2. SYNOPSIS

Name of Sponsor: Institut de Recherches Internationales Servier (I.R.I.S.)	*(For National Authority Use only)*
Name of Finished Product: Voranigo / Tibsovo **Name of Active Ingredient:** S095032 (vorasidenib) / S095031 (ivosidenib)	

Title of Study: A Phase 1, Multicenter, Randomized, Controlled, Open-label, Perioperative Study of AG-120 and AG-881 in Subjects with Recurrent, Non-enhancing, IDH1 Mutant, Low-grade Glioma

Protocol No.: AG120-881-C-001

ClinicalTrials.gov Identifier: NCT03343197

Principal Investigator /Coordinating Investigator:

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Number of Study Centers and Countries:

A total of 7 study sites participated in this study, all of which were in the United States.

Studied Period:

Initiation Date: 20 March 2018

Completion Date: 28 March 2025

Phase of Development of the Study: Phase 1

Publication (Reference):

Mellinghoff IK, Lu M, Wen PY, et al. Vorasidenib and ivosidenib in IDH1-mutant low-grade glioma: a randomized, perioperative phase 1 trial. Nat Med. 2023;29(3):615-622. doi:10.1038/s41591-022-02141-2

Background and Rationale for the Study:

The present Phase 1 perioperative study (AG120-881-C-001) was conducted to evaluate the pharmacodynamic activity of ivosidenib (S095031, previously known as AG-120) and vorasidenib (S095032, previously known as AG-881) by measuring 2-hydroxyglutarate (2-HG) suppression in brain tissue and to evaluate the pharmacokinetics (PK) by measuring drug concentration in tumor and plasma following drug administration. This study was also designed to identify the minimally efficacious dose of each drug, for up to 2 dose levels tested, at which 2-HG suppression was observed.

Objectives and Endpoints:

Objectives	Endpoints
Primary Objective(s) • To determine 2-HG concentration in tumors resected following pre-surgical treatment with ivosidenib or vorasidenib compared to untreated control tumors in participants with recurrent non-enhancing Grade 2/3 LGG with an IDH1 R132H mutation for whom surgical resection was indicated	Primary Endpoint(s) • 2-HG concentration in surgically resected tumors
Secondary Objective(s) • To evaluate the safety profile of up to 2 selected dose levels of ivosidenib or vorasidenib • To evaluate changes in 2-HG concentration in plasma pre- and post-treatment with ivosidenib or vorasidenib compared to untreated controls • To evaluate the PK of ivosidenib or vorasidenib in tumor tissue and plasma • To evaluate the preliminary clinical activity of ivosidenib or vorasidenib monotherapy in the residual disease setting as assessed by modified RANO-LGG	Secondary Endpoint(s) • AEs, SAEs, and AEs leading to discontinuation. The severity of AEs assessed by the NCI CTCAE, version 4.03 • Safety laboratory parameters, physical examination findings, vital signs, 12-lead ECGs, evaluation of LVEF, and KPS • Change from baseline in concentration of 2-HG in plasma • Concentration of ivosidenib or vorasidenib in post-treatment tumor tissue; plasma concentration-time profiles and PK parameters of ivosidenib or vorasidenib • Investigator assessment of serial radiographic evaluations (MRI) to determine response to treatment based on modified RANO-LGG criteria

Study Design:

A description of the study design is provided in the AG120-881-C-001 Interim CSR synopsis.

Number of Participants (Planned and Analyzed):

A description of the planned number of participants is provided in the AG120-881-C-001 Interim CSR synopsis.

Analyzed: A total of 49 participants were enrolled into the study, including 4 replacement participants (2 in the vorasidenib 50 mg group and 2 in the ivosidenib 500 mg group). Twelve participants were randomized to receive vorasidenib 50 mg QD, 10 participants were randomized to receive vorasidenib 10 mg QD, 12 participants were randomized to receive ivosidenib 500 mg QD, and 10 participants were randomized to receive ivosidenib 250 mg BID. Five participants were randomized to the untreated control group.

Diagnosis and Main Criteria for Inclusion/Exclusion:

A description of the study Inclusion and Exclusion Criteria is provided in the AG120-881-C-001 Interim CSR synopsis.

Investigational Medicinal Product/Test Drug:

All study drug products were supplied by the Sponsor.

Doses administered were as follows:

- Ivosidenib 500 mg QD
- Ivosidenib 250 mg QD
- Vorasidenib 50 mg QD
- Vorasidenib 10 mg QD

Vorasidenib was supplied as 5 and 25 mg uncoated tablets (Formulation 1) or 10 mg and 40 mg film-coated tablets (Formulation 2).

The vorasidenib 50 mg QD population included participants treated with 1 film-coated AG-881 40 mg QD tablet (Formulation 2). The vorasidenib 10 mg QD population includes participants treated with 1 film-coated AG-881 10 mg QD tablet (Formulation 2).

Ivosidenib was supplied as 250 mg tablets for oral administration. Vorasidenib was supplied as 5 and 25 mg uncoated tablets (Formulation 1) or 10 mg and 40 mg film-coated tablets (Formulation 2). Ivosidenib was supplied as 250 mg tablets for oral administration.

Comparator: N/A

N/A

Duration of Treatment:

Prior to surgery, participants in the treatment groups received 28 days (+7 days) of ivosidenib or vorasidenib administered orally. Participants in the untreated control group did not receive any study treatment prior to surgery. Participants were instructed to make every effort to receive all 28 days (+7 days) of study drug unless surgery was performed earlier if clinically indicated.

Following surgery, participants who opted to receive post-surgery study drug received ivosidenib or vorasidenib administered orally on Days 1 to 28 of a 28-day cycle. Dosing was continuous, without planned rest periods. Participants received treatment until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

Statistical Methodology:

A description of the statistical methodology is provided in the AG120-881-C-001 Interim CSR synopsis.

Summary of Results and Conclusions

Baseline Characteristics

The Intent-to-Treat Analysis Set is the primary analysis set for demographics, disposition, prior therapy, and baseline characteristics. Overall, 24 participants received at least 1 dose of vorasidenib and 25 participants received at least 1 dose of ivosidenib, including 12 participants who received 50 mg QD vorasidenib, 10 participants who received 10 mg QD vorasidenib, 12 participants who received 500 mg QD ivosidenib, and 10 participants who received 250 mg BID ivosidenib, and 5 participants who were initially assigned to the untreated group in the pre-surgery period of whom 2 participants were re-randomized to receive vorasidenib 50 mg QD post-surgery and 3 participants were re-randomized to ivosidenib 500 mg QD post-surgery.

Eleven participants (45.8%) who received vorasidenib and 10 participants (40.0%) who received ivosidenib discontinued the study. The most frequent reasons for treatment discontinuation were disease progression (12 participants [50.0%] who received vorasidenib and 14 participants [56.0%] who received ivosidenib), adverse event (AE; 1 participant [4.2%] who received vorasidenib and 2 participants [8.0%] who received ivosidenib), and investigator decision (2 participants [8.3%] who received vorasidenib and 1 participant [4.0%] who received ivosidenib). Nine participants (37.5%) who received vorasidenib and 5 participants (20.0%) who received ivosidenib discontinued the study for reasons categorized as Other; these participants continued in the Patient Assistance Program. No participants remained on study at the time of data cutoff.

Most participants had a histological subtype of oligodendroglioma, including 8 participants (53.3%) who received 500 mg QD ivosidenib, 4 participants (40.0%) who received 250 mg BID ivosidenib, 8 participants (57.1%) who received 50 mg QD vorasidenib, and 5 participants (50.0%) who received 10 mg QD vorasidenib. The histological subtype was astrocytoma for 6 participants (40.0%) who received 500 mg QD ivosidenib, 5 participants (50.0%) who received 250 mg BID ivosidenib, 6 participants (42.9%) who received 50 mg QD vorasidenib, and 5 participants (50.0%) who received 10 mg QD vorasidenib. One participant (10.0%) who received 250 mg BID ivosidenib had anaplastic oligoastrocytoma, and 1 participant (6.7%) who received 500 mg QD had anaplastic oligodendroglioma.

Most participants had 1p 19q co-deletion, including 8 participants (53.3%) who received 500 mg QD ivosidenib, 5 participants (50.0%) who received 250 mg BID ivosidenib, 8 participants (57.1%) who received 50 mg QD vorasidenib, and 4 participants (40.0%) who received 10 mg QD vorasidenib.

All participants had at least 1 prior treatment regimen. Among participants who received ivosidenib, 4 participants (26.7%) reported 1 prior regimen and 5 participants (33.3%) reported ≥ 2 prior regimens in the 500 mg QD dose group, and 3 participants (30.0%) reported 1 prior regimen and 2 participants (20.0%) reported ≥ 2 prior regimens in the 250 mg BID dose group. Among participants who received vorasidenib, 5 participants (35.7%) reported 1 prior regimen and 1 participant (7.1%) reported ≥2 prior regimens in the 50 mg QD dose group, and 4 participants (40.0%) reported 1 prior regimen in the 10 mg QD dose group with 0 participants reporting ≥ 2 regimens in this dose group.

Extent of Exposure

Post-surgery, the median duration of treatment across all treatment groups was 20.24 months (range: 0.0 to 64.5) for participants who received ivosidenib and 48.43 months (range: 0.9 to 80.4) for participants who received vorasidenib. Among those who received ivosidenib, the duration of treatment post-surgery was ≥ 12 months for 64% of participants, ≥ 24 months for 48.0% of participants, and ≥ 36 months for 36.0% of participants. Among those who received vorasidenib, the duration of treatment post-surgery was ≥ 12 months for 75.0% of participants, ≥ 24 months for 70.8% of participants, and ≥ 36 months for 58.3% of participants.

Efficacy Results:

Based on a Bayesian hierarchical model, the posterior median (95% credible interval) tumor 2-HG concentrations were 9481.4 (4673.2, 19051.4) and 8848.7 (4011.3, 19339.0) in participants receiving 500 mg QD and 250 mg BID ivosidenib, respectively, and 7919.5 (3783.6, 16483.6) and 39094.3 (17782.4, 86545.5) in participants receiving 50 mg QD and 10 mg QD vorasidenib, respectively, compared to 107698.5 (42637.1, 245690.5) in untreated participants. Posterior median 2-HG suppression (95% credible interval) was 91.2% (72.0%, 97.0%) among participants receiving 500 mg QD ivosidenib, 91.7% (72.5%, 97.4%) among participants receiving 250 mg BID ivosidenib, 92.6% (76.1%, 97.6%) among participants receiving 50 mg QD vorasidenib, and 63.5% (22.2%, 88.4%) among participants receiving 10 mg QD vorasidenib. This corresponded to a posterior mean of difference between the treated and untreated groups in $\log_{10}$ tumor 2-HG concentrations (95% credible interval) of -1.05 (-1.53, -0.55) and -1.08 (-1.59, -0.56) in participants receiving 500 mg QD and 250 mg BID ivosidenib, respectively, and -1.13 (-1.62, -0.62) and -0.43 (-0.94, 0.09) in participants receiving 50 mg QD and 10 mg QD vorasidenib, respectively. The posterior mean (95% credible interval) of $\log_{10}$ tumor 2-HG concentration in the untreated group was 5.03 (4.63-5.39).

The probability that the mean $\log_{10}$ tumor 2-HG concentration for participants in the vorasidenib 50 mg QD and vorasidenib 10 mg QD treatment group was less than that of the untreated control group was 100% and 95%, respectively. The probability that the mean $\log_{10}$ tumor 2-HG concentration was less than that of the untreated control group was 100% for the ivosidenib 500 mg QD treatment group and 100% for the ivosidenib 250 mg BID treatment group. The probability that the mean $\log_{10}$ 2-HG concentration of the treated group was lower than that of the untreated controls by at least -0.7 was 92% in participants receiving 500 mg QD ivosidenib, 92% in participants receiving 250 mg BID ivosidenib, 95% in participants receiving 50 mg QD vorasidenib, and 15% in participants receiving 10 mg QD vorasidenib.

Twenty-two participants who received ivosidenib were included in the efficacy analysis set, including 14 participants who received 500 mg QD ivosidenib and 8 participants who received 250 mg BID ivosidenib. The ORR (CR+PR+mR) for participants who received ivosidenib was 31.8% (95% CI: 13.9%, 54.9%), including 5 participants with PR and 2 participants with mR.

Twenty-two participants who received vorasidenib were included in the EAS, including 14 participants who received 50 mg QD vorasidenib and 8 participants who received 10 mg QD vorasidenib. The ORR for participants who received vorasidenib was 45.5% (95% CI: 24.4%, 67.8%), including 4 participants with PR and 6 participants with mR.

Safety Results:

All participants in the safety analysis set had at least 1 TEAE, and 7 participants (28.0%) who received ivosidenib and 10 participants (41.7%) who received vorasidenib had a serious TEAE. Treatment-related TEAEs were reported in 18 participants (72.0%) who received ivosidenib and 16 participants (66.7%) who received vorasidenib. One participant (4.2%) who received 50 mg QD vorasidenib had a treatment-related serious TEAE.

No deaths occurred during the study.

The most common TEAEs included headache (ivosidenib: 44.0% participants; vorasidenib: 54.2% participants), fatigue (ivosidenib: 24.0% participants; vorasidenib: 50.0% participants), and nausea (ivosidenib: 24.0% participants; vorasidenib: 50.0% participants).

Treatment-related TEAEs were reported in 18 participants (72.0%) who received ivosidenib and 16 participants (66.7%) who received vorasidenib. Treatment-related TEAEs occurring in ≥ 10% of participants in either the overall ivosidenib or overall vorasidenib group included anemia (ivosidenib: 32.0%; vorasidenib: 16.7%), ALT increased (ivosidenib: 0%; vorasidenib: 29.2%), AST increased (ivosidenib: 12.0%; vorasidenib: 16.7%), fatigue (ivosidenib: 8.0%; vorasidenib: 25.0%), diarrhoea (ivosidenib: 16.0%; vorasidenib: 25.0%), headache (ivosidenib: 20.0%; vorasidenib: 8.3%), nausea (ivosidenib: 12.0%; vorasidenib: 12.5%), constipation (ivosidenib: 8.0%; vorasidenib: 12.5%), cough (ivosidenib: 16.0%; vorasidenib: 0%), and hypokalaemia (ivosidenib: 12.0%; vorasidenib: 0%).

At least one Grade ≥ 3 TEAE was reported in 7 participants (28.0%) who received ivosidenib and in 15 participants (62.5%) who received vorasidenib. Grade ≥ 3 TEAEs reported in ≥ 5% of participants in either the overall ivosidenib or overall vorasidenib group included ALT increased (ivosidenib: 0%; vorasidenib: 8.3%), hypophosphataemia (ivosidenib: 0%; vorasidenib: 8.3%), mental status changes (ivosidenib: 8.0%; vorasidenib: 0%), and hypertension (ivosidenib: 0%; vorasidenib: 8.3%).

Serious TEAEs were reported in 7 participants (28.0%) who received ivosidenib and 10 participants (41.7%) who received vorasidenib. Serious TEAEs reported in ≥ 5% of participants in either the overall ivosidenib or overall vorasidenib group included seizure (ivosidenib: 0%; vorasidenib: 8.3%) and mental status changes (ivosidenib: 8.0%; vorasidenib: 0%).

Among participants who received ivosidenib, breast cancer recurrent and hypoxia led to treatment discontinuation in 1 participant (6.7%) in the 500 mg QD treatment group. Events of ALT increased and AST increased led to treatment discontinuation in 1 participant (7.1%) in the 50 mg QD vorasidenib treatment group.

One participant in the 50 mg QD vorasidenib dose group had a dose interruption due to a TEAE pre-surgery. In the SAS, 5 participants (20.0%) who received ivosidenib 500 mg QD had a dose interruption due to an AE and 9 participants (37.5%) who received vorasidenib had a dose interruption due to an AE, including 5 participants (35.7%) in the 50 mg QD group and 4 participants (40.0%) in the 10 mg QD group.

No participants had an AESI of QT prolongation in either the ivosidenib or the vorasidenib treatment groups.

An AESI of elevated liver transaminases was reported in 3 participants (12.5%) who received 50 mg QD vorasidenib and in no participants who received ivosidenib.

Overall, ivosidenib and vorasidenib provide a manageable safety profile with few participants requiring dose reduction, interruption, and discontinuation. TEAEs associated with ivosidenib and vorasidenib were manageable with risk minimization measures in the study protocol.

Conclusion:

Overall, results of this study confirm brain penetrance of ivosidenib and vorasidenib and suppression of the oncometabolite 2 HG in resected tumor tissue following pre-surgical treatment with ivosidenib and vorasidenib. These data, along with a manageable safety profile and evidence of preliminary activity in participants with IDH mutant Grade 2/3 non-enhancing gliomas, demonstrate that ivosidenib and vorasidenib have a favorable benefit-risk profile and warrants further evaluation in participants with gliomas harboring an IDH1 or IDH2 mutation.

Date of the Report: 24 February 2026