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:** AG-881 (S095032)	
Title of study: A Phase 1, Multicenter, Open-Label, Dose Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-881 in Patients with Advanced Solid Tumors, Including Gliomas, with an IDH1 and/or IDH2 Mutation **Protocol No.:** AG881-C-002	
Principal Investigator /Coordinating Investigator: Ingo Mellinghoff, MD, FACP, Department of Neurology Chair, Brain Tumor Service Chief Evnin Family Chair in Neuro-Oncology Memorial Sloan Kettering Cancer Center 1275 York Ave New York, NY 10065 Phone: (646) 888-2766 Email: mellingi@mskcc.org	
Number of study centers and countries: 10 sites in the United States	
Study period: Initiation date: 09 June 2015 (date of the first visit of the first patient) Completion date: 19 June 2024 (last subject last visit)	
Phase of development of the study: Phase 1	
Publication (reference): Mellinghoff IK, Penas-Prado M, Peters KB, et al. Vorasidenib, a dual inhibitor of mutant IDH1/2, in recurrent or progressive glioma; results of a first-in-human Phase I trial. *Clinical Cancer Res*. 2021;27(16):4491-4499. doi:10.1158/1078-0432.CCR-21-0611	
Background and rationale for the study: A summary of the background and rationale for the study is provided in the AG881-C-002 Interim CSR synopsis.	

Objectives and endpoints:

Objectives	Endpoints
Primary Objectives • To determine the MTD and/or the recommended PR2D of vorasidenib in subjects with advanced non-glioma solid tumors and in subjects with glioma. • To assess the safety and tolerability of treatment with vorasidenib administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle in subjects with advanced solid tumors, including gliomas.	Primary Endpoints • Incidence of DLTs[a] during the first cycle of treatment with vorasidenib. • AEs, SAEs, and AEs leading to discontinuation. The severity of AEs was assessed by the NCI-CTCAE, version 4.03. • Safety laboratory parameters, physical examination, vital signs, 12-lead ECGs, LVEF, and ECOG PS.
Secondary Objectives • To characterize the pharmacokinetics of vorasidenib in subjects with advanced solid tumors, including gliomas. • To evaluate the PK/PD relationship of vorasidenib and 2-HG inhibition in blood samples. • To characterize preliminary clinical activity associated with vorasidenib in subjects with advanced solid tumors, including gliomas.	Secondary Endpoints • Serial blood sampling at specified time points for determination of plasma concentration-time profiles and pharmacokinetic parameters of vorasidenib. • Blood sampling at specified time points for determination of 2-HG levels to characterize the pharmacodynamic effects of vorasidenib. • Investigator assessment of serial radiographic evaluations (CT or MRI) to determine response to treatment based on RECIST v1.1 for subjects without glioma or on modified RANO or RANO LGG for subjects with glioma. • Changes in tumor volume growth before and after treatment with vorasidenib in subjects with non-enhancing glioma using serial MRI examinations (FLAIR and/or T2 sequences), including pre-treatment scans (not including screening) when available.

Abbreviations: 2-HG=2-hydroxyglutarate; AE=adverse event; CT=computed tomography; CTCAE=Common Terminology for Adverse Events; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; FLAIR=fluid attenuated inversion recovery; LGG=low-grade glioma; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; NCI=National Cancer Institute; RANO=Response Assessment in Neuro-oncology; MTD=maximum tolerated dose; PK/PD=pharmacokinetic/pharmacodynamic; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended phase 2 dose ; SAE=serious adverse event.

a. A DLT was defined as any CTCAE Grade ≥3 event that occurred in Cycle 1 of treatment unless clearly related to the underlying disease or known complications of the underlying disease. All AEs that could not clearly be determined to be unrelated to vorasidenib were considered relevant to determining DLTs and were reviewed by the clinical study team. The clinical study team also reviewed any other emergent toxicities that were not explicitly defined by the DLT criteria, including events that may have occurred outside of Cycle 1, to determine if any warranted a DLT designation.

Study Design: A summary of the study design, screening period, treatment period and end of study/safety follow-up is provided in the AG881-C-002 Interim CSR synopsis.

Number of Subjects (Planned and Analyzed):

Planned: At least 21 subjects were expected to be treated in the non-glioma solid tumor dose escalation, and 18 subjects were expected to be treated in the glioma dose escalation.

Analyzed:

Glioma: a total of 52 subjects with glioma were enrolled and treated, of whom 22 had non-enhancing gliomas, and 30 had enhancing gliomas.

Non-glioma solid tumor: A total of 41 subjects with non-glioma solid tumor were enrolled and treated.

Diagnosis and Main Criteria for Inclusion/Exclusion: Diagnosis and main criteria for inclusion/exclusion are provided in the AG881-C-002 Interim CSR synopsis.

Investigational Medicinal Product/Test drug: A description of the IMP is provided in the AG881-C-002 Interim CSR synopsis.

Comparator: Not applicable

Duration of treatment: Duration of treatment is provided in the AG881-C-002 Interim CSR synopsis.

Statistical Methodology: A summary of the statistical methods is provided in the AG881-C-002 Interim CSR synopsis.

Summary of Results and Conclusions

Disposition and baseline characteristics:

Glioma: There were no changes to demographics or baseline characteristics in subjects with glioma since the interim data cutoff date of 17 October 2022, which was the basis of the AG881-C-002 Interim CSR. A description of demographic characteristics in subjects with glioma is provided in the AG881-C-002 Interim CSR synopsis.

At the time of database lock (DBL) for the Final CSR (07 October 2024), all 52 subjects with glioma had discontinued study treatment and the study. The most common reason for study treatment discontinuation was progressive disease (37 subjects [71.2%]). Six subjects discontinued study treatment but continued vorasidenib under single patient investigational new drug (sIND) applications.

Non-Glioma Solid Tumor: A total of 41 subjects with non-glioma solid tumor were enrolled and received at least 1 dose of vorasidenib across 6 dose cohorts (25 mg once daily [QD], 50 mg QD, 100 mg QD, 200 mg QD, 200 mg twice daily [BID], and 400 mg QD). The median age (range) was 57 (28, 89) years. There were more females (27 [65.9%]) in the study than males (14 [34.1%]) and 31 subjects (75.6%) reported race as White.

The most common solid tumor type at initial diagnosis was intrahepatic cholangiocarcinoma (22 subjects [53.7%]), followed by chondrosarcoma (9 subjects [22.0%]) and cholangiocarcinoma (1 subject [2.4%]). A total of 9 subjects (22.0%) had other tumor types. Most subjects with non-glioma solid tumor (27 [65.9%]) had an isocitrate dehydrogenase (IDH)1 mutation. The most common IDH1 mutation type based on local testing was R132C (19 subjects [46.3%]). An IDH2 mutation was reported in 14 subjects (34.1%).

Most subjects' (29 [70.7%]) tumors were American Joint Committee on Cancer (AJCC) stage IV at screening, according to the latest version of the AJCC classification. Baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores were 0 or 1 in most subjects with non-glioma solid tumor (11 subjects [26.8%] and 27 subjects [65.9%], respectively).

At the time of DBL for the Final CSR, all 41 subjects had discontinued study treatment and the study. The most common reason for study treatment discontinuation was progressive disease (28 subjects [68.3%]).

Extent of exposure:

Glioma: The median (range) treatment duration in subjects with glioma was 6.3 (0.2, 99.2) months overall. At 12 and 36 months, respectively, 19 (36.5%) and 12 subjects (23.1%) overall remained on treatment. As of the

database lock date for the final CSR, 6 subjects (11.5%) had been treated for ≥60 months, and the longest treatment duration overall was 99.2 months. For subjects with non-enhancing and enhancing gliomas, respectively, the median (range) treatment duration was 30.0 (1, 99.2) months and 3.3 (0.2, 97.2) months. Eleven of the 22 subjects (50.0%) with non-enhancing gliomas remained on treatment for at least 36 months, and 5 subjects (22.7%) remained on treatment for ≥60 months. In the enhancing glioma cohort, 4 of the 30 subjects (13.3%) remained on treatment ≥12 months and 1 subject (3.3%) remained on treatment for ≥60 months.

Non-Glioma Solid Tumor: The median (range) treatment duration in subjects with non-glioma solid tumor was 1.9 (0.2, 20.3) months, with 2 subjects (4.9%) on treatment for ≥18 months. As of the database lock date, no subjects were treated for ≥24 months.

Efficacy results:

Glioma: The secondary efficacy objective for subjects with glioma was explored by Investigator assessment of serial radiographic evaluations (MRI) to determine response to treatment based on modified Response Assessment in Neuro-oncology (RANO) or Response Assessment in Neuro-oncology for low-grade glioma (RANO LGG). Changes in tumor volume growth before and after treatment with vorasidenib were assessed in subjects with non-enhancing glioma using serial MRI examinations (fluid attenuated inversion recovery [FLAIR] and/or T2 sequences), including pre-treatment scans (not including screening) when available.

- Across all 52 subjects in the Full Analysis Set (FAS), the objective response rate (ORR) (95% confidence interval [CI]) was 11.5% (4.35%, 23.44%), including 3 (5.8%) partial responses (PRs) and 3 (5.8%) minor responses (mRs). A total of 31 subjects (59.6%) achieved a best overall response (BOR) of stable disease (SD).
  - Of the 22 subjects in the non-enhancing glioma cohort the ORR (95% CI) was 22.7% (7.82%, 45.37%), including 2 (9.1%) PRs and 3 (13.6%) mRs. Fifteen subjects (68.2%) achieved a BOR of SD.
  - Of the 30 subjects in the enhancing glioma cohort, the ORR (95% CI) was 3.3% (0.08%, 17.22%) with 1 subject (3.3%) achieving a PR. Sixteen subjects (53.3%) achieved a BOR of SD.
- In the non-enhancing cohort (N=22), 3 subjects (13.6%) had an mR (≥25% but <50% reduction in tumor size); 2 subjects achieved a PR (≥50% reduction in tumor size), and 15 subjects had a BOR of SD. Of the 15 subjects with SD, 12 (80.0%) demonstrated a reduction in tumor size not meeting the criteria for response; 7 of these subjects had a tumor size reduction of >10%.
- In the enhancing cohort (N=30), 1 subject (3.3%) achieved a PR. Of the 16 subjects with a BOR of SD, 5 (31.3%) showed a reduction in tumor size not meeting the criteria for response; 4 of these subjects had a tumor size reduction of >10%.
- The median (range) time to response (TTR) for 6 subjects (11.5%) overall with an objective response was 31.01 (9.5, 75.5) months. In the non-enhancing cohort, the median (range) TTR was 31 (9.5, 75.5) months (5 subjects), and in the enhancing cohort the TTR was 48.8 months (1 subject).
- In the non-enhancing cohort, 5 subjects (22.7%) had objective responses, with a duration of response (DOR) ranging from 7.4 to 68.1 months. One subject with mR and 2 subjects with PR remained on vorasidenib after study completion via transition to a sIND application.
- In the enhancing cohort 1 subject (3.3%) had an objective response with a DOR of 48.3 months and remained on vorasidenib after study completion via a sIND application.
- Among all subjects with glioma, the median (95% CI) progression-free survival (PFS) was 7.5 (3.7, 12.9) months with 75% of events reported. The median (95% CI) PFS for non-enhancing and enhancing gliomas was 36.8 (14.9, 60.2) months with 63.6% of events reported and 3.6 (1.9, 7.5) months with 83.3% of events reported, respectively.
- For non-enhancing gliomas, the estimated tumor growth rate (95% CI) by volume per 6 months on treatment was 3.4% (1.4%, 5.4%).

Non-Glioma Solid Tumor: The secondary efficacy objective for subjects with non-glioma solid tumor was explored by Investigator assessment of serial radiographic evaluations (computed tomography [CT] or MRI) to determine response to treatment based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

- The median (range) treatment duration for all 41 subjects with non-glioma solid tumor in the FAS was

1.9 (0.2, 20.3) months. As of the database lock date, no subjects were treated for ≥24 months.

- Across all 41 subjects with non-glioma solid tumor in the FAS, the ORR (95% CI) was 2.4% (0.06%, 12.86%).
- In subjects with non-glioma solid tumor (N=41) 1 subject (2.4%) achieved a PR (≥30% reduction in tumor size). Thirteen subjects (31.7%) had a BOR of SD. Of the subjects with SD, 4 demonstrated a reduction in tumor size not meeting the criteria for response; 2 of these subjects had a reduction of >10%.
- The TTR for 1 subject (2.4%) with non-glioma solid tumor who had an objective response was 5.6 months. The subject's DOR was 3.7 months.
- The median (95% CI) PFS for all subjects with non-glioma solid tumor was 1.9 (1.7, 3.5) months with 78.0% of events reported.

Pharmacokinetic/Pharmacodynamic Results: Detailed pharmacokinetic/pharmacodynamic (PK/PD) results and analyses are provided in a separate report.

Safety results:

Glioma: No new DLTs were reported since the interim data cutoff date. Differences between the interim data cutoff and DBL dates are summarized below. A full summary of safety results is provided in the AG881-C-002 interim CSR synopsis.

- Changes to the most commonly reported PTs (≥10% of subjects) since the interim data cutoff date included the following:
  - The preferred term (PT) "aphasia" recorded at the interim data cutoff date was corrected to "transient aphasia" for 1 subject in the final database. Thus, the total number of subjects with aphasia decreased from 6 subjects (11.5%) overall at the interim cutoff to 5 subjects (9.6%) at the DBL date.
  - The PT "vomiting" at the interim data cutoff date was corrected to "COVID-19" for 1 subject in the final database. Thus, the total number of subjects with vomiting decreased from 11 subjects (21.2%) overall to 10 subjects (19.2%) at the DBL date.
  - Cough: At the interim data cutoff date, cough had been reported in 2 subjects (10.0%) who received 100 mg QD vorasidenib for a total of 8 subjects (15.4%) overall. The PT "cough" was subsequently corrected to "COVID-19" for 1 subject in the database after the interim data cutoff date.
  - Hypocalcaemia: At the interim data cutoff date, hypocalcaemia had been reported in 1 subject (9.1%) who received 50 mg QD vorasidenib for a total of 5 subjects (9.6%) overall. One additional subject in the vorasidenib 50 mg cohort reported hypocalcaemia after the interim data cutoff date, bringing the total to 6 subjects (11.5%).
- For serum chemistry, a change in the incidence of subjects with a 2 or more-grade worsening from baseline was noted since the interim data cutoff date as follows:
  - For alanine aminotransferase (ALT), worsening from Grade 0 at baseline to Grade 2 postbaseline was reported in 1 additional subject (vorasidenib 200 mg QD). Thus, the number of subjects increased from 4 (7.7%) at the interim data cutoff to 5 (9.6%) at the DBL date. As a result of this, the incidence of subjects with an ALT result ≥3 × upper limit of normal (ULN) increased from 5 (22.7%) at the interim data cutoff date to 6 (27.3%) at DBL. The newly reported Grade 2 ALT result was not reported as an AESI in error; however, this subject had prior AESIs, so the overall incidence of subjects with AESIs did not change.

Non-Glioma Solid Tumor:

- All 41 subjects with non-glioma solid tumor in the Safety Analysis Set experienced at least 1 treatment-emergent adverse event (TEAE), with 26 subjects (63.4%) experiencing a treatment-related TEAE as determined by the Investigator.
- The most common TEAEs (occurring ≥20%) in all subjects included nausea and fatigue (19 subjects [46.3%] each), decreased appetite (16 subjects [39.0%]), constipation and vomiting (15 subjects [36.6%] each), dyspnea (14 subjects [34.1%]), aspartate aminotransferase (AST) increased (12 subjects [29.3%]), abdominal pain (10 subjects [24.4%]), and ALT increased (9 subjects [22.0%]).
- Nineteen subjects (46.3%) experienced a Grade ≥3 TEAE. The most common Grade ≥3 TEAEs included pleural effusion and blood alkaline phosphatase increased (3 subjects [7.3%] each) and ascites, blood bilirubin increased, pyrexia, and anemia (2 subjects [4.9%] each). Grade 4 TEAEs included hypercalcemia

and hyperuricemia (reported in a single subject [vorasidenib 25 mg QD]) and blood bilirubin increased (reported in a single subject [vorasidenib 100 mg QD]). Several Grade 4 TEAEs were reported in a subject who died due to a serious TEAE of intestinal perforation: abdominal pain, chills, large intestine perforation, septic shock, acidosis, hypotension, supraventricular tachycardia, oliguria, hypoxia, organ failure, and unresponsive to stimuli.

- Intestinal perforation was the only TEAE that led to death during the on-treatment period and was considered unrelated to vorasidenib.
- Eight subjects (19.5%) experienced a serious TEAE. All serious TEAEs were reported in 1 subject (2.4%) each, and none were related to the study treatment.
- Vorasidenib was permanently discontinued due to a TEAE in 1 subject; this was the subject who died due to the serious TEAE of intestinal perforation.
- Vorasidenib was interrupted in 10 subjects (24.4%). The most common TEAEs leading to dose interruptions included vomiting (3 subjects [7.3%]) and nausea, decreased appetite, dyspnea, and ALT increased (2 subjects [4.9%] each).
- The vorasidenib dose was reduced in 1 subject (2.4%) who received vorasidenib 200 mg BID due to TEAEs of ALT increased, AST increased, and blood bilirubin increased.
- Adverse events of special interest associated with elevated liver transaminases were reported in a total of 5 subjects (12.2%), and most were assessed by the Investigator as not related to vorasidenib. Grade 2 ALT increased was assessed as possibly and probably related to vorasidenib in 2 subjects.
- There were no clinically significant findings as per investigator assessment for chemistry results other than liver transaminase elevations. There were no clinically significant findings as per investigator assessment in postbaseline assessments for hematology or coagulation parameters.
- Alanine aminotransferase and AST results >10×ULN were reported only in the 100 mg QD group and were reported in a single subject.
- No subject met laboratory criteria for Hy's Law.
- No clinically significant results were observed for vital signs, physical examination assessments, electrocardiogram (ECG), left ventricular ejection fraction (LVEF), or ECOG PS.

Conclusions: In subjects with glioma, vorasidenib demonstrated a favorable safety profile at doses <100 mg QD. Dose-limiting toxicities of elevated liver transaminases were observed in subjects at doses of 100 mg and higher, therefore, doses of 100 mg and higher are not recommended for subjects with glioma. Based on the available safety, pharmacokinetic, and preliminary clinical activity data from the study, vorasidenib 50 mg QD was selected as the recommended Phase 2 dose in subjects with gliomas harboring an IDH1 or IDH2 mutation.

In subjects with non-glioma solid tumor, vorasidenib demonstrated a favorable safety profile, and no DLTs were observed at doses up to 400 mg QD. The maximum tolerated dose (MTD) was not reached per the Bayesian design. Given the preliminary clinical activity, safety, and PK/PD data observed in subjects with gliomas, further development in non-glioma solid tumor was discontinued by the Sponsor in order to focus on development in gliomas. Therefore, no dose of vorasidenib was selected for further study in non-glioma solid tumor.

Date of report: 12 May 2025