2 SYNOPSIS

Name of Sponsor: Institut de Recherches Internationales Servier (I.R.I.S.)	*(For National Authority Use only)*
Name of Finished Product: Vorasidenib **Name of Active Ingredient:** Vorasidenib (S095032, AG-881)	

Title of study: 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

Protocol No.: AG881-C-004

EudraCT No.: 2019-002481-13

Phase of development of the study: 3

Principal Investigator /Coordinating Investigator:

[redacted]

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065

[redacted]

Number of Study Centers and Countries: Ten countries participated in this study and enrolled subjects: Canada (2 sites), France (3 sites), Germany (4 sites), Israel (4 sites), Italy (4 sites), Netherlands (3 sites), Spain (3 sites), Switzerland (2 sites), United Kingdom (4 sites), and United States (38 sites). Subjects were counted under the site according to electronic data capture as of the 06 September 2022 data cutoff and may not be reflective of the initial consenting site as documented in the interactive web response system, in the case of subject transfers.

Study Period (Primary Clinical Study Report):

Initiation date: 08 January 2020

Data cutoff date: 06 September 2022

Publications (reference): Mellinghoff IK, van den Bent MJ, Blumenthal DT et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. N Engl J Med 2023; 389:589-601. DOI: 10.1056/NEJMoa2304194

Background and Rationale for the Study:

This is a Phase 3, global, multicenter, double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of vorasidenib (S095032, previously known as AG-881) and placebo in subjects with residual or recurrent Grade 2 glioma with an isocitrate dehydrogenase (IDH)1 or IDH2 mutation.

Objectives and Endpoints:

Primary Objective	Primary Endpoint
To demonstrate the efficacy of vorasidenib based on radiographic PFS per the 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.	• PFS defined as the time from date of randomization to date of first documented radiographic PD (as assessed by the BIRC per modified RANO-LGG) or date of death due to any cause, whichever occurs earlier.

Key Secondary Objective	• **Key Secondary Endpoint**
To demonstrate the efficacy of vorasidenib based on TTNI compared with placebo.	• 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.
Other Secondary Objectives	**Other Secondary Endpoints**
To evaluate the safety and tolerability of vorasidenib.	• AEs, SAEs, AEs leading to discontinuation or death, and severity of AEs as assessed by the NCI CTCAE, version 5.0. • Safety laboratory parameters, vital signs, 12-lead ECGs, LVEF, KPS/LPPS, and concomitant medications.
To evaluate vorasidenib and placebo with respect to TGR as assessed by volume per the BIRC.	• TGR as assessed by volume, defined as the percentage change in tumor volume every 6 months as assessed per the BIRC.
To evaluate the efficacy of vorasidenib and placebo based on objective response, CR+PR, TTR, time to CR+PR, DoR, and duration of CR+PR, with response assessed per the BIRC and the Investigator.	• OR, 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. • TTR, 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. • DoR, 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.
To evaluate vorasidenib and placebo with respect to OS.	• OS, defined as the time from the date of randomization to the date of death due to any cause.
To evaluate vorasidenib and placebo with respect to HRQoL as assessed by the FACT-Br questionnaire.	• HRQoL as assessed by the FACT-Br questionnaire.
To evaluate vorasidenib and placebo with respect to PFS per the Investigator assessment.	• PFS as assessed by the Investigator per modified RANO-LGG.
To evaluate the PK of vorasidenib and its circulating metabolite AGI-69460 in plasma.	• Serial or sparse blood sampling at specified time points for determination of plasma concentrations

	of vorasidenib and its circulating metabolite AGI-69460.

Abbreviations: AE = adverse event; BIRC = blinded independent review committee; CR = complete response; CSF = cerebrospinal fluid; DoR = duration of response; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5 Dimensions, 5-Level; FACT-Br = Functional Assessment of Cancer Therapy – Brain; HRQoL = health-related quality of life; IDH = isocitrate dehydrogenase; KPS = Karnofsky Performance Scale; LPPS = Lansky Play-Performance Scale; LVEF = left ventricular ejection fraction; mR = minor response; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OR = objective response; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PGI = patient global impression; PK = pharmacokinetics; PR = partial response; RANO-LGG = Response Assessment in Neuro-oncology for Low-grade Gliomas; SAE = serious AE; TGR = tumor growth rate; TTNI = time to next intervention; TTR = time to response.

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 subjects with residual or recurrent Grade 2 glioma with an IDH1 or IDH2 mutation.

Subject eligibility was determined by central confirmation of IDH mutation status during prescreening up to 84 days before subjects were randomized. After confirmation of IDH mutation status, subjects underwent a screening period, which occurred within 28 days before randomization.

Subjects who met all study eligibility criteria were randomized 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 was stratified by local 1p19q co-deletion 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 was continuous.

A Blinded Independent Review Committee (BIRC) assessed radiographic eligibility for study entry, the primary efficacy endpoint of radiographic progression-free survival (PFS) per modified Response Assessment in Neuro-oncology for Low-grade Gliomas (RANO-LGG) criteria, and the secondary efficacy endpoint of tumor growth rate (TGR) as assessed by tumor volume. The BIRC also was 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 was conducted at specified time points throughout the study or at any time PD was suspected. For Investigator assessment of tumor response, target lesion selection and tumor response per RANO-LGG criteria were performed the institutional radiologist/Investigator. Scan acquisition parameters required per protocol were detailed in a separate site-specific imaging core manual. All MRI scans were sent to the BIRC as detailed in the site-specific Imaging Core Manual.

This study was performed in accordance with Good Clinical Practice (GCP).

Number of Subjects:

Planned: Approximately 340 subjects were planned to be randomized 1:1 to receive daily oral 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).

Included: 331 subjects were randomized to either placebo (163 subjects) or vorasidenib (168 subjects) as of 06 September 2022 data cutoff. The study is ongoing. The following data sets were analyzed:

331 subjects were included in the Full Analysis Set (FAS) (all randomized subjects)
330 subjects were included in the Safety Analysis Set (SAS)
329 subjects were included in the Per-Protocol Set (PPS)

Diagnosis and Main Criteria for Inclusion/Exclusion:

Subjects were at least 12 years old, weighed at least 40 kg, and had a histologically confirmed diagnosis of IDH1 or IDH2 gene–mutated Grade 2 oligodendroglioma or astrocytoma (per the World Health Organization 2016 classification) with residual or recurrent disease. Subjects had at least 1 prior surgery (biopsy, subtotal resection, or gross-total resection), with the most recent surgery occurring at least 1 year and not more than 5 years before the date of randomization. Subjects were enrolled if they had not received any other treatment, including systemic chemotherapy or radiotherapy, and did not have any high-risk features and or need of immediate chemotherapy or radiotherapy in the opinion of the Investigator.

Study Treatment:

Vorasidenib was administered orally as either 40 mg or 10 mg tablets QD.

A dose of 50 mg QD of vorasidenib (uncoated tablet, clinical formulation) was selected as the starting dose for subjects in the original protocol of this study. This dose was used in a small number of subjects until a relative bioavailability study showed that a dose of 40 mg QD (film-coated, commercial formulation) was projected to achieve plasma area under the concentration versus time curve (AUC) exposures comparable to the exposures observed from 50 mg QD of the clinical formulation. As of protocol amendment 1, the clinical formulation was replaced by the commercial formulation.

Nine subjects were randomized under the original protocol and initially received the clinical formulation of the uncoated tablet, including 5 subjects who were randomized to and received vorasidenib and 4 subjects who were randomized to and received placebo. The 5 subjects randomized to vorasidenib who initially received the clinical formulation received between 1 month and 3 months of the clinical formulation before switching to the commercial formulation. Subjects randomized to receive vorasidenib under all protocol amendments started at 40 mg.

Tablets were administered QD in continuous 28-day cycles. Dose-modification guidelines were provided in the protocol for specific adverse events (AEs).

Comparator:

Vorasidenib-matched placebo mimicking the appearance of the vorasidenib tablet was used as a comparator.

Duration of Treatment:

Active treatment period: The median (Q1, Q3) treatment duration in the placebo and vorasidenib arms, respectively, was 11.17 (8.44, 14.95) months and 12.65 (8.67, 17.48) months.

Statistical Methodology:

Descriptive statistics for continuous data included the number of subjects with data to be summarized (n), mean, standard deviation (StD), median, quartiles, minimum, and maximum. Descriptive statistics for categorical/qualitative data included frequency counts and percentages.

Time-to-event endpoints were analyzed using the Kaplan-Meier (KM) method. Point estimates and 95% CIs were provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (eg, 3-, 6-, and 12-month rates), were produced. Listings were provided for selected endpoints.

Primary Efficacy Endpoint: The primary efficacy analysis compared the PFS per the BIRC between the 2 treatment arms using a 1-sided stratified log-rank test. The test was stratified by 1p19q status and baseline tumor size. A Cox proportional hazards (PH) model stratified by randomization stratification factors was used to estimate the hazard ratio (HR) of PFS, along with its 95% CI. The P-value from the 1-sided stratified log-rank test was presented.

Key Secondary Efficacy Endpoint: Time to next intervention (TTNI) was compared between the 2 treatment arms using a 1-sided stratified log-rank test. The test was stratified by 1p19q status and baseline tumor size. A Cox PH model stratified by randomization stratification factors was used to estimate the HR of TTNI, along with its 95% CI. The P-value from the 1-sided stratified log-rank test was also presented.

Other Secondary Efficacy Endpoints: Additional efficacy endpoints included 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 efficacy response endpoints were performed separately based on the BIRC assessment and based on Investigator assessment per modified RANO-LLG.

Safety Endpoints: Safety was evaluated by the incidence, severity, and type of AEs, and by evaluation of vital signs, Karnofsky Performance Scale / Lansky Play-Performance Scale, clinical laboratory results, electrocardiogram (ECG), and left ventricular fraction (LVEF) data (as clinically indicated). All safety data were 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 started on the date of the start of study treatment and ended 28 days after the end of study treatment or 1 day before the start of subsequent anticancer therapy, whichever was earlier.

Pharmacokinetic Endpoints: Descriptive statistics of plasma concentrations (arithmetic and geometric means, StD, coefficient of variation (CV%), CV% geometric mean, minimum, median, and maximum) of vorasidenib and its metabolite AGI-69460 were summarized.

The study data analyzed and reported in this clinical study report (CSR) are based on all subjects' data up to the data cutoff date (06 September 2022).

Analysis Sets:

The following analysis sets were evaluated and used for presentation of the data.

Analysis Set	Description	Endpoints
Full Analysis Set (FAS)	Included all subjects randomized. Subjects were classified according to the randomized treatment arm according to the ITT principle.	Demographic and other baseline characteristics, disposition, major protocol deviations, subsequent therapies, and efficacy
Per Protocol Set (PPS)	A subset of FAS. Subjects who met any of the following criteria were excluded from the PPS: • Did not receive at least 1 dose of the randomized treatment • Did not have any measurable lesions at baseline as assessed by the BIRC per modified RANO-LGG • Did not have histopathologically diagnosed Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria (ie, do not meet Inclusion Criterion #3). • Had had any prior anticancer therapy other than surgery (biopsy, subtotal resection, gross-total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, etc. (ie, met Exclusion Criterion #1).	PFS and TTNI
Safety Analysis Set (SAS)	Included all subjects who received at least 1 dose of the study treatment. Subjects were classified according to the treatment received; subjects randomized to placebo who received at least one dose of vorasidenib prior to crossover were classified to the vorasidenib arm.	Exposure and concomitant therapies, and safety

Abbreviations: BIRC = Blinded Independent Review Committee; IDH = isocitrate dehydrogenase; ITT = intent-to-treat; PFS = progression-free survival; PK = pharmacokinetic; RANO-LGG = Response Assessment in Neuro-oncology for Low-grade Gliomas; TTNI = time to next intervention; WHO = World Health Organization.

SUMMARY OF RESULTS AND CONCLUSIONS

DISPOSITION

At the time of data cutoff for this primary CSR, a higher proportion of subjects were continuing their assigned treatment in the vorasidenib arm (78.0%, n=131) than in the placebo arm (58.3%, n=95). In the vorasidenib arm, 36 subjects (21.4%) had discontinued their assigned treatment compared to 68 subjects (41.7%) in the placebo arm.

BASELINE CHARACTERISTICS

A total of 466 subjects entered prescreening for central confirmation of IDH mutation status; of these, 76 subjects were considered pre-screen failures, the majority due to IDH mutation status not being centrally confirmed. A total of 390 subjects were screened for the study; of these, 59 subjects were considered screen failures and were not enrolled because they did not meet the inclusion criteria, or they met at least one exclusion criterion. A total of 331 subjects were randomized to either placebo (163 subjects) or vorasidenib (168 subjects). Of these, 163 subjects received placebo and 167 subjects received vorasidenib. One subject in the vorasidenib arm withdrew consent prior to treatment and did not receive study drug.

Median age in the placebo and vorasidenib arms was 39.0 years and 40.5 years, respectively. To be eligible for this study, adolescent subjects had to be at least 12 years of age and weigh at least 40 kg. A single pediatric patient 16 years of age at time of enrollment was randomized to the placebo arm. All other subjects were between 18 and 71 years of age.

The proportion of males and females in the placebo arm was balanced; in the vorasidenib arm, more males (60.1%, n=101) were enrolled than females (39.9%, n=67).

Karnofsky Performance Scale scores ranged from 70 to 100, and the proportion of subjects reporting these scores was consistent between treatment arms.

The proportion of subjects with tumor histological subtypes (oligodendroglioma and astrocytoma) and the median time from initial diagnosis was consistent between the treatment arms. In the placebo and vorasidenib arms, respectively, 84 subjects (51.5%) and 88 subjects (52.4%) had oligodendroglioma, and 79 subjects (48.5%) and 80 subjects (47.6%) had astrocytoma. The median time from initial diagnosis was 29.60 months and 35.37 months in the placebo and vorasidenib arms, respectively.

All subjects had at least 1 prior surgery for glioma per the inclusion criteria. Most subjects had undergone 1 prior surgery in the placebo (82.2%, n=134) and vorasidenib (75.0%, n=126) arms. At least 2 prior surgeries were reported in 29 subjects (17.8%) and 42 subjects (25.0%), respectively, in the placebo and vorasidenib arms. The time from the most recent surgery was consistent between the two arms with a median (range) of 2.21 (0.9 to 5.0) years in the placebo arm and 2.52 (0.2 to 5.2) years in the vorasidenib arm.

EXTENT OF EXPOSURE

The median treatment duration in the placebo and vorasidenib arms, respectively, was 11.17 and 12.65 months, with most subjects treated between 6 and 18 months at the time of data cutoff. Treatment duration was between 0.6 and 29.9 months. The median actual dose intensities were consistent between the placebo and vorasidenib treatment arms, with median (range) relative dose intensities 99.43% (42.9% to 100.1%) and 99.39% (26.0% to 100.1%), respectively.

EFFICACY RESULTS

Interim Analysis 2 (IA2) was prespecified for superiority and futility. Per the protocol, IA2 was to take place when approximately 123 PFS events (75% of the expected 164 events) occurred. By 06 September 2022 (IA2 data cutoff date), there were 135 PFS events observed, corresponding to the 82% information fraction (135/164 PFS events). On 24 February 2023, the independent data monitoring committee (IDMC) held the second Interim Analysis Data Review Meeting. During the closed meeting session, when the unblinded data were reviewed, the IDMC recommended unblinding the study due to early demonstration of efficacy; the study met its primary endpoint and key secondary endpoint at IA2. Following the IDMC recommendation, Servier unblinded the study on 07 March 2023. On 09 March 2023, Investigators were informed that the study met its primary and key secondary endpoints and were instructed to perform unblinding of the subjects' treatment assignments. Subjects still receiving placebo at the time of study unblinding were given the opportunity to cross over to the vorasidenib arm provided certain eligibility criteria were met.

Primary Efficacy Endpoint:

The primary efficacy endpoint was met at IA2. Progression-free survival per the BIRC was tested following the prespecified hierarchical testing strategy and the α-spending function per protocol. Progression-free survival per the BIRC was significantly improved in the vorasidenib arm compared with placebo arm with an HR of 0.39 (95% CI, 0.27, 0.56; P=0.000000067). The median PFS was 27.7 (95% CI, 17.0, NE) months for the vorasidenib arm and 11.1 (11.0, 13.7) months for the placebo arm.

Results of PFS per the BIRC favored vorasidenib in all subgroup analyses and sensitivity analyses described in the SAP, consistent with the primary efficacy analysis of PFS in the FAS.

Key secondary endpoint:

The key secondary endpoint was also met at IA2. TTNI was tested following the prespecified hierarchical testing strategy and the α-spending function per protocol, given that the primary endpoint was statistically significant at IA2. TTNI was significantly improved in the vorasidenib arm compared with placebo arm with an HR for TTNI of 0.26 (95% CI, 0.15, 0.43; P=0.000000019).

Results of TTNI favored vorasidenib in all subgroup analyses described in the SAP, consistent with the primary efficacy analysis of TTNI in the FAS.

Other secondary endpoints:

The post-treatment tumor volume decreased in subjects randomized to vorasidenib by a mean of 2.5% (TGR of -2.5% [95% CI, -4.7, -0.2]) every 6 months, while tumor volume increased by a mean of 13.9% (TGR of 13.9% [95% CI, 11.1, 16.8]) every 6 months for the placebo arm. The mean percentage change on tumor volumes over time suggests that vorasidenib induced tumor shrinkage, while aggregate data from subjects on placebo had continuous tumor growth.

Results of the Investigator assessment of PFS were consistent with the primary efficacy analysis assessed by the BIRC. Progression-free survival assessed by the Investigator was improved in the vorasidenib arm compared with placebo arm with an HR of 0.35 (95% CI, 0.23, 0.54; P=0.000000243).

The post-treatment tumor volume decreased in subjects randomized to vorasidenib by a mean of 2.5% (TGR of 2.5% [95% CI, -4.7%, -0.2%]) every 6 months, while tumor volume increased by a mean of 13.9% (TGR of 13.9% [95% CI, 11.1%, 16.8%]) every 6 months for the placebo arm. The mean percentage change on tumor volumes over time suggests that vorasidenib induced tumor shrinkage, while aggregate data from subjects on placebo had continuous tumor growth.

Objective response as assessed by the BIRC favored the vorasidenib arm. The objective response rate (ORR) in the vorasidenib arm was 10.7%, including 2 PRs and 16 mRs, compared with 2.5% in the placebo arm, with no reported PRs. The odds ratio for ORR was 4.88 (95% CI 1.56, 15.25, P=0.003).

The results of the subgroup analyses of objective response favored vorasidenib across all the subgroups tested, including co-deletion status.

Of the 18 subjects who achieved a response (CR, PR, or mR) in the vorasidenib arm, the median duration of response per the BIRC was 16.6 (95% CI, 2.8, 16.6) months. Duration of response was not evaluable in the placebo arm (n=4 subjects)

The median (range) time to response (CR, PR, or mR) per the BIRC was 11.0 (6 to 14) months and 6.9 (3 to 11) months in the vorasidenib and placebo arms, respectively.

No subject in either treatment arm had a death event by the time of data cutoff. Median OS follow-up was consistent between the placebo and vorasidenib arms: 14.3 (95% CI, 12.7, 15.4) months and 14.0 (12.9, 15.4) months, respectively.

At baseline, FACT-Br total score and subscale scores were not meaningfully different between the arms. No postbaseline improvements in the FACT-Br total score, physical well-being and brain cancer subscale scores were observed favoring either arm at any time point up to and including Cycle 13. At EOT, the mean (StD) FACT-Br total score was not meaningfully different between the arms (151.8 [31.09] for placebo and 150.8 [29.5] for vorasidenib). No meaningful deterioration was observed for anchor or distribution estimates in the FACT-Br total score and subscale scores in either arm up to and including Cycle 13. Using the MMRM, there were no substantial differences in FACT-Br scores between the vorasidenib and placebo arms observed at any time point up to and including Month 13 for FACT-Br total score and physical well-being and brain cancer subscales.

Twenty subjects in each arm reported baseline seizure activity, defined as at least 1 seizure in the previous 30 days prior to study treatment. Up to and including Cycle 13, a reduction in the number of subjects reporting at least 1 seizure compared to baseline was observed at some cycles in each arm. At Cycle 13, 10 subjects in the placebo arm and 8 subjects in the vorasidenib arm reported at least 1 seizure.

SAFETY RESULTS

No deaths were reported in either arm as of the data cutoff date.

The proportion of subjects reporting any TEAE was similar in the vorasidenib (94.6%) and placebo arms (93.3%).

A higher proportion of subjects experienced treatment-related TEAEs in the vorasidenib arm (65.3%) than in the placebo arm (58.3%).

The proportion of subjects with Grade ≥3 TEAEs, treatment-related TEAEs of all grades, serious treatment-related TEAEs, TEAEs leading to discontinuation of study drug, dose interruption, and dose reduction, AESIs (serious and nonserious), and TEAEs associated with COVID-19 was higher in the vorasidenib arm than in the placebo arm.

Of the TEAEs (any grade) reported in ≥10% of subjects, the following TEAEs occurred at a ≥2% higher rate in the vorasidenib arm compared to the placebo arm: ALT increased (38.9% versus 14.7%), AST increased (28.7% versus 8.0%), COVID 19 (32.9% versus 28.8%), diarrhea (24.6% versus 16.6%), GGT increased (15.6% versus 4.9%), and seizure (13.8% versus 11.7%).

The following Grade ≥3 TEAEs occurred at a ≥2% higher incidence in the vorasidenib arm compared with the placebo arm: ALT (9.6% versus none) and AST increased (4.2% versus none).

Grade 4 treatment-related TEAEs were reported only by subjects in the vorasidenib arm (3.0%) and were associated with liver abnormalities: ALT increased (2.4%), AST increased (1.2%), autoimmune hepatitis and hepatic necrosis (0.6% each).

Grade 3 treatment-related TEAEs were reported in 17 subjects (10.2%) in the vorasidenib arm and included: ALT increased (7.2%), AST increased (3.0%), GGT increased (2.4%), blood bilirubin increased, bilirubin conjugated increased, neutrophil count decreased, diarrhea, fatigue, dyspnea, and hepatic failure (0.6% each).

The proportion of subjects experiencing serious TEAEs was similar in the placebo and vorasidenib arms, respectively, 4.9% and 6.6% of subjects reported at least 1 SAE.

SAEs reported in >1 subject included seizure (3 subjects [1.8%] in the placebo arm and 5 subjects [3.0%] in the vorasidenib arm) and suicidal ideation (reported by 2 subjects [1.2%] in the placebo arm). Serious TEAEs assessed by the Investigator as treatment-related were all associated with liver abnormalities; these occurred in 3 subjects (1.8%) in the vorasidenib arm only, and included autoimmune hepatitis, hepatic failure, and ALT increased 1 subject each (0.6%).

A total of 4 subjects in the vorasidenib arm experienced Grade 4 ALT increased and were discontinued from treatment. One of these subject's Grade 4 ALT was reported as a serious TEAE. Other events of Grade 4 ALT increased, Grade 3 ALT increased and Grade 3 AST increased that led to vorasidenib discontinuation were reported as nonserious AESIs.

A higher proportion of subjects experienced AESIs in the vorasidenib arm (18.6%) than in the placebo arm (2.5%). In the vorasidenib arm a higher proportion of subjects experienced Grade ≥2 ALT increased (18.0%) than Grade ≥2 AST increased (8.4%). Grade ≥3 AESIs were reported in 17 subjects (10.2%) in the vorasidenib arm only.

Serum chemistry worsening from baseline Grade 0 to postbaseline Grade 4 occurred in the vorasidenib arm only and included increased ALT, AST, and creatinine, and decreased glucose. Worsening from baseline Grade 0 or Grade 1 to postbaseline Grade 3 was reported in the vorasidenib arm as increased ALT, ALP, AST, bilirubin, GGT, and potassium and as decreased glucose, potassium, and sodium. Worsening of 3 grades in the placebo arm included increased ALP, bilirubin, and GGT and decreased potassium and sodium.

A ≥2% higher incidence of subjects in the vorasidenib arm compared to the placebo arm reported newly occurring or worsening serum chemistry abnormalities for high ALP, ALT, AST, creatinine, GGT, potassium, and low and high calcium. A ≥2% higher incidence of subjects in the placebo arm compared to the vorasidenib arm reported newly occurring or worsening serum chemistry abnormalities for low glucose, potassium, and sodium.

Elevations in ALT or AST of >3×ULN (corresponding to Grade 2) were reported by 3.1% and 19.2% of subjects in the placebo and vorasidenib arms, respectively. Elevations in ALT or AST of >5×ULN (corresponding to Grade 3) and >20×ULN (corresponding to Grade 4) were reported in 10.2% and 3.6% of subjects, respectively, in the vorasidenib arm only.

Two subjects who received vorasidenib met laboratory criteria for Hy's law. Both subjects experienced liver related SAEs; autoimmune hepatitis was reported in 1 subject and hepatic failure was reported in the other subject.

Decreased neutrophils was the only hematology parameter that worsened from baseline Grade 0 to postbaseline Grade 4 and was reported by 1 subject in the placebo arm.

Worsening from baseline Grade 0 to postbaseline Grade 3 was reported in the vorasidenib arm as decreased hemoglobin, leukocytes, lymphocytes, and neutrophils. Worsening from baseline Grade 0 or Grade 1 to postbaseline Grade 3 in the placebo arm included decreased lymphocytes, neutrophils, and leukocytes.

A ≥2% higher incidence of subjects in the vorasidenib arm compared to the placebo arm reported newly occurring or worsening hematology abnormalities for high hemoglobin, low lymphocytes, neutrophils, and platelets. A ≥2% higher incidence of subjects in the placebo arm compared to the vorasidenib arm reported newly occurring or worsening hematology abnormalities for low hemoglobin.

Changes from baseline for vital signs, LVEF, and ECG parameters were minor, and no safety signals were observed.

No notable differences for QTcF changes from baseline were noted in either treatment arm. No subjects in either arm reported a QTcF that exceeded 500 ms.

CONCLUSION

The clinically meaningful efficacy results observed in the AG881-C-004 study, along with the manageable safety profile of vorasidenib, demonstrate that vorasidenib is a safe and effective targeted therapy in patients with Grade 2 residual or recurrent IDH-mutant gliomas who have been treated with surgical intervention only.

Date of the report: 29 September 2023