicted exposures for adolescents (12 to <18 years old) and for adult subjects with glioma receiving 40 mg QD of the film-coated tablet formulation is within 42% based on the geometric mean ratios of the PK parameters. The difference in relative oral bioavailability due to formulation difference was accounted for in the population PK model using the geometric mean AUC ratio for the uncoated and coated tablet formulations (Study AG881-C-007).

In addition, preliminary exposure-safety analysis and clinical observations in subjects receiving 50 mg QD of the uncoated tablet formulation in the current Phase 1 studies show that no clinically relevant increase in risk of liver toxicities is anticipated for adolescents receiving vorasidenib administered 40 mg QD as a film-coated tablet in Study AG881-C-004.

Based on the above assessment, adolescents 12 to <18 years of age and weighing at least 40 kg will be eligible for the study and will receive the same fixed dose administered in adults (40 mg QD of the film-coated tablet formulation).

1.4. Benefit-Risk Assessment

Vorasidenib is an orally available, brain-penetrant, potent inhibitor of the mutant IDH1 and IDH2 proteins, which are frequently mutated in patients with LGG. As of 29 April 2020, a total of 163 subjects with advanced cancers, including 73 subjects with glioma, have been treated with vorasidenib across 3 Phase 1 clinical studies. Vorasidenib has a favorable safety profile at doses of <100 mg daily. Asymptomatic elevated liver transaminases have occurred in some subjects; these events have resolved to Grade 1 or baseline with dose interruption or discontinuation. Specific guidelines for the management of elevated liver transaminases to ensure adequate evaluation and monitoring are presented in Table 4. In the clinical setting, elevated liver transaminases have been identified as a risk in all populations, and differentiation syndrome remains a potential risk of vorasidenib in hematologic malignancies. The principal findings with vorasidenib in the nonclinical setting, which may be potential risks for humans, include neurologic disturbances, gastrointestinal disturbances, liver dysfunction, and skin changes. It is not known whether vorasidenib can cause fetal harm when administered to pregnant women, has an effect on reproduction capacity, or is excreted in human milk. All identified and potential risks continue to be monitored in the clinical setting.

Preliminary data from an ongoing perioperative study have shown brain penetrance of vorasidenib 50 mg QD, with >90% suppression of 2-HG in treated tumors compared with untreated control tumors. As of 03 March 2020, vorasidenib has also demonstrated preliminary clinical activity with an objective response rate of 18.2% (1 PR, 3 MR) and a median treatment duration of 25.8 months in subjects with non-enhancing gliomas. A median PFS of 31.4 months was observed in subjects with non-enhancing glioma, with 59.1% of events reported.

Based on the cumulative nonclinical and clinical data generated with vorasidenib to date, the risks of vorasidenib treatment do not outweigh the potential benefit in patients with Grade 2 non-enhancing glioma, the intended patient population for this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of vorasidenib based on radiographic PFS per BIRC compared with placebo in subjects with residual or recurrent Grade 2 oligodendroglioma and astrocytoma with an IDH1 or IDH2 mutation who have undergone surgery as their only treatment.

2.2. Key Secondary Objective

The key secondary objective of the study is to demonstrate the efficacy of vorasidenib based on TTNI compared with placebo.

2.3. Other Secondary Objectives

The other secondary objectives of the study are:

- To evaluate the safety and tolerability of vorasidenib.
- To evaluate vorasidenib and placebo with respect to tumor growth rate (TGR) as assessed by volume per the BIRC.
- To evaluate the efficacy of vorasidenib and placebo based on objective response, CR+PR, time to response (TTR), time to CR+PR, duration of response (DoR), and duration of CR+PR, with response assessed per the BIRC and the Investigator.
- To evaluate vorasidenib and placebo with respect to OS.
- To evaluate vorasidenib and placebo with respect to health-related quality of life (HRQoL) as assessed by the Functional Assessment of Cancer Therapy – Brain (FACT-Br) questionnaire.
- To evaluate vorasidenib and placebo with respect to PFS per the Investigator assessment.
- To evaluate the PK of vorasidenib and its circulating metabolite AGI-69460 in plasma.

2.4. Exploratory Objectives

The following objectives are also to be explored:

- To evaluate, for subjects who cross over from placebo to vorasidenib, the time from first dose of vorasidenib to documented progression on vorasidenib, as assessed by the Investigator, or death due to any cause, whichever occurs first.
- To evaluate TGR before and after treatment with vorasidenib among subjects who cross over from placebo to vorasidenib.
- To evaluate HRQoL with vorasidenib and placebo as assessed by the EuroQol 5 Dimensions, 5-Level (EQ-5D-5L) questionnaire and Patient Global Impression (PGI) questions.

- To evaluate neurocognitive function in subjects receiving vorasidenib and placebo as assessed by a validated battery of cognitive performance instruments.
- To evaluate seizure activity in subjects receiving vorasidenib and placebo.
- To evaluate the molecular and cellular markers that may be predictive of response and/or resistance, where feasible, in blood and archival tumor tissue.
- To evaluate TGR before and after treatment with vorasidenib and placebo.
- To evaluate time to malignant transformation and radiographic changes associated with histopathology-proven malignant transformation in subjects who have surgery or biopsy as an intervention.

2.5. Study Endpoints

2.5.1. Primary Endpoint

The primary endpoint is PFS, defined as the time from date of randomization to date of first documented radiographic PD (as assessed by the BIRC per modified Response Assessment for Neuro-oncology for Low-Grade Gliomas [RANO-LGG; Appendix 11.1]) or date of death due to any cause, whichever occurs earlier.

2.5.2. Key Secondary Endpoint

The key secondary endpoint is TTNI, defined as the time from randomization to the initiation of the first subsequent anticancer therapy (including vorasidenib, for subjects randomized to placebo who subsequently cross over) or death due to any cause.

2.5.3. Other Secondary Endpoints

The other secondary endpoints are:

- Adverse events, serious adverse events (SAEs), and AEs leading to discontinuation or death, and severity of AEs as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.
- Safety laboratory parameters, vital signs, 12-lead electrocardiograms (ECGs),left ventricular ejection fraction (LVEF), Karnofsky Performance Scale (KPS)/Lansky Play-Performance Scale (LPPS), and concomitant medications.
- TGR as assessed by volume, defined as the percentage change in tumor volume every 6 months as assessed per BIRC.
- Objective response, defined as a best overall response of CR, PR, or MR as assessed by the Investigator and by the BIRC per modified RANO-LGG.
- CR+PR, defined as a best overall response of CR or PR as assessed by the Investigator and by the BIRC per modified RANO-LGG.
- Time to response, defined as the time from the date of randomization to the date of first documented CR, PR, or MR for responders as assessed by the Investigator and by the BIRC per modified RANO-LGG.

- Time to CR+PR, defined as the time from the date of randomization to the date of first documented CR or PR for subjects with CR or PR as assessed by the Investigator and by the BIRC per modified RANO-LGG.
- Duration of response, defined as the time from the date of first documented CR, PR, or MR to the earlier of the date of death due to any cause or first documented radiographic PD as assessed by the Investigator and by the BIRC per modified RANO-LGG.
- Duration of CR+PR, defined as the time from the date of first documented CR or PR to the earlier of the date of death due to any cause or first documented radiographic PD as assessed by the Investigator and by the BIRC per modified RANO-LGG.
- Overall survival, defined as the time from the date of randomization to the date of death due to any cause.
- HRQoL as assessed by the FACT-Br questionnaire.
- Progression-free survival as assessed by the Investigator per modified RANO-LGG.
- Serial or sparse blood sampling at specified time points for determination of plasma concentrations of vorasidenib and its circulating metabolite AGI-69460.

2.5.4. Exploratory Endpoints

The exploratory endpoints are:

- In the subset of subjects who cross over from placebo to vorasidenib after centrally confirmed radiographic PD by BIRC, the time from first dose of vorasidenib to the date of documented progression on vorasidenib, as assessed by the Investigator per modified RANO-LGG, or death due to any cause, whichever occurs first.
- In the subset of subjects who cross over from placebo to vorasidenib after centrally confirmed radiographic PD by BIRC, TGR before and after treatment with vorasidenib.
- HRQoL as assessed by the EQ-5D-5L questionnaire and PGI questions.
- Neurocognitive function as assessed by a validated battery of cognitive performance instruments measuring verbal learning, psychomotor function, working memory, attention, and executive function.
- Frequency, severity, and type of seizures, seizure AEs, number of antiepileptic drugs, and changes in antiseizure medications (dose, frequency).
- Baseline molecular and protein profiling in tumors, and morphologic, functional, epigenetic, biologic, and metabolic profiling in blood, plasma, and/or cerebrospinal fluid (CSF).
- TGR before and after treatment with vorasidenib and placebo.
- Time to malignant transformation and radiographic changes, defined as the time from the date of randomization to the date of first histopathologic evidence of transformation and radiographic changes (eg, new enhancement, TGR changes, bidimensional changes) in subjects who have surgery or biopsy as an intervention.

3. STUDY DESIGN

3.1. Overall Study Design

This is a Phase 3, global, multicenter, double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of vorasidenib and placebo in approximately 340 subjects with residual or recurrent Grade 2 glioma with an IDH1 or IDH2 mutation.

Subject eligibility will be determined during a Prescreening period (central confirmation of IDH mutation status only), which is to occur up to 84 days before randomization (central confirmation of IDH mutation status only), and a Screening period, which will occur within 28 days before randomization (all other eligibility requirements, including central confirmation of non-enhancing disease by imaging). Subjects are required to have a histologically confirmed diagnosis of IDH1 or IDH2 gene–mutated Grade 2 oligodendroglioma or astrocytoma (per WHO 2016 classification) with residual or recurrent disease. Subjects must have had at least 1 prior surgery (biopsy, sub-total resection, or gross-total resection), with the most recent surgery occurring at least 1 year (-1 month) and not more than 5 years (+3 months) before the date of randomization, no other treatment including systemic chemotherapy or radiotherapy, and not be in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator. Central confirmation of IDH1 or IDH2 mutation status in the tumor sample (archived [preferably from most recent surgery] or fresh biopsy) and presence of measurable non-enhancing disease based on imaging review by the BIRC are required before randomization.

Subjects who meet all eligibility criteria will be randomized 1:1 to receive vorasidenib orally at a dose of 40 mg or vorasidenib–matched oral placebo QD. Subjects will receive study treatment in continuous 28-day cycles. Subjects may continue treatment with their assigned study treatment until centrally confirmed radiographic PD by the BIRC; development of unacceptable toxicity; need for initiation of chemotherapy, radiotherapy, or other anticancer therapy in the opinion of the Investigator in the absence of centrally confirmed radiographic PD by the BIRC; confirmed pregnancy; death; withdrawal of consent from treatment; lost to follow-up; or Sponsor ending the study, whichever occurs first.

Subjects who discontinue study treatment for reasons other than centrally confirmed radiographic PD by the BIRC or withdrawal of consent from treatment and overall study participation (and not just study treatment) will enter PFS Follow-up with the same schedule of assessments as before study treatment discontinuation until radiographic PD is documented by the BIRC. Overall Survival Follow-up assessments will occur approximately 6 months (±4 weeks) after EOT (for subjects in PFS Follow-up, OS Follow-up will begin once PFS Follow-up has ended) and will continue for up to 5 years after the last subject is randomized, or all subjects have died, withdrawn consent from overall study participation, or are lost to follow-up, or the Sponsor ends the study, whichever occurs first.

End of study is defined as the time at which all subjects have discontinued study treatment and completed the OS Follow-up period, died, withdrawn consent from overall study participation, are lost to follow-up, or the Sponsor ends the study, whichever occurs first. Final analysis for OS will be conducted at the end of the study.

3.2. Unblinding and Crossover

Once radiographic criteria for PD by RANO-LGG are met according to the Investigator, MRI scans for the subject will be assessed by the BIRC for central confirmation of radiographic PD by RANO-LGG criteria before unblinding to determine eligibility for crossover. If radiographic PD is not confirmed by the BIRC, a confirmatory scan may be collected before the next scheduled disease assessment (but at least 4 weeks from the previous scan) and submitted for BIRC review. After confirmation of radiographic PD by the BIRC, the subject and site staff will be unblinded to treatment assignment.

If radiographic PD by RANO-LGG criteria is not confirmed by the BIRC, unblinding for determination of eligibility for crossover will not be permitted. If a medical decision is made to discontinue study treatment for reasons other than centrally confirmed radiographic PD by the BIRC, treatment assignment will not be unblinded. If radiographic PD is centrally confirmed during PFS Follow-up, treatment assignment will then be unblinded to determine eligibility for crossover.

Subjects who are determined to be receiving placebo upon unblinding after centrally confirmed radiographic PD, and who are not in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator, will have the option to cross over to receive vorasidenib, in consultation with the Medical Monitor, provided the following eligibility criteria are met based on the EOT assessments: all initial screening eligibility criteria except Inclusion Criteria numbers 1, 3, 4, 5, 6, and 12 and Exclusion Criteria numbers 1, 6, and 8. Subjects who cross over to vorasidenib will restart the schedule of assessments at C1D1 and follow the same schedule of assessments as in the blinded treatment phase. Subjects who cross over to vorasidenib may continue to receive vorasidenib until PD according to the Investigator, development of unacceptable toxicity, start of subsequent anticancer therapy, confirmed pregnancy, death, withdrawal of consent from treatment, lost to follow-up, or Sponsor ending the study, whichever occurs first.

Subjects who are determined to be receiving vorasidenib upon unblinding after centrally confirmed radiographic PD will not be permitted to continue vorasidenib.

3.3. Blinded Independent Review Committee

A BIRC, composed of a group of independent neuro-radiologists, will be used to assess radiographic eligibility for study entry, the primary efficacy endpoint of radiographic PFS per modified RANO-LGG criteria, and the secondary efficacy endpoint of TGR as assessed by volume. The BIRC will also be used to confirm radiographic PD by the Investigator to permit unblinding and crossover.

The BIRC will review the screening MRI scan to confirm the presence of measurable non-enhancing disease and that any enhancement present is minimal, non-nodular, and non-measurable. The BIRC will provide on-treatment response assessments per modified RANO-LGG criteria as part of the primary efficacy analysis, and tumor volume assessments as part of the secondary efficacy analysis of TGR. All MRI scans will be sent to the BIRC for assessment as detailed in the site-specific Imaging Core Manual.

The requirements of these reviews will be specified in the Independent Radiology Review Imaging Charter.

3.4. Independent Data Monitoring Committee

Safety and other clinical data will be reviewed regularly by an independent data monitoring committee (IDMC) to ensure the safety of therapy. The first safety review meeting will be conducted when approximately 20 subjects have completed 2 cycles of therapy or have discontinued earlier; thereafter, meetings will be conducted approximately every 6 months or on an ad hoc basis. In addition to the safety data review, the IDMC will review efficacy data of PFS at each of the prespecified interim efficacy analyses. Members of the IDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The Sponsor will remain blinded to the data during the IDMC review.

All summaries and analyses by treatment arm for the IDMC review will be prepared by an independent statistical group. Following their data review, the IDMC will provide a recommendation as to whether the study may continue, whether an amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

The requirements of these reviews will be specified in the IDMC charter.

3.5. Criteria for Study Closure

This study may be prematurely closed if, in the opinion of the Sponsor, there is sufficiently reasonable cause. In the event of such action, written notification documenting the reason for study closure will be provided to each Investigator.

Circumstances that may warrant premature study closure include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects (an IDMC will review the safety data on a regular basis to ensure the benefit-risk ratio)
- Interim analyses indicate futility or need to cross subjects over to active therapy
- Failure to enroll subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Plans to modify, suspend, or discontinue the development of the study drug
- Other administrative reasons

If the study is terminated early for any reason other than unacceptable toxicity, the Sponsor will continue to provide study drug in this study or a separate rollover study to subjects who, in the opinion of the Investigator, are benefitting from treatment. Should the study terminate prematurely because of unacceptable toxicity, all study materials must be destroyed or returned to the Sponsor or Sponsor's designee.

3.6. Temporary Modifications Allowed During COVID-19 Public Health Emergencies

In the event of a public health emergency related to coronavirus disease 2019 (COVID-19) that affects a geographic area (eg, state, province, country, region, continent) and impedes adherence to protocol-specified procedures, certain modifications (Section 3.6.1) are temporarily allowable

to ensure subject safety, maintain compliance with good clinical practice (GCP), and minimize risks to trial integrity; the protocol must be followed to the fullest extent possible.

These modifications are only allowable 1) when consistent with applicable regulations and guidance and 2) for the duration of the COVID-19 public health emergency. During this period, the need for all implemented modifications will be reassessed, and the Sponsor will no longer allow these modifications once the situation resolves.

Documented approval from the Sponsor is required before these modifications can be implemented.

The Sponsor has conducted a risk assessment for concomitant use of a COVID-19 vaccine with vorasidenib with specific consideration for the trial population and determined that the COVID-19 vaccine given to a trial subject is considered a simple concomitant medication with no interaction that requires advice on timing of the vaccine or other aspects that need to be mitigated.

3.6.1. Allowable Temporary Modifications

The following temporary modifications are allowed in the event of a COVID-19 public health emergency and must be reported as protocol deviations; refer to Table 1 for the timing of assessments:

- Alternative distribution of study drug
  - Study drug may be shipped to a local health-care provider or pharmacy or, if necessary, directly to a subject. The quantity to be shipped must be reviewed and approved in advance by the Sponsor (or designee), in agreement with the Investigator.
  - Secure, trackable delivery methods (delivery service companies [eg, DHL], couriers, and hand delivery) must be used.
  - Sponsor (or designee) approval is required before each shipment. Shipment will be permitted only if, at minimum, a telemedicine visit has been conducted that incorporates appropriate safety assessments.
- Returning unused study drug, empty study drug packaging, and relevant drug diary pages
  - Return of unused study drug and empty study drug packaging may be delayed until the subject's next visit to the study site. In certain circumstances, the nature of the return process may vary (eg, personal protective equipment may be required).
  - Return of paper drug diaries may be delayed. Site, with Sponsor agreement, should provide instructions to subjects regarding timing and method for returning relevant drug diary pages.
- Telemedicine visits for assessments other than patient-reported outcomes (PROs)

  - Telemedicine visits, preferably via video conference, are permissible for all assessments that can be completed via this mode (eg, medical history, concomitant medications, review of AEs).

- Telemedicine for collection of PROs
  - Sponsor agreement is needed before implementing alternative solutions for PROs that were intended to be collected at the site.
- Use of laboratories and health-care providers not specified in the clinical trial documentation
  - For assessments that cannot be completed via telemedicine, the use of health-care providers and laboratories that are not specified in the clinical trial documentation (eg, an imaging facility, clinic, or local practice that is more readily accessible by the subject) is permissible for all assessments that can be completed via this mode (eg, blood collection for laboratory assessments, ECG, physical examinations, imaging).
  - Use of a laboratory or health-care provider not specified in the clinical trial documentation requires coordination between the subject, the Investigator, and the subject's local health-care provider.
  - The Investigator must document their review of the results provided by laboratories and health-care providers not specified in the clinical trial documentation.
- Home health study support
  - For assessments that cannot be completed via telemedicine, home health-care provider visits are permissible for all assessments that can be completed via this mode (eg, physical examination, collection of laboratory samples).
  - The Investigator must document their review of the results of home health-care provider visits.
- Virtual informed consent/reconsent in lieu of in-person informed consent/reconsent
  - Consent to participate in the portion of the study intended solely to determine eligibility for the full study (ie, prescreening) may be completed virtually and documented in the relevant subject medical records.
  - Reconsent (ie, consenting to an amended version of the protocol) may be completed virtually and documented in the relevant subject medical records.
  - The other allowable modifications described in this section may require consent from the subject because their implementation requires a variation from the specifications in the protocol to which the subject has consented (eg, consent for a home visit, consent to provide name and address to a third-party delivery service, consent to a new mode of completing study procedures and receiving study drug). In these instances, consent may be completed virtually where allowed by the applicable regulations and documented in the relevant subject medical records.

4. STUDY POPULATION

4.1. Number of Subjects

A total of approximately 340 subjects will be randomized in a 1:1 ratio to receive vorasidenib or vorasidenib-matched placebo, stratified by local 1p19q status (co-deleted or not co-deleted) and baseline tumor size per local assessment (longest diameter of ≥2 cm or <2 cm).

4.2. Inclusion Criteria

Subjects must meet all the following criteria to be enrolled in the study:

1. Be at least 12 years of age and weigh at least 40 kg.
2. Be able to understand and willing to sign informed consent or assent as determined by local requirements and willing to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling and urine sampling, during the study. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's institutional review board (IRB)/independent ethics committee (IEC). A parent or legal guardian must sign informed consent for adolescent subjects who sign assent. (Note: Subjects who do not read and/or speak one of the languages in which the HRQoL instruments are provided will be permitted to enroll and not complete these HRQoL outcome instruments, assuming all other eligibility criteria are met.)
3. Have Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria.
4. Have had at least 1 prior surgery for glioma (biopsy, sub-total resection, gross-total resection), with the most recent surgery having occurred at least 1 year (-1 month) and not more than 5 years (+3 months) before the date of randomization, and no other prior anticancer therapy, including chemotherapy and radiotherapy, and not be in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator. (Note: Subjects undergoing biopsy solely to obtain tissue for central confirmation of IDH mutation status [eg, tissue from previous surgery was exhausted or not available] will be considered an exception and will not need to wait an additional year from biopsy to be eligible.)
5. Have confirmed IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status disease by central laboratory testing during the Prescreening period and available 1p19q status by local testing (eg, fluorescence in situ hybridization [FISH], comparative genomic hybridization [CGH] array, sequencing) using an accredited laboratory.
6. Have MRI-evaluable, measurable, non-enhancing disease, as confirmed by the BIRC, assessed at Screening on 2D T2-weighted or 2D T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI with ≤4 mm slice thickness and no interslice gap. Measurable non-enhancing disease is defined as at least 1 target lesion measuring ≥1 cm × ≥1 cm (bidimensional). Enhancement that is centrally confirmed by the BIRC to be minimal,

non-nodular, and non-measurable and that has not changed between the 2 most recent scans (including screening scan) will be permitted.

7. Have a KPS (Appendix 11.8) score (for subjects ≥16 years of age) or LPPS (Appendix 11.7) score (for subjects <16 years of age) of ≥80%.
8. Have expected survival of ≥12 months.
9. Have adequate bone marrow function as evidenced by:
    a. Absolute neutrophil count ≥1,500 mm^3 or ≥1.5 × 10^9/L
    b. Hemoglobin ≥9 g/dL
    c. Platelets ≥100,000 mm^3 or ≥100 × 10^9/L.
10. Have adequate hepatic function as evidenced by:
    a. Serum total bilirubin ≤1.5 × upper limit of normal (ULN) unless considered due to Gilbert's disease after approval by the Medical Monitor, and
    b. AST at or below ULN and ALT at or below ULN, and
    c. Alkaline phosphatase (ALP) ≤2.5 × ULN.
11. Have adequate renal function as evidenced by:
    a. Serum creatinine ≤2.0 × ULN, OR
    b. Creatinine clearance >40 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation: (140 – Age) × (Weight in kg) × (0.85 if female) / 72 × Serum Creatinine (for subjects ≥18 years of age). For subjects <18 years of age, the Bedside Schwartz method (Schwartz and Work, 2009) is to be used: 0.413 × (Height in cm / Serum Creatinine in mg/dL).
12. Have recovered from any clinically relevant toxicities associated with any prior surgery for the treatment of glioma unless stabilized under medical management.
13. Female subjects of childbearing potential must have a negative serum pregnancy test before the start of therapy. Women of childbearing potential are defined as having had onset of their first menstrual period and have not undergone a hysterectomy or bilateral oophorectomy or are not naturally postmenopausal (ie, have not menstruated at all in the preceding 24 consecutive months). Women of childbearing potential as well as fertile men with partners who are women of childbearing potential must agree to abstain from sexual intercourse or to use 2 highly effective forms of contraception, at least one of which must be a barrier method, from the time of giving informed consent or assent, throughout the study, and for 90 days after the last dose of vorasidenib. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject; periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Highly effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone release systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

4.3. Exclusion Criteria

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Have had any prior anticancer therapy other than surgery (biopsy, sub-total resection, gross-total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, laser ablation, etc.
2. Have features assessed as high-risk by the Investigator, including brainstem involvement either as primary location or by tumor extension, clinically relevant functional or neurocognitive deficits due to the tumor in the opinion of the Investigator (deficits resulting from surgery are allowed), or uncontrolled seizures (defined as persistent seizures interfering with activities of daily life AND failed 3 lines of antiepileptic drug regimens including at least 1 combination regimen).
3. Concurrent active malignancy except for a) curatively resected nonmelanoma skin cancer or b) curatively treated carcinoma in situ. Subjects with previously treated malignancies are eligible provided they have been disease-free for 3 years at Screening.
4. Are pregnant or breastfeeding.
5. Have an active infection that requires systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of C1D1.
6. Have a known hypersensitivity to any of the components of vorasidenib.
7. Have significant active cardiac disease within 6 months before the start of study treatment, including New York Heart Association Class III or IV congestive heart failure (Appendix 11.2), myocardial infarction, unstable angina, and/or stroke.
8. Have LVEF <40% by echocardiogram (ECHO) (or by other methods according to institutional practice) obtained within 28 days before the start of study treatment.
9. Have a heart-rate corrected QT interval using Fridericia's formula (QTcF) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with bundle branch block and prolonged QTcF are permitted with approval of the Medical Monitor.
10. Are taking therapeutic doses of steroids for signs/symptoms of glioma. Subjects taking physiologic doses (defined as equivalent of ≤10 mg prednisone daily) for medical conditions not related to glioma will be permitted.
11. Exclusion Criterion 11 removed in Protocol Amendment 1 (v2.0).
12. Are taking any medications that are CYP2C8, CYP2C9, CYP2C19, or CYP3A substrates with a narrow therapeutic index as listed in Appendix 11.3. (Subjects should be transferred to other medications before receiving the first dose of study drug.)
13. Have known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, known positive human immunodeficiency virus antibody results, or AIDS-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed by institutional practice will be permitted.

14. Have known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other condition that limits the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).
15. Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of C1D1) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

4.4. Subject Identification and Registration

Subjects who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria (Section 4.2 and Section 4.3, respectively) have been satisfied and that the subject is eligible for participation in this clinical study. The Medical Monitor and Sponsor will review targeted eligibility criteria for all subjects for confirmation of eligibility before randomization.

4.5. Treatment Discontinuation

Subjects may discontinue treatment with study drug for any of the following reasons:

- Adverse event
- Radiographic PD
- Clinical PD in the absence of centrally confirmed radiographic PD by the BIRC
- Investigator decision
- Subject decision to withdraw from study treatment
- Protocol violation; noncompliance with study drug regimen or protocol requirements
- Confirmed pregnancy
- Subject death
- Lost to follow-up
- Study terminated by Sponsor

When a subject discontinues study drug, the primary reason(s) for discontinuation or withdrawal must be recorded in the appropriate sections of the electronic case report forms (eCRFs), and all efforts will be made to complete and report protocol-defined study observations as thoroughly as possible.

Subjects who discontinue study treatment for reasons other than centrally confirmed radiographic PD by the BIRC or withdrawal of consent from treatment and overall study participation (and not just study treatment) will enter PFS Follow-up with the same schedule of

assessments as before study treatment discontinuation until radiographic PD is documented by the BIRC.

4.6. Subject Withdrawal and Study Completion

Subjects may voluntarily withdraw from the study at any time for any reason. A subject's withdrawal from the study will not jeopardize the relationship with their health-care providers or affect their future care. Subjects will be withdrawn from the study for the following reasons:

- Subject lost to follow-up
- Termination of the study by Sponsor
- Voluntary withdrawal from overall study participation by subject

If a subject withdraws consent from overall study participation (and not just study treatment), no further evaluations should be performed, and no attempts should be made to collect additional data.

Subjects who withdraw from the study will not be replaced.

Subjects are considered to have completed the study once they complete the OS Follow-up period (defined as up to 5 years after the last subject is randomized). The study is considered completed at the end of the OS Follow-up period, when all subjects have completed the OS Follow-up period, have died, are lost to follow-up, have withdrawn consent from overall study participation, or the Sponsor has terminated the study, whichever occurs first.

5. STUDY TREATMENT

5.1. Study Drug

Vorasidenib will be provided as 10-mg and 40-mg strength tablets to be administered orally. Placebo will be supplied as matched tablets to be administered orally.

All study drugs are for investigational use only and are to be used only within the context of this study. All study drug products will be supplied by the Sponsor. Please see the Investigator's Brochure for further details regarding study drug.

5.2. Study Drug Packaging and Labeling

Vorasidenib tablets and matched placebo will be supplied in appropriate containers with child-resistant closures and will be labeled appropriately as investigational product for this study.

Packaging and labeling will be prepared to meet all regulatory requirements.

5.3. Study Drug Storage

Bottles of vorasidenib tablets and matched placebo must be stored according to the package label.

All study drug products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

5.4. Method of Assigning Subjects to Treatment

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive vorasidenib orally at a dose of 40 mg QD or vorasidenib–matched oral placebo QD. Randomization will be stratified by local 1p19q status (co-deleted or not co-deleted) and baseline tumor size per local assessment (longest diameter of ≥2 cm or <2 cm).

The randomization schedule will be generated by an independent statistical group. The randomization assignment will be implemented by an interactive web response system (IWRS).

5.5. Blinding

Study subjects, Investigators, relevant clinical site staff, and the Sponsor will be blinded to study treatment assignment. The IWRS will assign each subject specific Medication ID–labeled study drug containers. vorasidenib and placebo will be packaged and labeled identically so that the study pharmacist will remain blinded to treatment assignment.

Study subjects and relevant clinical site staff will remain blinded for the duration of study treatment until centrally confirmed radiographic PD by BIRC. The Sponsor, except for select identified individuals, will remain blinded to the treatment assignment and data until the final analysis for the primary endpoint.

5.6. Unblinding

The Investigator may request unblinding of a subject's treatment assignment by the Medical Monitor or designee to determine if the subject is eligible for crossover only after centrally

confirmed radiographic PD by the BIRC (Section 3.2). In the event of a medical emergency or confirmed pregnancy in a female subject or in the sexual partner of a male subject, in which knowledge of the investigational product is critical to the subject's management, the Investigator may access the IWRS to reveal the identity of the treatment for that subject. Investigators are encouraged to discuss in advance a plan to break the blinding code with the Medical Monitor or the Sponsor's Responsible Medical Officer.

Once the decision to unblind has been made, the Investigator must record the nature of the emergency that required the unblinding, along with the date and time of the unblinding, on the proper source documentation and notify the Sponsor's Medical Monitor (or Responsible Medical Officer) of the unblinding.

If a subject's treatment assignment is unblinded, either accidentally or in the case of emergency unblinding, the subject will be allowed to continue study treatment. In the case of emergency unblinding, if the subject is receiving placebo, crossover to vorasidenib will not be permitted until documentation of centrally confirmed radiographic PD during on-treatment response assessments or PFS Follow-up and provided certain eligibility criteria are met.

For all subjects, after confirmation of radiographic PD by the BIRC, the subject's treatment assignment will be unblinded via the IWRS. At this time, the subject, Investigator, relevant clinical site staff, and clinical research organization (CRO) study members will be unblinded to the subject's treatment assignment.

Select identified Sponsor and CRO individuals will have access to crossover data as necessary. Details regarding access to crossover data will be detailed in a separate blinding plan.

5.7. Study Drug Administration

Subjects randomized to vorasidenib or matched placebo will receive 40 mg QD orally on Days 1 to 28 in 28-day cycles. Starting with C1D1, dosing is continuous; there are no planned intercycle rest periods.

Subjects should be instructed to take their daily dose at approximately the same time each day. Each dose should be taken with a glass of water and consumed over as short a time as possible. Subjects should be instructed to swallow tablets whole and to not chew the tablets.

Each daily dose should be taken after at least 2 hours of fasting (water is allowed). Food intake should be avoided for at least 1 hour after study drug administration.

If the subject forgets to take the daily dose, then they should take their dose within 6 hours after the missed dose. If more than 6 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose.

5.8. Dose Interruption or Modification

For any AE, including AEs not specifically mentioned in Table 3 or Table 4, the Investigator may decide to interrupt or modify the dose of vorasidenib/placebo based on clinical judgement. These decisions should be discussed with the Medical Monitor before implementation if feasible. The first dose reduction level will be from 40 mg QD to 20 mg QD, and if necessary, a second dose reduction from 20 mg QD to 10 mg QD will be permitted on study for management of AEs (Table 3 and Table 4). Reescalation may be allowed with approval from the Medical Monitor.

Dose interruptions up to 28 days will be permitted at the discretion of the Investigator in consultation with the Medical Monitor for reasons including management of AEs and for mitigating circumstances (eg, planned procedures).

If the subject cannot resume study treatment within 28 days, the subject should be discontinued from study medication; exceptions may be made in consultation with the Medical Monitor. If study treatment is discontinued, the subject will complete the EOT and Follow-up visits.

An interruption in study treatment is recommended for subjects who require a minor surgical procedure (eg, tooth extraction) during the study period. Study drug should be interrupted 24 to 48 hours before the surgery and resumed 24 to 48 hours after the surgery is completed.

5.9. Management of Adverse Events

Table 3 includes dose hold and modification guidelines for vorasidenib to manage AEs during study treatment, except for elevated liver transaminases, which are described in Table 4. Management guidelines for AEs of special interest (AESIs) are provided in Section 5.10.

Table 3: Vorasidenib Dose Modification Guidelines for Adverse Events (Excluding Elevated Liver Transaminases)

Adverse Event	Action
Grade 2 nausea or vomiting (related or unrelated)	Consider holding dose of vorasidenib/placebo until resolution of AE to Grade ≤1 within 28 days of supportive therapy. Manage with supportive therapy according to the institutional standard of care. Resume vorasidenib/placebo at the current dose level.
Grade 3 AEs (related) Except for nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis	First occurrence: Hold dose of vorasidenib/placebo and manage with supportive therapy according to the institutional standard of care. Upon resolution to Grade 1 or baseline, resume vorasidenib/placebo at 1 dose level reduction. Second occurrence: If the same Grade 3 AE recurs, discontinue vorasidenib/placebo and consult with the Medical Monitor whenever feasible.
Grade 3 nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis (related)	First occurrence: Hold dose of vorasidenib/placebo and manage with supportive therapy according to the institutional standard of care. Upon resolution to Grade 1 or baseline, resume vorasidenib/placebo at the current dose level. Second occurrence: If the same Grade 3 AE recurs, hold dose of vorasidenib/placebo and manage with supportive therapy according to the institutional standard of care. Upon resolution to Grade 1 or baseline, resume vorasidenib/placebo at 1 dose level reduction. Third occurrence: If the same Grade 3 AE recurs despite dose reduction, discontinue vorasidenib/placebo and consult with the Medical Monitor whenever feasible.
Grade 4 AEs (related) Except for neutropenia without fever; thrombocytopenia without hemorrhage lasting <7days	First occurrence: Discontinue vorasidenib/placebo.
Grade 4 neutropenia without fever; thrombocytopenia without hemorrhage lasting <7days (related)	First occurrence: Hold vorasidenib/placebo and manage with supportive therapy according to institutional standard of care. Upon resolution to Grade 1 or baseline, resume vorasidenib/placebo at 1 dose level reduction. Second occurrence: If same Grade 4 AE recurs despite dose reduction, discontinue vorasidenib/placebo.

Abbreviation: AE = adverse event.

5.10. Management of Adverse Events of Special Interest

The following are guidelines for the management of AESIs based on the nonclinical and clinical safety findings to date.

5.10.1. Guidelines for Management of Elevated Liver Transaminases

Elevated liver transaminases are an identified risk of vorasidenib. Subjects with transaminase elevations should be investigated for alternative causes such as viral hepatitis, cytomegalovirus or Epstein-Barr virus infection, and screen for autoimmune conditions. Please see Section 7.2 for details on reporting requirements.

Table 4 provides dose modification guidelines for the management of elevated liver transaminases.

Table 4: Vorasidenib Dose Modification Guidelines for Elevated Liver Transaminases With or Without Elevated Bilirubin

CTCAE Grade	Action to be Taken	Recommended Monitoring
Grade 1 (>ULN-3.0 × ULN if baseline was normal; 1.5-3.0 × baseline if baseline was abnormal)	Continue vorasidenib/placebo and investigate for alternate causes.	Monitor LFTs weekly until stabilized then per protocol.
Grade 2 (>3.0-5.0 × ULN if baseline was normal; >3.0-5.0 × baseline if baseline was abnormal) Transaminases without elevated bilirubin	First occurrence: Hold vorasidenib/placebo and investigate for alternative causes. Once resolved to Grade ≤1 or baseline, vorasidenib/placebo can be resumed at the same dose. If Grade 2 elevation does not resolve within 28 days, Medical Monitor consultation will be required before resuming at same dose. Second occurrence: If Grade 2 elevation recurs and no alternative cause has been identified, hold vorasidenib/placebo until resolution to baseline or Grade ≤1 and reduce the vorasidenib/placebo 1 dose level and consult with the Medical Monitor. Third occurrence: If Grade 2 elevation recurs despite dose reduction and no alternative cause has been identified, hold vorasidenib/placebo until resolution to baseline or Grade ≤1, then reduce the vorasidenib/placebo 1 dose level and consult with the Medical Monitor. Fourth occurrence: If elevation persists despite 2 dose reductions, benefit-risk to the study participant should be reassessed and discontinuation of vorasidenib/placebo should be considered in consultation with the Medical Monitor. Note: Any Grade 2 ALT or AST elevation regardless of seriousness should be reported as an AESI.	Monitor LFTs per institutional guidance until resolution, or please monitor according to the following parameters: Repeat LFT (ALT; AST; total, direct, and indirect bilirubin; alkaline phosphatase; GGT) within 3 days of initial elevation and at least 2 times weekly until stabilization. Frequency of monitoring can be decreased to once weekly or less after stabilization, or if vorasidenib/placebo has been discontinued and the subject is asymptomatic.

CTCAE Grade	Action to be Taken	Recommended Monitoring
Grade 3 (>5.0-20.0 × ULN if baseline was normal; >5.0-20.0 × baseline if baseline was abnormal) Transaminases without elevated bilirubin	First occurrence: Interrupt vorasidenib/placebo and investigate for alternate causes. Continue to hold vorasidenib/placebo until resolution to baseline or Grade ≤1, then resume vorasidenib/placebo at a 1-dose-level reduction and consult with the Medical Monitor. Second occurrence: If, in absence of alternative cause of transaminases elevation, these laboratory abnormalities recur (second time), discontinue vorasidenib/placebo and consult with Medical Monitor. Note: Any Grade 3 ALT or AST elevation regardless of seriousness should be reported as an AESI.	Monitor LFTs per institutional guidance until resolution, or please monitor according to the following parameters: Repeat LFT (ALT; AST; total, direct, and indirect bilirubin; alkaline phosphatase; GGT) within 3 days of initial elevation and at least 2 times weekly until stabilization. Frequency of monitoring can be decreased to once weekly or less after stabilization, or if vorasidenib/placebo has been discontinued and the subject is asymptomatic.
Grade 2 or 3 (>3.0-20.0 × ULN if baseline was normal; >5.0-20.0 × baseline if baseline was abnormal) Transaminases with elevated total bilirubin ≥2 × ULN	First occurrence: Interrupt vorasidenib/placebo, investigate for alternate causes, and consult with Medical Monitor. If an alternate cause is identified and treated and transaminase/bilirubin levels resolve to baseline or Grade ≤1, consult with Medical Monitor to assess possible rechallenge at a 1-dose-level reduction. Permanently discontinue vorasidenib/placebo if no alternative cause can be identified or if there is a second occurrence after rechallenge. Note: Any Grade 2 or 3 ALT or AST elevation with an elevated total bilirubin ≥2 × ULN is to be reported as an SAE following reporting requirements.	Investigate for another clear cause such as sepsis or biliary obstruction or biliary infection. Monitor LFTs per institutional guidance until resolution, or please monitor according to the following parameters: Repeat LFT (ALT; AST; total, direct, and indirect bilirubin; alkaline phosphatase; GGT) within 3 days of initial elevation and at least 2 times weekly until stabilization. Frequency of monitoring can be decreased to once weekly or less after stabilization, or if vorasidenib/placebo has been discontinued and the subject is asymptomatic.

CTCAE Grade	Action to be Taken	Recommended Monitoring
Grade 4 (>20 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal) Transaminases	First occurrence: Permanently discontinue vorasidenib/placebo. Consider hospitalization to evaluate, monitor, and treat the subject per institutional practice, informing the Medical Monitor as soon as possible. Note: Any Grade 4 ALT or AST elevation regardless of seriousness should be reported as an AESI. Note: Any Grade 4 ALT or AST elevation with an elevated total bilirubin ≥2 × ULN is to be reported as an SAE following reporting requirements.	Monitor LFTs per institutional guidance until resolution, or please monitor according to the following parameters: Repeat LFT (ALT; AST; total, direct, and indirect bilirubin; alkaline phosphatase; GGT) within 3 days of initial elevation and at least 2 times weekly until stabilization. Frequency of monitoring can be decreased to once weekly or less after stabilization, and the subject is asymptomatic.

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GGT = gamma-glutamyl transferase; LFT = liver function test; SAE = serious adverse event; ULN = upper limit of normal.

5.11. Management of QT Prolongation

The discussion of the emergency management of torsade de pointes and its hemodynamic consequences is beyond the scope of this guideline.

Prolongation of QTc was observed in a single monkey at a non-tolerated dose of vorasidenib (Section 1.2.1.5) and is a potential risk for vorasidenib. In clinical studies, as of 29 April 2019, AEs of QT prolongation have been observed in less than 10% of subjects with glioma.

Subjects who experience QT prolongation Grade 2 or higher (CTCAE version 5.0) while treated with vorasidenib/placebo should be promptly evaluated for causality of the QTcF prolongation and managed according to the following guidelines:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects. (See www.crediblemeds.org.)
- If no other cause is identified and the Investigator believes it is appropriate, particularly if QTcF remains elevated (after above measures have been implemented, or as determined by the Investigator), study drug may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated. If QTcF has recovered or improved and the Investigator believes it is safe to do so, rechallenge with vorasidenib/placebo should be considered if previously held.
- Electrocardiograms should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks after QTcF reduction to ≤480 msec.

Grade 2 (Average QTcF >480 and ≤500 msec)

- The dose of vorasidenib/placebo may be reduced to a dose approved by the Medical Monitor without interruption of dosing. The vorasidenib/placebo dose may be reescalated to the prior dose in ≥14 days after QT prolongation has decreased to Grade ≤1.

Grade 3 (Average QTcF >500 msec; >60 msec Change From Baseline)

- Hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered.
- Dosing with vorasidenib/placebo will be interrupted. If QTcF returns to within 30 msec of baseline or <450 msec within 14 days, treatment may be resumed, possibly at a reduced dose, after discussion with the Medical Monitor.
- The vorasidenib/placebo dose cannot be reescalated after dose reduction for Grade 3 QTcF prolongation unless the prolongation was clearly associated with an electrolyte abnormality or concomitant medication.

Grade 4 (Torsade de Pointes; Polymorphic Ventricular Tachycardia; Signs/Symptoms of Serious Arrhythmia)

- Subjects should be admitted to hospital for continuous cardiac monitoring and discharged only after review by a cardiologist.
- Dosing with vorasidenib/placebo should be permanently discontinued.

5.12. Duration of Subject Participation

Subjects may continue treatment with their assigned study treatment until centrally confirmed radiographic PD by the BIRC; development of unacceptable toxicity; need for chemotherapy, radiotherapy, or other anticancer therapy in the opinion of the Investigator; confirmed pregnancy; death; withdrawal of consent from treatment; lost to follow-up; or Sponsor ending the study, whichever occurs first. All subjects are to undergo an EOT assessment (within approximately 7 days of the last dose of study drug).

After discontinuation of study treatment, subjects are to attend a posttreatment Safety Follow-up visit at least 28 days and no more than 33 days after the last dose of study drug.

Subjects who discontinue study treatment for reasons other than centrally confirmed radiographic PD by the BIRC or withdrawal of consent from treatment and overall study participation (and not just study treatment) will enter PFS Follow-up with the same schedule of assessments as before study treatment discontinuation until radiographic PD is documented by the BIRC.

Overall Survival Follow-up assessments will occur approximately 6 months (±4 weeks) after EOT. For subjects in PFS Follow-up, OS Follow-up will begin once PFS Follow-up has ended. Overall Survival Follow-up will continue for up to 5 years after the last subject is randomized or until all subjects have died, withdrawn consent from overall study participation, are lost to follow-up or the Sponsor ends the study, whichever occurs first.

5.13. Treatment Compliance

Subjects will be dispensed the appropriate number of Sponsor-packaged, labeled bottle(s) to allow for 28 days of dosing on Day 1 of each cycle; alternatively, they may be dispensed appropriate bottle(s) until the next scheduled visit. Subjects will be asked to return all unused tablets (or the empty bottles) on Day 1 of each treatment cycle or at their next scheduled visit.

Subjects will be given a Sponsor- and IRB/IEC-approved dosing diary for each treatment cycle. They should record relevant information regarding their study treatment in the diary (eg, dosing occurred in accordance with the dosing instructions per the Pharmacy Manual and dosing diary). Treatment compliance will be assessed using the dosing diary and/or return of unused drug. The dosing diary will also be used for subjects to record relevant details regarding their seizures for each of the treatment cycles (Section 6.17).

5.14. Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to Sponsor or its designee (or disposal of the drug, if approved by Sponsor). These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from Sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and subject numbers. The Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

Study drug must not be used for any purpose other than the present study. Study drug that has been dispensed to a subject and returned unused must not be redispensed to a different subject.

Subjects will receive instructions for home administration of study drug along with a diary to record the date and time of each dose, as well as the number and strength (mg) of tablets taken.

All unused and used study drug should be retained at the site until inventoried by the study monitor. All used, unused, or expired study drug will be returned to the Sponsor or its designee, or if authorized, disposed of at the study site per the site's standard operating procedures and documented. All material containing vorasidenib/placebo will be treated and disposed of as hazardous waste in accordance with governing regulations.

5.15. Prior and Concomitant Medications and Treatments

5.15.1. Prior Medications and Procedures

All medications administered and procedures conducted within 28 days before C1D1 through 28 days after last dose of study drug are to be recorded on the eCRF.

5.15.2. Prohibited Concomitant Medications

The following medications are prohibited:

- Anticancer therapy other than the treatment outlined in the protocol is not permitted while subject is receiving study drug. If alternative therapy is required for treatment of the subject's disease, the subject should be discontinued from the study treatment.
- Medications that are CYP2C8, CYP2C9, CYP2C19, or CYP3A substrates with a narrow therapeutic index listed in Appendix 11.3 are not permitted while subject is receiving study drug. In vitro studies suggest that vorasidenib may have the potential to induce the activity of these enzymes and thereby reduce exposure to and the therapeutic effects of medications metabolized by these enzymes.

5.15.3. Concomitant Therapy to be Avoided or Used With Caution

5.15.3.1. Medications With a Potential for QT Prolongation

Concomitant use of drugs with a potential for QT prolongation should be avoided and replaced with alternative treatments. If this is not possible, subjects receiving these drugs should be appropriately monitored.

These medications include but are not limited to the following drugs:

- Fluoroquinolones such as ciprofloxacin and moxifloxacin
- Azole antifungals such as fluconazole and posaconazole
- Serotonin (5-HT_3) antagonists such as granisetron and ondansetron

Other examples of drugs known to prolong the QT interval are listed in Appendix 11.4.

5.15.3.2. Sensitive Substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A

Coadministration of medications that are sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A (Appendix 11.5) requires careful monitoring, if the subject cannot be transferred to a suitable alternative. In vitro studies suggest that vorasidenib may have the potential to induce the activity of these enzymes and thereby reduce exposure to and the therapeutic effects of medications metabolized by this enzyme.

5.15.3.3. Moderate Sensitive Substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A

Medications that are moderate sensitive substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A (Appendix 11.6) should be used with caution while subjects are receiving study drug.

5.15.4. Allowed Concomitant Therapy

Medications and treatments other than those specified above are permitted during the study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care.

Subjects should receive analgesics, antiemetics, anti-infectives, antipyretics, blood products, and any other best supportive care measures (excluding anticancer therapy) as necessary, assuming no drug interaction potential.

Growth factors (granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) can be used to support subjects who have developed dose-limiting Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection. The use of erythropoiesis-stimulating agents is permitted according to the American Society of Clinical Oncology Guidelines (Rizzo et al, 2010).

A physiologic dose of steroids (eg, 10 mg/day prednisone or equivalent) is permitted for medical conditions not related to glioma. The use of chronic steroids to treat an underlying medical condition that is not a malignancy should be reviewed by the Medical Monitor. The dose and type of all corticosteroids administered for the 5 days before each MRI are to be reported in the subject dosing diary for all subjects.

5.16. Precautions

5.16.1. Potential for QT Prolongation

A marginal QTc prolongation of 32 msec was observed in a single male monkey at a nontolerable dose of vorasidenib (40 mg/kg/day) and is considered to be a potential risk with vorasidenib. Nonserious AEs of QTc prolongation have been reported in clinical studies, including patients with glioma.

Investigators should exclude subjects with a history of severe and/or uncontrolled ventricular arrhythmias, a QTc ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome), or who are taking medications that are known to prolong the QT interval unless they can be transferred to other medications within ≥5 half-lives before dosing. Investigators should avoid concomitant medications known to increase the QTc.

5.16.2. Pregnancy

Female subjects of childbearing potential must have a negative serum pregnancy test before the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Women of childbearing potential, as well as fertile male subjects and their partners who are women of childbearing potential, must agree to abstain from sexual intercourse or to use 2 highly effective forms of contraception, at least 1 of which must be a barrier method, from the time of giving informed consent or assent, throughout the study, and for 90 days after the last dose of study drug. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject; periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Women of childbearing potential are defined as having had onset of their first menstrual period and have not undergone a hysterectomy or bilateral oophorectomy or are not naturally postmenopausal (ie, not menstruated at all in the preceding 24 consecutive months).

Highly effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone release systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Schedule of Events

Table 1 and Table 2 provide the schedule of assessments for this study.

Study center visits will be conducted on an outpatient basis whenever possible. The study visit should occur on the scheduled visit day whenever possible; a ±2-day window is allowed from Cycle 1 through Cycle 12 to accommodate subjects' schedules. Beginning with Cycle 13, a ±5-day scheduling window will be allowed. Beginning at Cycle 37, subjects on treatment with vorasidenib/placebo will have in-clinic study visits every other cycle. If more frequent laboratory monitoring is needed for ongoing AEs per the dose modification guidelines (eg, elevated transaminases), additional laboratory assessments may be performed at the off-cycles using central or local labs and recorded as unscheduled visits. Instructions for the collection (including considerations for blood volume and sample collection and prioritization for adolescents), processing, storage, and shipment of all study samples for analysis will be provided in a separate study laboratory manual and sample collection flow chart. Details regarding blood volume collections per visit are provided in Table 5 (Section 6.31).

6.2. Prescreening Informed Consent or Assent

Potential subjects will sign a prescreening informed consent or assent, as determined by local requirements, before testing for the purpose of determining IDH mutation status. Pre-screening is to occur up to 84 days prior to randomization, and prior to or concurrently with Screening procedures; however, central confirmation of IDH mutation status must be available to confirm eligibility prior to randomization.

6.3. Banked Tumor Tissue or Fresh Tumor Biopsy for IDH Gene Mutation Status

A banked tumor sample (preferably from the most recent surgery) or fresh tumor biopsy (if banked tumor sample is not available) is required to confirm IDH1 gene mutation status (IDH1 R132H/C/G/S/L mutation variants tested) and IDH2 gene mutation status (IDH2 R172K/M/W/S/G mutation variants tested). Samples will be analyzed by an accredited central laboratory as part of the subject's eligibility for enrollment.

During the Prescreening period, 10 freshly cut, unstained slides (4-5 micron each) of formalin-fixed paraffin-embedded (FFPE) tissue and 1 hematoxylin and eosin (H&E)-stained slide, along with the corresponding pathology report, will be shipped to a central laboratory designated by the Sponsor for central confirmation of IDH mutation status to determine eligibility. These samples will also be used for additional exploratory biomarker analysis.

After confirmation of eligibility for the study, additional slides are requested for exploratory biomarker analysis. At least 10 freshly cut, unstained slides (4-5 micron each) of FFPE tissue or a tumor tissue block, with corresponding pathology report, are to be shipped to a laboratory designated by the Sponsor. Details regarding sample processing and shipment will be detailed in a separate laboratory manual.

These samples may be used for further molecular and/or protein analyses to gain insights into response or resistance biomarkers.

6.4. Main Study Informed Consent or Assent

A complete description of the study is to be presented to each potential subject, and a signed and dated informed consent or assent as determined by local requirements, is to be obtained before any study-specific procedures (other than pre-screening IDH mutation testing) are performed. Main study consent may be signed at the same time as the pre-screening consent; however, all Screening procedures must be performed within 28 days before randomization. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's IRB/IEC. A parent or legal guardian must sign the informed consent form (ICF) for adolescent subjects who sign assent.

6.5. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 4.2 and Section 4.3, respectively) will be reviewed for each potential subject and documented in the subject medical record and eCRF.

6.6. Demographic Data, and Medical, Surgical, and Disease History

Subject demographic data, including sex, date of birth, age, race, and ethnicity, will be obtained during Screening, according to applicable local regulations.

A complete medical, surgical, and disease history, including the primary histological subtype of glioma, primary site of disease, and the date of confirmation of the histologic diagnosis of the underlying glioma, will be obtained during Screening. The medical history is to include all relevant prior medical history as well as all current medical conditions.

All medications administered and procedures conducted within 28 days before the first dose of study drug through 28 days after last dose of study drug should be reported in the eCRF.

6.7. 1p19q Testing

Assessment of 1p19q status by local testing (eg, FISH, CGH array, sequencing) from an accredited laboratory must be available during the Screening period and submitted as part of eligibility review. Previous testing results may be used. If no prior testing was performed, or results are not available, testing must be repeated during the Screening period (preferably from the most recent surgery, and preferably from the same tumor specimen used for central IDH mutation status testing).

6.8. Screening MRI

During Screening, at minimum 2D T1-weighted MRI pre- and postcontrast enhancement, 2D T2-weighted MRI, and 2D FLAIR scans will be submitted to a central imaging facility for central confirmation by the BIRC of measurable non-enhancing disease (at least 1 lesion ≥1 cm × ≥1 cm) and that any enhancement is minimal, non-nodular, and non-measurable.

If the most recent scan is collected as part of standard of care within 28 days (+7 days) before randomization, it may be used as the screening scan, provided it was acquired using the exact

parameters as described in the site-specific imaging core manual. Scan acquisition parameters required per protocol will be detailed in a separate site-specific imaging core manual.

In addition, up to 3 pretreatment (historical) MRI scans, collected as part of standard of care before Screening (do not need to meet exact parameters required for Screening and on-study scans), are requested to be submitted, if available; of these, at least 1 submitted should be at least 3 months before Screening, if available. All scans collected will be submitted to a central imaging vendor as detailed in a separate site-specific imaging core manual.

6.9. Karnofsky Performance Scale/Lansky Play-Performance Scale

Subjects ≥16 years of age will be evaluated using the KPS, while subjects <16 years of age will be evaluated using the LPPS. Determination of KPS/LPPS scores will be performed at Screening, Day 1 of each treatment cycle thereafter, at the EOT visit, and at the Safety Follow-up visit. On C1D1 and Crossover C1D1, assessment should be conducted predose.

6.10. Physical Examination

A complete physical examination, including height and weight and neurological exam, will be obtained at Screening and at the EOT visit in all subjects. A limited physical examination, including weight, respiratory, cardiovascular, abdominal, and neurologic body systems, should be completed at the time points specified in Table 1. Subjects who are 12-17 years of age and who are being assessed to determine Tanner stage will also have height collected at the same visits as the Tanner stage assessment. Subjects should be monitored for rash at physical examinations and during assessments of adverse reactions. Additional targeted assessments may be performed as clinically indicated.

6.10.1. Tanner Stage Assessment of Sexual Maturity

Subjects who are 12-17 years of age at C1D1 will be assessed to determine Tanner stage (Appendix 11.9). Subjects who are less than Stage V (ie, Stage I to Stage IV) will be assessed to determine Tanner stage every 3 months through Cycle 37, every 6 months thereafter, and at EOT or until they reach Stage V. Subjects who are assessed as Stage V at C1D1 will not need to be assessed at subsequent visits. Any abnormal or unexpected findings should be recorded as AEs, and consultation with an endocrinologist should be considered.

6.11. Vital Signs

Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature, will be obtained at Screening and at the time points specified in Table 1. Assessments should be conducted while the subject is seated or supine.

6.12. Electrocardiogram

The 12-lead ECGs are to be obtained at Screening and at the time points specified in Table 2. When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (within 10 minutes).

All ECGs should be obtained after 3 minutes of recumbency or semirecumbency. Unscheduled ECGs may be performed at any time during study treatment if clinically indicated.

6.13. Assessment of Left Ventricular Ejection Fraction

Subjects are to have LVEF determined by ECHO (or by other methods according to institutional practice) at Screening and EOT, and as clinically indicated.

6.14. Safety Laboratory Assessments

Clinical laboratory evaluations will be performed by a central laboratory. Screening eligibility is to be determined based on central laboratory results. Sample collection, processing, and shipment instructions will be provided in a separate laboratory manual.

Clinical laboratory evaluations are to be conducted according to the schedule of assessments (Table 1). Clinical laboratory evaluations may be collected up to 24 hours before the study visit as long as the labs were collected within the visit window (±2 days in Cycles 1-12; ±5 days in Cycle 13+). Hematology and serum chemistry assessments performed within 3 days before C1D1 do not need to be repeated at the C1D1 visit. Hematology and serum chemistry assessments are required at both EOT and Crossover C1D1 visits. EOT assessments performed within 3 days of the Crossover C1D1 visit do not need to be repeated. In addition, all clinically significant laboratory abnormalities noted on testing will be followed by repeated testing and further investigated according to the judgment of the Investigator.

The safety laboratory parameters to be evaluated by the Investigator are:

Hematology: Hematocrit, hemoglobin, RBC count, WBC count with differential, and platelet count

Serum Chemistry: Sodium, potassium, chloride, calcium, magnesium, phosphorus, CO_2, albumin, glucose, blood urea nitrogen, creatinine, ALP, ALT, AST, GGT, total bilirubin, and direct bilirubin

Coagulation Studies: Activated partial thromboplastin time and either prothrombin time or international normalized ratio

Urinalysis: Color, appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic of inspection sediment

Pregnancy Test: All women of childbearing potential must have a negative pregnancy test to be eligible for the study. A serum pregnancy test will be performed at Screening; a serum or urine pregnancy test must be conducted and confirmed negative on the first day of study treatment, before dosing on Day 1 of all subsequent cycles, and at EOT. If the Screening central serum pregnancy test is missed or needs to be repeated, a local serum pregnancy test may be used for eligibility. A local serum or urine pregnancy test will also be performed at the 28-day (+5 days) Safety Follow-up visit.

6.15. Randomization

Subjects who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive vorasidenib or vorasidenib–matched oral placebo. The randomization schedule will be generated

by an independent statistical group. The randomization assignment will be implemented by an IWRS.

6.16. Study Drug Administration

Vorasidenib and/or matched placebo will be administered orally QD starting on C1D1 in continuous 28-day cycles (as described in Section 5.7).

6.17. Study Drug Compliance and Seizure Diary

Subject study medication compliance will be assessed using a subject dosing diary. This same diary will be used by the subject to record daily seizure activity including frequency, seizure severity, and loss of consciousness due to seizures. Subjects will record the number of seizures (if any) experienced on the prior calendar day, and if any seizure was experienced, subjects will also record the severity of the most severe seizure experienced the prior day on a scale of 1 (not bad) to 10 (as bad as you can imagine), and any involvement of loss of consciousness due to seizures.

The completed diary is to be reviewed for compliance (eg, dosing occurred in accordance with the dosing instructions per the Pharmacy Manual and dosing diary) at each clinic visit. Treatment compliance will be assessed using the dosing diary and/or return of unused drug.

6.18. Adverse Events

Adverse events will be collected at the time points indicated in Table 1.

Complete details on AE monitoring are provided in Section 7.

6.19. Tumor Response

Response will be assessed by the BIRC per modified RANO-LGG criteria and conducted every 3 months at time points specified in Table 1. Beginning at C37D1, response assessments will be conducted every 6 months (eg, Cycle 43, Cycle 49) for the next 2 years, and annually after that. Each MRI scan should include at minimum 2D T1-weighted MRI pre- and postcontrast enhancement, 2D T2-weighted MRI, and 2D FLAIR series. Scan acquisition parameters required per protocol will be detailed in a separate site-specific imaging core manual. When radiographic PD is determined by the Investigator, all scans will be reviewed by the BIRC for confirmation of radiographic PD to permit unblinding and determine eligibility for crossover. In the case of radiographic PD assessed by the Investigator that is not confirmed by BIRC, a confirmatory scan may be collected before the next scheduled response assessment (but at least 4 weeks after the previous scan) and submitted for BIRC review. Subjects who discontinue study treatment for reasons other than centrally confirmed radiographic PD by the BIRC or withdrawal of consent from treatment and overall study participation (not just study treatment) will have response assessments conducted at the EOT visit. These subjects will continue to have disease response assessments at the same schedule of assessments as before study treatment discontinuation until radiographic PD is documented by the BIRC. After PD is confirmed by the BIRC, eligible subjects can cross over if they were randomized to placebo, provided another anticancer therapy has not been initiated. Subjects who cross over to receive vorasidenib open-label will follow the

same schedule of response assessments starting at C1D1; during the Crossover period, response and progression will be assessed only by the Investigator according to modified RANO-LGG.

6.20. FACT-Br

The FACT-Br is a patient-reported measure designed to assess the quality of life for patients with brain tumors. The FACT-Br includes one of many newly constructed subscales that are designed as additions to the Functional Assessment of Cancer Therapy – General (FACT-G) measure, which assesses quality of life on 4 domains for patients receiving therapy for cancer. As such, the FACT-Br is a 50-item measure comprising the following subscales: Physical Well-Being, Functional Well-Being, Emotional Well-Being, and Social Well-Being subscales from the FACT-G, with the addition of a 23-item brain tumor–specific subscale.

6.21. EQ-5D-5L

The EQ-5D-5L, which includes the EQ-visual analog scale (EQ-VAS), will be administered to allow for the derivation of utility values that can be used to calculate quality-adjusted life years in economic models. The EQ-5D-5L is a widely used, validated generic health status measure used in clinical trials in cancer and covers 5 domains (mobility, self-care, usual activity, pain/distress, and anxiety/depression) based on subjects' current health status. The 5-level version will be used (no problems, slight problems, some problems, severe problems, or unable to do activity). The EQ-VAS is presented as a 20-cm vertical line on which subjects are asked to mark their current health status, with scores ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

6.22. PGI Questions

Five PGI questions will be administered to aid in the interpretation of HRQoL and other patient-reported and performance outcome endpoints.

The PGI of Severity (PGI-S) is a self-rated evaluative instrument that will be administered to assess static, current-state severity of symptoms as perceived by the subject on a 4-point scale ranging from "none" to "severe." The following concepts will be assessed in separate PGI-S questions:

- Glioma symptoms
- Neurocognitive functioning
- Seizures

The PGI of Frequency (PGI-F) is a self-rated evaluative instrument that will be administered to assess static, current-state frequency of seizures as perceived by the subject on a 4-point scale ranging from "none" to "very often."

The PGI of Change (PGI-C) is a self-rated evaluative instrument that will be administered to assess change in overall health/status as perceived by the subject on a 7-point scale ranging from "very much worse" to "very much improved."

6.23. Neurocognitive Status

Neurocognitive function will be assessed by a validated battery of tests of cognitive performance instruments measuring verbal learning, psychomotor function, working memory, attention, and executive function. These computerized, standardized cognitive tests have been designed, developed, and validated for use in clinical trials, do not require a neuropsychologist for administration, and can be completed within 10 to 15 minutes.

Five tests will be administered to each subject at time points specified in Table 1. The battery of tests consists of the detection test, which measures psychomotor functioning; the Groton-Maze Learning test, which assesses executive function using a maze learning paradigm; the Identification test, which measures reaction time; international shopping list, which measures verbal learning using a word list learning paradigm; and the one-back, which measures working memory (Maruff et al, 2009; Pietrzak et al, 2008; Pietrzak et al, 2009).

HRQoL questionnaires and neurocognitive function assessments should be conducted sequentially and, whenever possible, should be the first assessments of the clinic visit, and performed before the results of the MRI scans are reviewed.

6.24. In-Clinic Seizure Assessment

At each clinic visit, the frequency and severity of the seizures reported by the subject on the seizure diary will be reviewed. In addition, determination of the types of seizures experienced by the subject, including the type of the most severe seizure, during the previous cycle(s) covered by the diary, will be assessed by the Investigator in consultation with the subject at the time points specified in Table 1. Baseline seizure activity will be collected on C1D1 and should include assessment of the subject's seizure history over the previous 30 days, including frequency, severity of the most severe seizure (scale of 1 [not bad] to 10 [as bad as you can imagine]), and loss of consciousness due to seizures. Investigator will also determine the types of seizures experienced by the subject, including the type of the most severe seizure over the previous 30 days.

In addition, antiseizure concomitant medications and seizure-related AEs will be routinely collected during the study.

6.25. Pharmacokinetic Assessments

Blood samples for PK assessments will be drawn at time points specified in Table 2. Serial or sparse blood samples will be drawn before and after dosing of study treatment to determine plasma concentrations of vorasidenib and its circulating metabolite AGI-69460.

When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample. The blood sample should be collected within ±10 minutes of the scheduled time point and within 10 minutes after completion of the ECG, if applicable.

For subjects who cross over to receive vorasidenib open-label, blood samples during the Crossover period will be obtained according to the time points in Table 2.

6.26. Buccal Swab for Germline Mutation Analysis (Optional)

For subjects who provide consent, a buccal swab for germline mutation analysis will be obtained from all subjects predose on C1D1. This sample will be used to extract DNA for subtractional mutation analysis to identify genetic changes, which will be compared to genetic changes in the tumor to elucidate potential mechanisms for response or resistance. For subjects who cross over to receive vorasidenib open-label, this sample does not need to be collected again at Crossover C1D1.

6.27. Blood Samples for Exploratory Biomarkers

Blood samples will be obtained for exploratory biomarkers and correlative studies predose at the time points specified in Table 1. For subjects who cross over to receive vorasidenib open-label, blood samples will be obtained according to the time points in Table 1 during the Crossover period.

6.28. Tumor Biopsy for Biomarker Analysis

For any subject who discontinues treatment and proceeds to have a biopsy or surgery as an intervention, a tumor sample from that surgery is requested if available. Sample processing instructions will be provided in a separate sample processing laboratory manual.

6.29. Cerebrospinal Fluid Samples for Subjects Who Cross Over to Vorasidenib

For subjects who cross over to receive vorasidenib open-label, a CSF sample is requested to be obtained at Crossover C1D1 and at EOT when vorasidenib is discontinued. CSF samples will be used for exploratory biomarker analysis, including detection of circulating tumor DNA.

6.30. Sample Processing, Storage, and Shipment

Instructions for the collection (including considerations for blood volume and sample collection and prioritization for adolescents), processing, storage, and shipment of all study samples for analysis will be provided in a separate study laboratory manual and sample collection flow chart.

6.31. Blood Volume to be Collected per Subject per Visit

During the study, it is expected that blood volumes ranging from approximately 11 mL to approximately 49 mL will be drawn from each subject regardless of sex. This total volume includes collections for intensive PK sampling collected at the Cycle 1 Day 1 and Cycle 2 Day 1 visits. The amount of blood to be drawn for each assessment at any visit is an estimate and may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. The blood volume drawn from each subject for each visit is included in Table 5.

Note: If a blood volume for a subject/visit is limiting (eg, total volume allowed for a visit or cycle for an adolescent subject has been reached), samples should be prioritized in the following order:

- Safety labs
  - Coagulation
  - Chemistry (includes serum human chorionic gonadotropin (HCG) except for an unscheduled visit, where a separate tube for serum HCG must be provided according to the study laboratory manual and sample collection flow chart)
  - Hematology
- Blood for PK
- Blood for exploratory biomarkers

Table 5: Blood Volumes Per Subject Per Visit

Study Visit	Total Volume Collected (mL)			
	Safety Labs	**Blood for PK**	**Blood for Exploratory Biomarkers**	**Total for Visit**
Screening	10.7	NA	NA	10.7
C1D1	8	24	17	49
C1D15	8	6	17	31
C2D1	8	24	NA	32
C2D15	8	NA	NA	8
C3D1	8	6	NA	14
C4D1 through C37D1 (every first and second cycle [eg, C4 and C5, C7 and C8, etc])	8	6	NA	14
C4D1 through C37D1 (every third cycle [eg, C6, C9, etc])	8	6	17	31
C39 and beyond	8	6	17 (every 6 months)	14 (31 every 6 months)
End of Treatment	10.7	6	17	33.7

Abbreviations: CXDY = Cycle X Day Y; NA = not applicable; PK = pharmacokinetics.
Note: Further details regarding individual samples to be collected at each visit are included in Table 1.

7. SAFETY DATA COLLECTION: DEFINITIONS AND PROCEDURES FOR RECORDING AND REPORTING

7.1. Adverse Events

7.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (eg, headache) not present at Baseline
- Any deterioration in a laboratory value or other clinical test (eg, ECG, x-ray) that is associated with clinical signs and symptoms, leads to a modification or discontinuation of study drug or concomitant treatment, requires medical or surgical intervention, or is considered by the Investigator to be clinically significant
- Adverse events that are related to a protocol-mandated intervention, including those that occur before assignment of study treatment (eg, screening invasive procedures such as biopsies)

Disease progression or death due to PD will not be considered an AE (or an SAE) in this study but will be collected as an outcome or reason for discontinuation, as appropriate. Adverse events (or SAEs) considered to be complications of PD should be reported.

7.1.2. Definition of Serious Adverse Event

An SAE is any AE or suspected adverse reaction that:

- Results in death
- Is immediately life-threatening (Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.)
- Requires inpatient hospitalization or prolongation of existing hospitalization (Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial eg, surgery was performed earlier or later than planned.)

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly/birth defect
- Is considered an important medical event (An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or the development of drug dependency or drug abuse.)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI CTCAE version 5.0 criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

7.1.3. Adverse Events of Special Interest

Adverse events of special interest can be serious or nonserious treatment-emergent AEs that are of special interest to the Sponsor. Ongoing monitoring and rapid communication (within 24 hours) by the Investigator to the Sponsor is required to allow for further characterization and reporting to regulatory authorities. Adverse events of special interest in this study are elevated liver transaminases in subjects who receive vorasidenib/placebo.

7.1.3.1. Elevated Liver Transaminases

Any Grade 2 or worse ALT or AST elevation occurring in a subject receiving vorasidenib/placebo, irrespective of seriousness, should be reported as an AESI to the Sponsor within 24 hours. Any Grade 2 or worse ALT or AST elevation with an elevated bilirubin greater or equal to 2 times the ULN should be reported as an SAE. See Section 5.10.1 for details on guidelines for the management of elevated liver transaminases in subjects receiving vorasidenib/placebo.

7.1.4. Abnormal Laboratory Events

A laboratory test result should be reported as an AE if it meets any of the following criteria:

- Associated with clinical signs and symptoms
- Results in delay, interruption, or discontinuation of study drug
- Requires medical or surgical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) should be recorded on the AE eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating if the test result is above or below the normal range.

7.2. Recording Adverse Events and Serious Adverse Events

Adverse events will be recorded on the eCRF from the time of first dose of study drug until 28 days after administration of the last dose of study drug. After the Screening informed consent or assent has been signed, but before first dose, only SAEs that are caused by a protocol-mandated intervention (eg, SAEs related to invasive study procedures such as biopsies) will be recorded. All AEs and SAEs will be recorded starting at first dose through 28 days after the last dose of study drug for all subjects. After the 28-day follow-up period, only SAEs that are considered to be related to study drug should be reported in the safety database.

Adverse events spontaneously reported by the subject and/or in response to open nonleading questions (eg, "How are you feeling?") from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be collected at every visit and recorded in the subject's medical record and in the appropriate section of the eCRF.

Adverse events will be followed until 28 days after the last administration of study drug or until study discontinuation/termination or initiation of subsequent anticancer therapy, whichever occurs first. Subjects will be assessed at the Safety Follow-up visit to determine if any new AEs have occurred. After this period, Investigators should report only SAEs that are considered to be related to vorasidenib/placebo.

Any clinically relevant deterioration in laboratory assessments (Section 7.1.4) or other clinical finding that is considered an AE must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- Whether the event is serious
- Severity of the event (Section 7.2.1)
- Relationship of the event to study treatment (Section 7.2.2)
- Action taken: none; change in the study drug administration (eg, temporary interruption in dosing); drug treatment required; non-drug treatment required; hospitalization or prolongation of hospitalization required (complete SAE page); diagnostic procedure performed; subject discontinued from the study

- Outcome: subject recovered without sequelae; subject recovered with sequelae; event ongoing; subject died (notify the Medical Monitor immediately, and complete the SAE form)

7.2.1. Severity of Adverse Events

The severity of all AEs, including clinically significant treatment-emergent laboratory abnormalities, will be assessed by the Investigator according to the NCI CTCAE version 5.0 on a 5-point severity scale (Grade 1 through Grade 5). Adverse events associated with laboratory abnormalities should be graded based on central laboratory results. (Local laboratory results will be used if no central laboratory results are available.) Adverse events not listed by the CTCAE will be graded as follows:

- Mild (Grade 1): The event is noticeable to the subject but does not interfere with routine activity.
- Moderate (Grade 2): The event interferes with routine activity but responds to symptomatic therapy or rest.
- Severe (Grade 3): The event significantly limits the subject's ability to perform routine activities despite symptomatic therapy.
- Life-threatening (Grade 4): an event in which the subject was at risk of death at the time of the event.
- Fatal (Grade 5): an event that results in the death of the subject.

7.2.2. Relationship to Study Drug

Investigators must determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly (Table 6).

Table 6: Attribution Guidance

Is the AE suspected to be caused by the study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study treatment; and/or the AE abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon rechallenge.
NO	Adverse events will be considered related, unless they fulfill the criteria as specified below: Evidence exists that the AE has an etiology other than the study treatment (eg, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study treatment (eg, cancer diagnosed 2 days after first dose of study treatment).

Abbreviation: AE = adverse event.

The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

7.3. Reporting Serious Adverse Events

All SAEs that occur after the first dose of study drug through 28 days after the last dose of study drug must be reported to the Sponsor within 24 hours from the point in time when the Investigator becomes aware of the SAE. This 24-hour notification applies to the initial SAE information and all follow-up SAE information.

Serious AEs must be reported by the Investigator and entered in the electronic data capture (EDC) system for submission as per the safety reporting instructions. All SAEs must be reported whether or not they are considered causally related to vorasidenib/placebo.

Note: SAEs that occur from the time of informed consent or assent through the Screening period that are caused by a protocol-mandated intervention (eg, SAEs related to invasive study procedures such as biopsies) should be reported to the Sponsor within 24 hours from the point in time when the Investigator becomes aware of the SAE. Serious AEs that occur more than 28 days after the last dose of study drug that the Investigator considers to be related to study drug must be reported to the Sponsor any time the Investigator becomes aware of such an event.

Serious AE forms will be completed, and the information collected will include subject number, a narrative description of the event, and an assessment by the Investigator as to the severity of the event and relationship to study drug. Follow-up information on the SAE may be requested by the Sponsor or Medical Monitor.

If the EDC system is unavailable for greater than 24 hours, SAEs should be reported using the EDC downtime paper SAE report form, per instructions attached to the form.

If there are serious, unexpected adverse drug reactions associated with the use of vorasidenib or placebo, the Sponsor will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis. The local IRB/IEC will be promptly notified based on local regulations where required by the IRB/IEC of all serious, unexpected adverse drug reactions involving risk to human subjects.

7.4. Reporting Adverse Events of Special Interest

Adverse events of special interest are to be reported to the Sponsor per the same timelines and methods as SAEs.

7.5. Other Safety-Related Issues

7.5.1. Overdose or Dose Administration Error

Study treatment overdose is the accidental use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects.

Any study treatment overdose or incorrect administration of study treatment should be noted on the study drug administration eCRF page.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the AE eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event.

7.5.2. Deaths

All on-treatment deaths, regardless of relationship to study treatment, must be recorded on the AE eCRF and reported to the Sponsor within 24 hours. Deaths that occur during the protocol-specified AE reporting period (Section 7.2) that are attributed by the Investigator solely to progression of glioma should not be reported as SAEs and should be recorded only on the treatment and study discontinuation eCRFs.

Death should be considered an outcome and not a distinct event. All on-treatment deaths (within 28 days after last dose of study treatment) should have an associated SAE captured for the event that led to death, except in the event of PD. The underlying medical diagnosis or suspected diagnosis that caused or contributed to the fatal outcome should be reported on the AE eCRF. Generally, only 1 such event should be reported. The term “sudden death” should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the AE eCRF. If the cause of death later becomes available (eg, after autopsy), “unexplained death” should be replaced by the established cause of death.

During OS Follow-up, all deaths will continue to be collected, but only those unrelated to PD will be classified as SAEs.

7.5.3. Reporting Drug Exposure During Pregnancy and/or Lactation

Pregnancy is not reported as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication or a complication relating to the pregnancy occurs that may qualify as an SAE (eg, spontaneous abortion). The Investigator must report any pregnancy (including the pregnancy of a male subject’s partner) that occurs during the treatment period and within 28 days after the last dose of study drug, even if no AE has occurred. Pregnancy must be reported within 24 hours of learning of its occurrence according to study instructions using a clinical study pregnancy reporting form. Any SAE (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) that occurs during pregnancy must

be recorded on the SAE report form and reported within 24 hours of awareness in accordance with the procedure for reporting SAEs.

Female subjects who become pregnant while on the study will be immediately discontinued from study treatment and will complete the EOT visit and Safety Follow-up visit (28 [+5] days after last dose). All AEs that occur during this time, including any related to the pregnancy, will be reported. The female subject or partner of a male subject should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. The Investigator must follow up and document the course and outcome of all pregnancies. Monitoring should continue until conclusion of the pregnancy.

All outcomes of pregnancy (from a female subject or the sexual partner of a male subject) must be reported by the Investigator to the Sponsor or Medical Monitor in the pregnancy outcome section of the pregnancy reporting paper form immediately after he/she has gained knowledge of the delivery or elective abortion. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. Follow-up information will be obtained where possible and allowable by local practice and regulations (ie, with the consent of the subject or subject's partner) regarding the course and outcome of the pregnancy, including any postnatal sequelae in the infant, for up to 2 years after successful completion of the pregnancy. The Investigator must follow up even if the subject was discontinued from the study or if the study has completed. Information on the status of the mother and child will be forwarded to the sponsor.

8. STATISTICAL METHODS

The Statistical Analysis Plan (SAP) will be finalized before the database lock for the primary analysis and will include a more detailed description of the statistical analyses described in this section.

8.1. General Methods

Summaries will be produced for subject disposition, demographic and baseline disease characteristics, efficacy, safety, PK, and pharmacodynamics, as appropriate.

Categorical data will be summarized by frequency distributions (number and percentages of subjects). Continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Time-to-event endpoints will be analyzed using the Kaplan-Meier method. Point estimates and 95% CIs will be provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates), will be produced. All data will be provided in by-subject listings.

The primary efficacy and safety analyses are expected to be performed when statistical significance of PFS is reached. After the primary analysis for PFS, the study will remain open. Subjects still receiving study drug or who are being followed on the study will continue per the schedule of assessments.

The study will end and the final OS analysis will be performed approximately 5 years after the last subject has been randomized to the study or all subjects have died, withdrawn consent from overall study participation, are lost to follow-up, or the Sponsor ends the study, whichever occurs first. All available efficacy and safety data from all subjects will be analyzed and reported in the final clinical study report.

8.2. Statistical Hypotheses and Sample Size Estimation

The following statistical hypothesis will be tested to address the primary objective:

$H_{01}: \Theta_1 \geq 0$ versus $H_{11}: \Theta_1 < 0$

where Θ_1 is the log hazard ratio of PFS in the vorasidenib arm versus the placebo arm.

In addition, the following statistical hypothesis will be tested to address the key secondary objective associated with TTNI:

$H_{02}: \Theta_2 \geq 0$ versus $H_{12}: \Theta_2 < 0$

where Θ_2 is the log hazard ratio of TTNI in the vorasidenib arm versus the placebo arm.

Approximately 340 subjects will be randomized to the treatment arms using a 1:1 randomization, stratified by chromosome 1p19q codeletion status (codeleted or not codeleted) and baseline tumor size per local assessment (longest diameter of ≥2 cm or <2 cm).

For the primary endpoint, a total of 164 PFS events will be required to have at least 90% power to detect a hazard ratio of 0.6 using a 1-sided log-rank test stratified by the randomization stratification factors at a significance level of 0.025, and a 3-look group sequential design with a Gamma family (-24) α-spending function to determine the efficacy boundaries and a Gamma family (-5) β-spending function to determine the nonbinding futility boundary.

For TTNI, a total of 152 TTNI events will be required to have approximately 80% power to detect a hazard ratio of 0.636 using a 1-sided log-rank test stratified by the randomization stratification factors at a significance level of 0.025, and a 2-look group sequential design with a Gamma family (-22) α-spending function to determine the efficacy boundaries. To preserve the overall type I error in the study, the fixed sequence testing procedure (Westfall and Krishen, 2001) will be followed; TTNI will be tested only if PFS has reached statistical significance (at the time of interim analysis 2 for PFS or final analysis for PFS).

The sample size for the study is determined based on the following assumptions.

- Based on a retrospective natural history study on which the Sponsor collaborated in patients with Grade 2 and Grade 3 non-enhancing IDH mutation–positive glioma, the median time from surgery to next intervention is approximately 24 months (Huang et al, 2017). Given the requirement of at least 1 year from the most recent surgery for eligibility, the median PFS for subjects in the placebo arm is assumed to be 18 months and the median PFS for subjects in the vorasidenib arm is assumed to be 30 months; this corresponds to a hazard ratio of 0.6 under the exponential model assumption.
- Assuming TTNI to be equal to PFS plus an additional 3 months to accommodate any required washout periods for subsequent anticancer therapy and to prepare for subsequent anticancer therapy, the median TTNI for subjects in the placebo arm is estimated to be 21 (18+3) months, and the median TTNI for subjects in the vorasidenib arm is estimated to be 33 (30+3) months; this corresponds to a hazard ratio of 0.636 under the exponential model assumption.
- PFS and TTNI dropout rates of approximately 10% at 12 months
- Non-uniform recruitment period of approximately 42 months

The data cutoff for the final PFS analysis will occur after all subjects have been randomized and the target number of PFS events has been reached.

The study will have met its primary objective if PFS is statistically significant at the time of the interim or final analysis at the corresponding α-level per the α-spending strategy.

8.3. Analysis Sets

The following analysis sets will be evaluated and used for presentation of the data. Only subjects who sign informed consent will be included in the analyses:

- Full Analysis Set (FAS): all subjects who are randomized. Subjects will be classified according to the randomized treatment arm per the intent-to-treat principle. The FAS will be the default analysis set for all efficacy analyses including analysis of primary endpoint, unless otherwise specified.
- Per-Protocol Set (PPS): a subset of the FAS. Subjects who do not receive at least 1 dose of the randomized treatment will be excluded from the PPS. Other criteria leading to exclusion of subjects will be prespecified in the SAP. The PPS will be used to perform sensitivity analyses for the primary endpoint.

- Safety Analysis Set: all subjects who receive at least 1 dose of the study treatment. Subjects will be classified according to the treatment received. The safety analysis set will be the primary analysis set for all safety analyses, unless otherwise specified.
- Pharmacokinetic Analysis Set: a subset of the safety analysis set and includes all subjects who have at least 1 postdose blood sample providing evaluable PK data for vorasidenib or its metabolite AGI-69460.

8.4. Subject Disposition

A tabulation of subject disposition, including the number of subjects screened, the number enrolled in each treatment arm, the number of subjects in each population for analysis, the number of protocol violations, the number who discontinued treatment and reasons for treatment discontinuation, and the number who withdrew from study and reasons for withdrawal, will be presented.

8.5. Demographics and Baseline Characteristics

Demographic and baseline disease characteristic data will be listed individually by subject and summarized descriptively by treatment arm.

8.6. Study Drug Exposure and Compliance

Study drug exposure, including number of doses administered, total dose, duration of treatment, dose intensity (computed as the ratio of actual dose received and actual duration), relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), and the proportion of subjects with dose modifications will be summarized using descriptive statistics.

8.7. Concomitant Medications

Concomitant medications and significant nondrug therapies before and after the start of the study drug will be listed by subject and summarized by the Anatomical Therapeutic Chemical Classification term.

8.8. Efficacy Analysis

To control the overall type I error rate at the 1-sided 2.5% level, the fixed sequence testing procedure (Westfall and Krishen, 2001) will be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoint. These endpoints will be tested in the following order:

- Primary endpoint of radiographic PFS per BIRC
- Key secondary endpoint of TTNI

If PFS is statistically significant, then TTNI will be tested; otherwise, no formal testing of TTNI will be conducted. The study will have met its primary objective if the primary efficacy endpoint is statistically significant at the time of the interim or final analysis at the corresponding α-level per the statistical testing strategy (Section 8.2).

All efficacy analyses will be conducted on the FAS unless otherwise specified.

8.8.1. Analysis of Primary Endpoint

The primary objective of the study is to demonstrate the efficacy of vorasidenib based on radiographic PFS per BIRC compared with placebo in subjects with residual or recurrent Grade 2 oligodendroglioma or astrocytoma with an IDH1 or IDH2 mutation who have undergone surgery as their only treatment. The primary endpoint of PFS is defined as the time from date of randomization to the date of first occurrence of centrally confirmed radiographic PD by RANO-LGG assessed by the BIRC or death from any cause, whichever occurs earlier. PFS for subjects without centrally confirmed radiographic PD by RANO-LGG by the BIRC or death will be censored at the date of the last disease assessment. Censoring reasons also include start of a subsequent anticancer therapy, withdrawal of consent from overall study participation, and loss to follow-up.

- Subjects without an event or with an event after 2 or more inadequate or missing postbaseline tumor assessments will be censored on the date of the last adequate tumor assessment that documented no PD by BIRC; regardless, deaths within 24 weeks after randomization for subjects who did not start a subsequent anticancer therapy will be considered an event.
- If a subsequent anticancer therapy is started before an event, the subject will be censored on the date of the last adequate tumor assessment that documented no PD by BIRC before the start of a subsequent anticancer therapy.
- Subjects with no adequate baseline tumor assessment or with no adequate postbaseline tumor assessments within 24 weeks after randomization will be censored on the date of randomization, unless the subject dies within 24 weeks after randomization, in which case, death will be an event on date of death.

The primary efficacy analysis will compare the PFS time between the 2 treatment arms using a 1-sided stratified log-rank test. The test will be stratified by 1p19q status and baseline tumor size. A Cox proportional hazards (PH) model stratified by randomization stratification factors will be used to estimate the hazard ratio of PFS, along with its 95% CI.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rate at 3, 6, 12, 18, 24, 30, 36, 42, and 48 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer and Crowley, 1982), and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch and Prentice, 2002) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using the Greenwood formula.

Sensitivity analyses will be performed to explore the robustness of the primary analysis results and will include analyses counting all PD assessed by BIRC and deaths as PFS events (regardless of missing assessments, time of the event, or initiation of anticancer therapy), analysis based on the PPS, and analysis based on an unstratified log-rank test using the FAS. All planned sensitivity analyses will be specified in the SAP.

8.8.2. Analysis of Key Secondary Endpoint (Time to Next Intervention)

Time to next intervention is defined as the time from randomization to initiation of first subsequent anticancer therapy (including vorasidenib, for subjects randomized to placebo who subsequently cross over) or death due to any cause. If a subject does not initiate a subsequent anticancer therapy or does not die by the data cutoff date, TTNI will be censored at the last known alive date.

Time to next intervention will be compared between the 2 treatment arms using a 1-sided stratified log-rank test following the testing strategy described in Section 8.2. The test will be stratified by 1p19q status and baseline tumor size. A Cox PH model stratified by randomization stratification factors will be used to estimate the hazard ratio of TTNI, along with its 95% CI.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median TTNI with 2-sided 95% CI. In particular, the TTNI rate at 3, 6, 12, 18, 24, 30, 36, 42, and 48 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer and Crowley, 1982), and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch and Prentice, 2002) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using the Greenwood formula.

8.8.3. Analyses of Additional Secondary Efficacy Endpoints

Additional efficacy endpoints include TGR, objective response, CR+PR, time to response, time to CR+PR, DoR, duration of CR+PR, OS, HRQoL as measured by the FACT-Br scores, and PFS assessed by the Investigator. Unless otherwise specified, analyses for tumor-related endpoints will be performed separately based on BIRC assessment and based on Investigator assessment per modified RANO-LLG.

8.8.3.1. Tumor Growth Rate

Tumor growth rate is defined as the on-treatment percentage change in tumor volume every 6 months. The difference in TGR between the vorasidenib and placebo arms will be assessed by slope of tumor growth over time using a linear mixed model on log-transformed tumor volume measured by the BIRC at baseline and at each postrandomization tumor assessment. The model will include baseline tumor volume (log), 1p19q status, time from randomization to tumor assessment (in months), treatment arm, and time by treatment arm interaction as fixed effects, and intercept and slope of time as random effects. An unstructured covariance structure will be used to model the covariance matrix for the vector of random intercept and slope of time for each subject. Should the estimation algorithm fail to converge, then a compound symmetry matrix or variance component structure will be considered. The log-likelihood ratio test will be used to test for the homogeneity between the residuals across treatment groups. If the homogeneity of the test is rejected at the 2-sided 0.05 significance level, a heterogeneous model different with different residual variances across treatment groups will be used.

Tumor growth rate every 6 months by treatment arm will be calculated along with its 95% CI using the estimated slopes from the fitted model.

8.8.3.2. Objective Response

Objective response is defined as a best overall response of CR, PR, or MR. Objective response rate is the proportion of subjects with objective response.

A summary of best objective response by treatment arm will be produced. The estimated objective response rate by treatment arm will be calculated along with the 95% exact CI.

8.8.3.3. CR+PR

The endpoint CR+PR is defined as a best overall response of CR or PR. The analysis described in Section 8.8.3.2 will be repeated by counting subjects who achieve MR as nonresponders in the assessment of objective response.

8.8.3.4. Time to Response

Time to response is defined, for subjects with objective response, as the time from randomization to the first documentation of objective response.

Time to response will be summarized by treatment arm using simple descriptive statistics.

8.8.3.5. Time to CR+PR

Time to CR+PR is defined, for subjects with CR or PR, as the time from randomization to the first documentation of CR or PR.

Time to CR+PR will be summarized by treatment arm using simple descriptive statistics.

8.8.3.6. Duration of Response

Among responders who achieve radiographic CR, PR, or MR, DoR is defined as the time from the first documentation of objective response (CR, PR, or MR) to the date of first documented PD or death due to any cause. Subjects without radiographic PD or death will be censored at the last response assessment date. Detailed censoring rules will be included in the SAP.

Kaplan-Meier estimates of DoR will be presented by treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates).

8.8.3.7. Duration of CR+PR

Duration of CR+PR is defined, for subjects with CR or PR, as the time from the first documentation of CR or PR to the first documentation of PD or death due to any cause. Subjects without radiographic PD or death will be censored at the last response assessment date. Detailed censoring rules will be included in the SAP.

Kaplan-Meier estimates of duration of CR+PR will be presented by treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates).

8.8.3.8. Overall Survival

Overall survival is the time from the date of randomization to the date of death due to any cause. Subjects who are alive at the analysis cutoff date will be censored at the date of last contact.

The hazard ratio for OS will be estimated using a Cox PH model stratified by the randomization strata.

Kaplan-Meier estimates of OS will be presented by treatment arm based on the FAS, including estimates of the median and other quantiles, as well as individual time points (eg, 12-month, 24-month, and 36-month rates).

8.8.3.9. HRQoL as Measured by the FACT-Br

The FACT-Br will be scored according to published scoring guidelines.

If a subject is not able to speak any language that is covered by the FACT-Br, the data from those assessments will be missing throughout the duration of that subject's involvement in the study. The number and percentage of subjects with the entire questionnaire or assessment missing will be summarized by treatment.

Descriptive statistics (eg, means, medians, and proportions) will be used to summarize the individual items, subscale scores, total scores and change from baseline in the total and subscale scores at each scheduled assessment time point by treatment. A repeated measurements analysis model may be used to compare the 2 treatment groups with respect to changes in the total and subscale scores from baseline, longitudinally over time. In addition, anchor-based analyses may be used to establish thresholds of clinically meaningful change for specific FACT-Br domains using PGI ratings as a basis for anchors.

A detailed analysis plan including the missing data handling will be specified in the SAP.

8.8.3.10. Progression-Free Survival per Investigator

Progression-free survival is the time from randomization to the first documented radiographic PD as determined by the Investigator per RANO-LGG or death from any cause, whichever occurs first.

Kaplan-Meier estimates of PFS, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates), will be presented along with corresponding 95% CIs for each treatment arm based on the Full Analysis Set.

8.9. Safety

Safety will be evaluated by the incidence, severity, and type of AEs, and by evaluation of vital signs, KPS/LPPS, clinical laboratory results, ECGs, and LVEF data (as clinically indicated).

All safety data will be listed by subject and summarized by treatment arm based on the Safety Analysis Set and the on-treatment period, unless otherwise specified.

The on-treatment period starts on the date of the start of study treatment and ends 28 days after the end of study treatment or 1 day before the start of subsequent anticancer therapy, whichever is earlier.

8.9.1. Adverse Events

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to the NCI CTCAE version 5.0 grading system.

Summary tables and listings for AEs will include treatment-emergent AEs, defined as any AE with a first onset date during the on-treatment period or worsening from baseline. The incidence of AEs (new or worsening from baseline) will be summarized according to MedDRA by System Organ Class (SOC) and Preferred Term, severity (based on NCI CTCAE version 5.0 grading as assessed by the Investigator), seriousness, and relation to study treatment. The following summaries will be produced:

- All AEs
- AEs leading to dose modifications
- AEs leading to death
- Treatment-related AEs
- Grade 3 or higher AEs
- Grade 3 or higher treatment-related AEs
- The most commonly reported AEs (ie, those events reported by ≥10% of all subjects)
- SAEs
- AEs that led to treatment discontinuation
- AESIs

By-subject listings will be provided for on-treatment deaths, AEs, SAEs, AESIs, and AEs leading to discontinuation of treatment.

8.9.2. Laboratory Abnormalities

For laboratory tests included in the NCI CTCAE version 5.0, laboratory data will be graded accordingly; Grade 0 will be assigned for all nonmissing values not graded as 1 or higher. For laboratory tests where grades are not defined by NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, serum chemistry, and coagulation studies, and urinalysis laboratory tests:

- Descriptive statistics for the actual values and/or change from baseline of clinical laboratory parameters over time
- Shift tables using NCI CTCAE grades to compare baseline to the worst on-treatment value (for laboratory tests where NCI CTCAE grades are not defined, shift tables using the low/normal/high/[low and high] classification to compare baseline to the worst on-treatment may be generated)
- Listing of all laboratory data with values flagged to show the corresponding NCI CTCAE grades and the classifications relative to the laboratory normal ranges

In addition to the above-mentioned tables and listings, graphical displays of key safety parameters, such as scatter plots of actual or change in laboratory tests over time or box plots may be specified in the SAP.

8.9.3. Other Safety Data

Descriptive statistics for the actual values and/or the changes from baseline of vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) over time will be summarized.

Categorical analysis of QTcF may be performed. Maximum QTcF and maximum changes from baseline may also be summarized similarly in a separate display. Electrocardiogram abnormalities, if collected, will be presented in a data listing.

Additional safety analyses may be performed if deemed necessary.

8.10. Pharmacokinetic Analyses

Descriptive statistics of plasma concentrations (arithmetic and geometric means, standard deviation, coefficient of variation [CV%], CV% geometric mean, minimum, median and maximum) of vorasidenib and its metabolite AGI-69460 will be summarized. The plasma concentration-time data will be analyzed and reported as a separate document along with the detailed analysis plan.

8.11. Exploratory Analysis

8.11.1. Progression-Free Survival After Crossover

Time from first dose of vorasidenib to second documented PD according to the Investigator (or death) will be calculated for subjects who cross over from the placebo arm to the vorasidenib arm.

Kaplan-Meier estimates including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates), will be presented along with corresponding 95% CIs for each treatment arm based on the FAS.

8.11.2. Pre- and Postcrossover TGR

The pre- and postcrossover TGR as assessed by volume will be estimated using a piece-wise linear mixed model for the subset of placebo subjects who have crossed over to the vorasidenib arm.

8.11.3. Pre- and Posttreatment TGR

The pre- and posttreatment TGR as assessed by volume will be estimated by treatment arm using a piece-wise linear mixed model. The change in TGR will also be estimated by treatment arm with its corresponding 95% CI.

8.11.4. Time to Malignant Transformation

Time to malignant transformation will be assessed from the time of randomization to the date of first histopathologic evidence of malignant transformation as assessed by the Investigator in subjects who have surgery or biopsy as an intervention.

Time to malignant transformation, for subjects with malignant transformation, will be summarized by treatment arm using simple descriptive statistics.

8.11.5. Patient-Reported and Performance Outcomes and Seizures

HRQoL will further be characterized as exploratory endpoints using the EQ-5D-5L questionnaire and the PGI questions. The EQ-5D-5L will be scored according to published scoring guidelines.

Neurocognitive function will be assessed as an exploratory endpoint using a validated battery of neurocognitive performance tests.

Seizure activity will also be assessed as an exploratory endpoint, including the monthly frequency and severity of seizures, type of seizures, seizure AEs, and changes in anti-seizure medications (dose, frequency, etc).

Descriptive statistics (eg, means, medians, and proportions) will be used to summarize the individual items and total scores of the EQ-5D-5L, the PGI-S, PGI-F, and PGI-C questions, neurocognitive function assessment results, and seizure activity at each scheduled assessment time point by treatment. Additionally, change from baseline on the exploratory endpoints at the time of each assessment will be summarized by treatment.

8.12. Interim Analyses

The purposes of the interim analyses are to allow early stopping of the trial for efficacy or futility, and to assess safety of the study treatment. There are 3 planned analyses for PFS: an interim analysis for futility, an interim analysis for superiority, and a final analysis.

The Gamma family (-24) α-spending function will be used to determine the efficacy boundaries to control type I error and a Gamma family (-5) β-spending function will be used to determine the nonbinding futility boundary. A small alpha will be allocated to the PFS futility analysis based on the selected α-spending function.

The interim analyses for PFS will be performed based on the FAS and will take place after the target number of events has occurred as described below.

- Interim analysis 1 (IA1, futility only): will be conducted when approximately 55 PFS events (33.5% of the expected 164 events) have occurred; this data cut will be used only for a futility assessment of PFS, although an α of $3 \times 10\text{-}9$ will be spent, per the α-spending function, to protect the integrity of the study.
- Interim analysis 2 (IA2, superiority and futility): will be conducted when all subjects are randomized and approximately 123 PFS events (75% of the expected 164 events) have occurred.
- Final analysis (FA): will be conducted when all subjects are randomized and 164 PFS events have occurred.

Table 7 displays the maximum number of analyses and the associated efficacy and futility boundaries for the primary endpoint, if the analyses are performed at the planned number of events as shown in the table.

Table 7: Efficacy and Futility Boundaries for PFS

Analysis	IA1	IA2	FA
Number of events (information fraction)	55 (33.5%)	123 (75%)	164 (100%)
1-sided p-value (z-value) for efficacy	NA[1]	≤0.00006 (≤-3.838)	<0.025 (<-1.96)
1-sided p-value (z-value) for futility[2]	≥0.806 (≥0.864)	≥0.185 (≥-0.898)	NA

Abbreviations: FA = final analysis; IA1 = interim analysis 1; IA2 = interim analysis 2; NA = not applicable; PFS = progression-free survival.
Note: The observed number of events at the IAs may not match the planned number of events. The efficacy and futility boundaries will be updated based on the actual number of observed events using the prespecified α-and β-spending functions.
[1] The study will not stop for efficacy at IA1. However, to preserve the integrity of the study, 1-sided $\alpha = 3 \times 10^{-9}$ will be spent at the time of IA1.
[2] Nonbinding.

There are 2 planned analyses for TTNI to test for superiority at the time of the PFS IA2 and FA, respectively, per the testing strategy outlined in Section 8.2.

The significance levels for the analyses of TTNI are determined by the hierarchical testing strategy and the α-spending function for TTNI (Gamma (-22)). Table 8 displays the analysis triggers for TTNI and the associated efficacy boundaries, if the analyses are performed at the planned number of events as shown in the table.

Table 8: Efficacy Boundaries for TTNI

Analysis	IA	FA
Analysis cutoff trigger	123 PFS events	164 PFS events
Number of TTNI events (information fraction)[1]	110 (72.4%)	152 (100%)
1-sided p-value (z-value) for efficacy	<0.00006 (<-3.858)	<0.025 (<-1.96)

Abbreviations: FA = final analysis; IA = interim analysis; PFS = progression-free survival; TTNI = time to next intervention.
Note: The observed number of events at the IA may not match the planned number of events. The efficacy boundary will be updated based on the actual number of observed events using the prespecified α-spending function.
[1] Number of events expected under H_{12} assuming a hazard ratio for TTNI of 0.636

Because the number of events at IA1 for PFS, IA2 for PFS, or an IA for TTNI may not be exactly equal to the planned number of events, the efficacy and, for the primary endpoint, futility boundaries will be updated based on the actual number of observed events using the prespecified α- and β-spending functions. Therefore, the observed test statistic at the IA(s) will be compared

with the updated efficacy, and for the primary endpoint, futility boundaries. If the study continues to the FA, the p-value that will be used to declare statistical significance at the FA for each endpoint will be based on the actual number of events at the final analysis, the α already spent at the IA(s), and the hierarchical testing strategy.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Good Clinical Practices

This study will be conducted in accordance with the ICH Guidelines for GCP and appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and relevant Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

9.2. Ethical Considerations

This study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki.

The Investigator must obtain IRB/IEC approval for the study and must submit written documentation of the approval to the Sponsor before enrolling any subjects. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The study protocol, Investigator's Brochure, informed consent, assent, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC. The IRB/IEC is to be notified of any amendment to the protocol in accordance with local requirements. Progress reports and notifications of serious unexpected adverse drug reactions are to be provided to the IRB/IEC according to local regulations and guidelines.

9.3. Written Informed Consent or Assent

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks, and benefit of the study. Subjects must also be informed that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

After the study has been fully explained, a signed ICF or assent form, as determined by local requirements, will be obtained from the subject before study participation. A parent or legal guardian must sign the ICF for adolescent subjects who sign assent.

The subject's signed and dated informed consent or assent must be obtained before conducting any study-related procedures. The Investigator must maintain the original, signed ICF or assent; a copy of the signed ICF or assent must be given to the subject.

The method of obtaining and documenting the informed consent or assent and the contents of the consent will comply with all ICH GCP Guidelines and all applicable regulatory requirement(s).

If a subject is suspected to have become incapable of giving consent during the study, the subject's capacity to give consent must be determined by an independent specialist; it should be confirmed and documented that the subject is in the position to understand the nature, significance, and implications of the study and express their wishes accordingly.

9.4. Subject Confidentiality

To maintain subject privacy, all source documents/eCRFs, study drug accountability records, study reports, and communications will identify the subject only by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the source documents/eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable, where regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with applicable regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or Medical Monitor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

9.6. Data Management

An eCRF will be completed for each subject in the EDC system. The EDC system (Medidata Rave®) is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. The system is fully Code of Federal Regulations 21 Part 11 compliant.

Source documentation supporting the data should indicate participation in the study and should document the dates and details of study procedures, AEs, and subject status. The Investigator, or trained designee, should complete the eCRFs and the Investigator should verify the source documents as the information is collected. Any outstanding entries must be completed after the final examination. An explanation should be given for all missing data.

Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic queries. The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc) designed to record all observations and other pertinent data for each subject receiving study treatment.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/IEC to have direct access to all documents pertaining to the study.

9.7. Source Documentation

Source documents will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source document/eCRF. The source document should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the source document as soon as possible after information is collected for a subject's examination, treatment, or any other study procedure. Any outstanding entries must be completed after the final examination. An explanation should be given for all missing data.

The Investigator will retain all completed source documents.

9.8. Site Monitor Access to Source Data

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of source documents/eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. A review of subject's medical records will be performed in a manner that ensures subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to the protocol and that regulatory requirements are being met through frequent communications (ie, letter, telephone, email, and fax) with site staff.

All unused study drug and other study materials should be destroyed or returned to the Sponsor or designee after the study has been completed, as directed by the Sponsor.

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, eCRFs, and other study documentation for an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.9. Retention of Records

The Investigator will maintain all study records according to ICH GCP Guidelines and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate individual who is willing and able to accept that responsibility. The Sponsor must be notified in writing if such a custodial change occurs.

9.10. Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating subjects and arising out of this research performed strictly in accordance with the study protocol as well as with applicable legal, regulatory, and professional standards.

9.11. Reporting and Publication of Results and Use of Information

All information regarding vorasidenib supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information only to conduct the study and not to use it for any other purpose without explicit consent from the Sponsor.

It is understood that there is an obligation on the Investigator's part to provide the Sponsor with the complete data obtained during the study. Such information will be used in the clinical development of vorasidenib and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

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11. APPENDICES

11.1. RANO Response Criteria for Low-Grade Glioma

Fluid-attenuated inversion recovery (FLAIR) sequences provide the clearest and most reproducible definition of WHO Grade 2 glioma margins, although the exact relation between these sequences and the histological tumor margin has not been established (Pallud et al, 2006; Pallud et al, 2010; van den Bent et al, 2011). In contrast to RANO, for high-grade glioma, the tumor size using RANO-LGG should be determined by the product of the maximal cross-sectional non-enhancing lesion diameters instead of enhancing lesion diameters.

Subjects should be assessed with the same imaging modality that follows the same acquisition parameters throughout the trial; details of the minimum acquisition parameters standard are included in detail in the site-specific Imaging Core Manual; in brief, **required** MRI for non-enhancing glioma includes:

- Axial FLAIR (canthomeatal alignment): ≤4 mm sections, with no interslice gaps; slice registration should be preserved as much as possible between sequential studies.
- Axial T2: ≤4 mm sections, with no interslice gap.
- Axial 3D T1 weighted images pre- and post-gadolinium injection: ≤1.5 mm, with no interslice gap.

Clinical Status and Steroid Usage

- Neurological status data will be collected on a neurological status eCRF and on the RANO Overall Response Assessment eCRF.
- If the necessary clinical data are not available, the clinical status will be recorded as *Not Available,* and the time point can only be reviewed for an objective response of PD (otherwise unevaluable).

Steroid Usage

- Steroid usage will be collected on a concomitant medications eCRF.

Radiographic and Integrated Time Point Response as Assessed by Modified RANO-LGG Criteria

Radiographic Time Point Response:

Target Response (criteria applied in order below)	
Not applicable	No target non-enhancing lesions identified at Baseline.
Progressive disease (PD)	≥25% increase in sum of the products of perpendicular diameters of T2-weighted or T2-weighted fluid-attenuated inversion recovery (FLAIR) hyperintense non-enhancing lesions compared with the smallest tumor measurement obtained either at Baseline (if no decrease) or after initiation of therapy (ie, nadir) not attributable to comorbid events.
Unevaluable (UE)	≥1 target non-enhancing lesion was not assessed.
Complete response (CR)	Complete disappearance of the lesion(s) on T2-weighted or T2-weighted FLAIR imaging (if enhancement had been present, it must have resolved completely).
Partial response (PR)	≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable non-enhancing lesions on T2-weighted or T2-weighted FLAIR imaging.
Minor response (MR)	≥25 to <50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable non-enhancing lesions on T2-weighted or T2-weighted FLAIR imaging.
Stable disease	Radiographic criteria not met for PD, UE, CR, PR, or MR.

New Lesion Response (criteria applied in order below)	
Yes	One or more new lesions (enhancing [T1-weighted postcontrast] or non-enhancing [T1-weighted precontrast or T2-weighted/T2-weighted fluid-attenuated inversion recovery (FLAIR) or new clinically significant mass effect]) compared with the baseline magnetic resonance imaging (MRI). Appearance of a nodular and measurable enhancement in the background of previously reported stable, non-nodular, nonmeasurable enhancement will be reported as a new enhancing lesion. An increase of enhancement (radiological evidence of malignant transformation) will also be marked as a new lesion (because target lesion measurements alone will not reflect this).
Unevaluable	Absence of new lesions was not established (eg, incomplete anatomical coverage).
No	No new lesions compared with baseline MRI scan, no new T2-weighted or T2-weighted FLAIR abnormalities, and no new or increased enhancement.

Evaluate the following criteria in order:		
Target Lesion Response	**New Lesions**	**Radiographic Disease Response**
PD	ANY	PD
ANY	Yes	PD
ANY	UE	UE
UE	No	UE
NA	No	NA
SD	No	SD
MR	No	MR
PR	No	PR
CR	No	CR

Abbreviations: CR = complete response; MR = minor response; NA = not applicable; PD = progressive disease; PR = partial response; SD = stable disease; UE = unevaluable.

11.2. New York Heart Association Classification

Class	**Symptomatology**
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

11.3. CYP2C8, CYP2C9, CYP2C19, and CYP3A Substrates With a Narrow Therapeutic Index

The following medications are prohibited while subjects are receiving study drug.

CYP3A Substrates With a Narrow Therapeutic Index			
alfentanil	dihydroergotamine	pimozide	terfenadine[1]
astemizole[1]	everolimus	quinidine	
cisapride	ergotamine	sirolimus	
cyclosporine	fentanyl	tacrolimus	
CYP2C8 Substrates With a Narrow Therapeutic Index			
paclitaxel			
CYP2C9 Substrates With a Narrow Therapeutic Index			
phenytoin	warfarin		
CYP2C19 Substrates With a Narrow Therapeutic Index			
s-mephenytoin			

Abbreviations: CYP = cytochrome P450; P-gp = P-glycoprotein.
Note: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.
Note: CYP or P-gp substrates with a narrow therapeutic window refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, torsades de pointes).
[1] Withdrawn from the United States market because of safety reasons.

11.4. Medications Known to Prolong the QT Interval

The following medications should be avoided, and subjects transferred to an alternative medication. If this is not possible, subjects should be adequately monitored.

amiodarone	dofetilide	grepafloxacin	moxifloxacin	quinidine
astemizole	dolasetron	halofantrine	norfloxacin	sevoflurane
azithromycin	domperidone	haloperidol	ofloxacin	sotalol
bepridil	droperidol	ibutilide	ondansetron	sparfloxacin
chloroquine	escitalopram	itraconazole	palonosetron	terfenadine
chlorpromazine	erythromycin	ketoconazole	pentamidine	thioridazine
ciprofloxacin	flecainide	levofloxacin	pimozide	voriconazole
citalopram	gatifloxacin	levomethadyl	posaconazole	
clarithromycin	gemifloxacin	mesoridazine	probucol	
disopyramide	granisetron	methadone	procainamide	

Note: This is not an exhaustive list. For an updated list, see the following link: https://crediblemeds.org/healthcare-providers.

11.5. Sensitive CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A Substrates

The following medications should be avoided while subjects are receiving study drug and subjects transferred to an alternative medication, if possible. If this is not possible, subjects should be adequately monitored.

Enzymes	**Sensitive Substrates**
CYP2B6	bupropion
CYP2C8	repaglinide
CYP2C9	celecoxib
CYP2C19	S-mephenytoin, omeprazole, tilidine,
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil

Abbreviation: CYP = cytochrome P450.

11.6. Moderate Sensitive CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A Substrates

The following medications should be used with caution while subjects are receiving study drug.

Enzymes	**Moderate Sensitive Substrates**
CYP2B6	efavirenz
CYP2C8	montelukast, pioglitazone, rosiglitazone
CYP2C9	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	diazepam, lansoprazole, rabeprazole, voriconazole
CYP3A	alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

Abbreviation: CYP = cytochrome P450.

11.7. Lansky Play-Performance Scale

The Lansky Play-Performance Scale for children is designed to provide a standardized measure of the performance status of the child with cancer. The play-performance scale is rated by the parent on the basis of the past week and can be re-administered to assess change over time or following treatment.

Rating	Description
100	fully active, normal
90	minor restrictions in physically strenuous activity
80	active, but tires more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play; keeps busy with quieter activities
50	gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	in bed; needs assistance even for quiet play
20	often sleeping; play entirely limited to very passive activities
10	no play; does not get out of bed
0	unresponsive

Source: Lansky DA, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. *Cancer.* 1987;60 (7):1651–1656.

11.8. Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Sources:

Crooks, V, Waller S, Smith T, Hann T. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. *J Gerontol*. 1991; 46(4): M139-M144.

de Haan R, Aaronson N, Limburg M, Langton Hewer R, van Crevel. Measuring quality of life in stroke. *Stroke*. 1993;24:320-327.

Hollen PJ, Gralla RJ, Kris MG, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. *Cancer*. 1994;73(8):2087-2098.

O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. *West J Med*. 1991;155(4):384-387.

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11.9. Tanner Stages

The following table describes the Tanner stages in detail for clinical reference. For all 3 sites of development, Tanner Stage 1 corresponds to the prepubertal form, with progression to Tanner Stage 5, the final adult form. Breast and genital staging as well as other physical markers of puberty such as height velocity should be relied on more than pubic hair staging to assess pubertal development because of the independent maturation of the adrenal axis.

Pubic Hair Scale (both males and females) • Stage 1: No hair • Stage 2: Downy hair • Stage 3: Scant terminal hair • Stage 4: Terminal hair that fills the entire triangle overlying the pubic region • Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh
Female Breast Development Scale • Stage 1: No glandular breast tissue palpable • Stage 2: Breast bud palpable under areola (first pubertal sign in females) • Stage 3: Breast tissue palpable outside areola; no areolar development • Stage 4: Areola elevated above contour of the breast, forming “double scoop” appearance • Stage 5: Areolar mound recedes back into single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion
Male External Genitalia Scale • Stage 1: Prepubertal • Stage 2: Enlargement of testes and scrotum; scrotal skin reddens and changes in texture • Stage 3: Enlargement of penis (length at first); further growth of testes • Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker • Stage 5: Adult genitalia

Sources:

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44(235):291-303.
Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45(239):13-23.

11.10. Protocol Amendment History

Changes that had a major impact on the conduct of the study are summarized here.

Amendment 2, Version 3.2 (Germany only):

- Removed language regarding home health study support and virtual informed consent from Section 3.6.1 (Allowable Temporary Modifications) because such modifications are not permitted by Germany's national requirements.

Amendment 2, Version 3.1 (Germany only):

- Revised the statistical design, including study power and hazard ratio assumption.
- Removed TGR from the testing order and identified TTNI as the only key secondary endpoint; modified the definition of TTNI to include death as an event.
- Added the evaluation of the circulating metabolite of vorasidenib, AGI-69460, in plasma to the pharmacokinetic (PK) secondary objective.
- Added complete response (CR)+partial response (PR), time to CR+PR, and duration of CR+PR as secondary efficacy endpoints.
- Added exploratory objective to evaluate TGR before and after treatment with vorasidenib and placebo.
- Added Patient Global Impression (PGI) of Severity (PGI-S) and PGI of Frequency (PGI-F) as additional measures of health-related quality of life (HRQoL).
- Added more details in the statistical methods section.
- Added Per-protocol Set (PPS) to the analysis sets.
- Added guidance on allowable temporary modifications to study conduct during COVID-19 public health emergencies during which adherence to protocol-specified procedures may be impeded.
- Updated prohibited concomitant medications to include medications that are CYP2C8 or CYP2C19 substrates with a narrow therapeutic index.
- Added 40-mg strength tablets.
- Removed language around vorasidenib possibly being a phototoxicant.

Amendment 2, Version 3.0 (Global except Germany):

- Revised the statistical design, including study power and hazard ratio assumption.
- Removed TGR from the testing order and identified TTNI as the only key secondary endpoint.
- Modified the definition of TTNI to include death as an event.
- Added the evaluation of the circulating metabolite of vorasidenib, AGI-69460, in plasma to the pharmacokinetic (PK) secondary objective.

- Added complete response (CR)+partial response (PR), time to CR+PR, and duration of CR+PR as secondary efficacy endpoints.
- Added exploratory objective to evaluate TGR before and after treatment with vorasidenib and placebo.
- Added Patient Global Impression (PGI) of Severity (PGI-S) and PGI of Frequency (PGI-F) as additional measures of health-related quality of life (HRQoL).
- Added more details in the statistical methods section.
- Added Per-protocol Set (PPS) to the analysis sets.
- Added guidance on allowable temporary modifications to study conduct during COVID-19 public health emergencies during which adherence to protocol-specified procedures may be impeded.
- Revised definition of women of childbearing potential and clarified definition of abstinence.
- Updated prohibited concomitant medications to include medications that are CYP2C8 or CYP2C19 substrates with a narrow therapeutic index.
- Added 40-mg strength tablets.
- Removed language around vorasidenib possibly being a phototoxicant.
- Added Tanner staging of sexual maturity at the Cycle 1, Day 1 (C1D1) visit for all subjects 12-17 years of age at time of enrollment as well as on-treatment assessment at regular intervals in subjects who are less than Stage 5 at the C1D1 assessment.
- Increased the frequency of height collection for subjects 12-17 years of age who are being assessed for Tanner stage to occur at the same visits as the Tanner stage assessments.

Amendment 1, Version 2.5 (Germany only):

- Revised the language around contraceptives in Inclusion Criterion 13 in Section 4.2 (Inclusion Criteria) and in Section 5.16.3 (Pregnancy).
- Deleted Section 5.15.3.3. (Hormonal Contraceptives).

Amendment 1, Version 2.4 (Italy only):

- Revised Section 1.3.3.3 (Dosing Considerations for Adolescents) to add additional details around modeling of predicted exposure.
- Added Section 1.4 (Benefit-Risk Assessment).
- Added medications that are CYP2C8 and CYP2C19 substrates with a narrow therapeutic index to Exclusion Criterion 12 in Section 4.3 (Exclusion Criteria), to Section 5.15.2 (Prohibited Concomitant Medications), and to Appendix 11.3 (CYP3A, CYP2C8, CYP2C9, and CYP2C19 Substrates With a Narrow Therapeutic Index).
- Revised Section 5.5 (Blinding) and Section 5.6 (Unblinding).

- Added references to the separate study laboratory manual and sample collection flow chart to Section 6.1 (Schedule of Events) and to Section 6.30 (Sample Processing, Storage, and Shipment).

Amendment 1, Version 2.3 (Germany only):

- Revised inclusion criteria for Germany to exclude subjects under 18 and to disallow legally authorized representatives to consent on behalf of a subject who are otherwise unable to provide informed consent.
- Revised contraception language to allow subjects to use 1 highly effective method and 1 at least acceptable method instead of 2 highly effective forms.
- Added a new Section 5.15.3.3. (Hormonal Contraceptives) to specify that coadministration of vorasidenib may decrease the concentrations of hormonal contraceptives.
- Added language to define the process for determining if a subject has become incapable of giving consent during the study.

Amendment 1, Version 2.2 (UK only):

- Defined abstinence to clarify what is and is not acceptable.
- Added a pregnancy test at the 28-day Safety Follow-up Visit.
- Added a footnote to the Schedule of Assessment to specify that SAEs considered related to study drug should be reported in the safety database after the 28-day follow-up period.

Amendment 1, Version 2.1 (Canada only):

- Added Tanner staging of sexual maturity at the C1D1 visit for all subjects 12-17 years of age at time of enrollment as well as at every 3 months through Cycle 37, every 6 months after Cycle 37, and at End of Treatment (EOT) for subjects 12-17 years of age who are less than Stage V at C1D1 until they reach Stage V.
- Increased the frequency of height collection from Screening and EOT to the same visits as the Tanner stage assessments for subjects 12-17 years of age who are being assessed for Tanner stage.

Amendment 1, Version 2.0 (Global):

- Changed formulation of vorasidenib from vorasidenib uncoated tablets to vorasidenib film-coated tablets.
- Changed the starting dose of vorasidenib from 50 mg QD of the uncoated tablet formulation to 40 mg QD of the film-coated tablet formulation.
- Changed the dose reduction levels to reflect the film-coated tablet formulation and the new starting dose.
- Added the Lansky Play Performance Scale as a performance assessment measure for subjects <16 years of age.

- Added the Bedside Schwartz method as a way of measuring creatinine clearance for subjects <18 years of age.
- Removed the lamotrigine exclusion criterion.