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FDA Approval Summary: Vorasidenib for *IDH*-mutant Grade 2 Astrocytoma or Oligodendroglioma following surgery

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Abstract

On August 6, 2024, the U.S. Food and Drug Administration (FDA) granted traditional approval to vorasidenib (VORANIGO, Servier Pharmaceuticals, LLC) for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 or 2 (*IDH1* or *IDH2*) mutation following surgery including biopsy, sub-total resection, or gross total resection. The approval was based on data from a randomized, multicenter, double-blind trial of vorasidenib compared to placebo. The primary objective was to demonstrate the efficacy of vorasidenib based on radiographic progression-free survival (PFS) per blinded independent central review (BICR) according to the modified Response Assessment for Neuro-oncology for Low-Grade Gliomas (RANO-LGG) criteria. PFS was assessed in 331 patients, and the hazard ratio (HR) was 0.39 (95% CI: 0.27, 0.56; p-value <0.0001). The most common (≥15%) adverse reactions included fatigue, headache, COVID-19, musculoskeletal pain, diarrhea, nausea, and seizure. PFS was considered an appropriate endpoint for this disease considering the long natural history and the randomized design allowed for interpretation of the treatment effect in this rare malignancy. This was the first FDA approval of a targeted therapy for *IDH*-mutant, Grade 2 gliomas.

Introduction

Approximately 3,500 new cases of Grade 2, diffuse glioma (low-grade glioma [LGG]) occur annually in the United States.[1] Classification for gliomas has evolved over the past decade as the understanding of molecular features of these tumors has changed. According to

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World Health Organization (WHO) 2016 criteria, LGG classification is based on molecular features, *IDH* mutation status, and 1p19q status. Oligodendroglioma is differentiated from astrocytoma by the presence of 1p19q co-deletion. The age of diagnosis generally ranges from adolescence to late adulthood where the peak incidence ranges from 35 to 44 years of age. There is a slight male predominance, and tumors occur more often in White patients.[2] *IDH*-mutations are required for the diagnosis of grade 2 astrocytomas and oligodendrogliomas (CNS WHO 2021). Seventy to 80% of LGGs have an *IDH1* mutation and 3% to 5% have an *IDH2* mutation.[3]

There is a long natural history associated with this disease and patient population; reported median overall survival (OS) for patients with Grade 2 LGGs ranges from 10 to 12 years.[4,5] However, Grade 2 LGGs are considered incurable and can progress to higher grade tumors, which has been described as malignant transformation (MT), the process of progressing from a LGG to a higher grade glioma, which is associated with an aggressive clinical course and shortened survival.[6] The reported incidence of MT ranges from 23% to 72% with a median time range of 2.7 to 5.4 years[7]. In addition to the risk of tumor transformation into a higher grade, patients often have sequelae of their disease and treatment which include seizures, cognitive dysfunction, weakness, and language impairment and coordination impairment.

There are no approved therapies specifically for patients with *IDH*-mutant LGG; however, conventional therapy for low-risk disease in WHO Grade 2 LGGs consists of surgery followed by observation or a clinical trial. For patients with high-risk disease, surgery is followed by a clinical trial or systemic cytotoxic therapy with the most commonly used regimens being adjuvant procarbazine/lomustine/vincristine (PCV) and temozolomide (TMZ).[8,9,10,11]

Vorasidenib is an oral inhibitor of *IDH1* and *IDH2* mutant enzymes and is the first approved targeted therapy specifically for *IDH*-mutant LGG. In this summary, FDA's review of the marketing application that led to the approval of vorasidenib for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible *IDH1* or *IDH2* mutation following surgery including biopsy, sub-total resection, or gross total resection will be discussed.

Regulatory History

The development of vorasidenib for treatment of patients with *IDH*-mutant glioma was initiated on April 30, 2015, and on September 18, 2018, vorasidenib was granted orphan drug status for the treatment of patients with *IDH*-mutant glioma.[12] Fast Track and Breakthrough Therapy Designations were granted on February 24, 2023 and August 7, 2023, respectively, for the treatment of patients with residual or recurrent Grade 2 diffuse glioma with an *IDH1* or *IDH2* mutation who have undergone surgery as their only treatment. The new drug application (NDA) for the new molecular entity (NME) vorasidenib, was submitted on December 20, 2023. The NDA voluntarily included use of the Assessment Aid to facilitate FDA review, received Priority Review Designation, and was reviewed under FDA's Project Orbis which included collaboration with Australia, Brazil, Canada, Israel, and Switzerland.[13,14,15,16,17]

Mechanism of Action

Vorasidenib is a small molecule inhibitor that targets IDH1 and IDH2 enzymes. In vitro, vorasidenib inhibited the *IDH1* wild type and mutant variants, including R132H, and the *IDH2* wild type and mutant variants. In cell-based and in vivo tumor models expressing IDH1 or IDH2 mutated proteins, vorasidenib decreased production of 2-hydroxyglutarate (2-HG) and partially restored cellular differentiation[18].

Clinical Pharmacology

The approved recommended dosage of vorasidenib is 40 mg once daily in the indicated patient population for adults and pediatric patients (12 and <17 years) weighing 40 kg or greater while the recommended dosage is 20 mg once daily for pediatric patients weighing less than 40 kg. Vorasidenib can be administered with or without food as the magnitude of increase in vorasidenib exposure when administered with high-fat or low-fat meals is not expected to have a negative impact on vorasidenib safety based on the observed safety profiles in the dose range of 10 to 300 mg QD.

The approved recommended body weight (BW) tiered dosage (40 mg QD for BW of 40 kg or greater; 20 mg QD for BW less than 40 kg) for adolescent patients is supported by the predicted vorasidenib systemic exposures in adolescents falling in the range of values observed in adults at the recommended dosages.

The concomitant administration of strong and moderate CYP1A2 inhibitors should be avoided as exposures may increase by 2.5 – 7.2-fold. The concomitant administration of moderate CYP1A2 inducers or tobacco smoking should also be avoided as the exposure of vorasidenib may be reduced by 40% and may lead to reduced therapeutic effect. Concomitant use of vorasidenib with CYP3A substrates with a narrow therapeutic index should be avoided as vorasidenib may reduce the exposure of CYP3A4 substrates by 80% and reduce the efficacy. The pharmacokinetics of vorasidenib has not been studied in patients with severe hepatic impairment.

Clinical Trials

The approval of vorasidenib was based on the results of INDIGO, a randomized (1:1), multicenter, double-blind, placebo-controlled trial of vorasidenib in patients with Grade 2, *IDH1* or *IDH2* mutant astrocytoma or oligodendroglioma who had prior surgery including biopsy, sub-total resection, or gross total resection more than 1 year but less than 5 years from the time of enrollment. Patients were treated with vorasidenib 40 mg orally once daily or placebo. Although most patients on the INDIGO study had baseline tumor diameter ≥ 2 cm (83% on the vorasidenib arm) and only 51% of patients had gross total resection, their treating physicians did not consider to need immediate radiation or chemotherapy. Therefore, a placebo was considered acceptable given the option for observation in routine clinical care of patients receiving low-risk disease treatment. Crossover to the investigational arm was permitted after centrally confirmed radiographic disease progression. Randomization was 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 major efficacy outcome measure was PFS per blinded independent central

review (BICR) according to the modified Response Assessment for Neuro-oncology for Low-Grade Gliomas [RANO-LGG]. Additional efficacy outcome measures included time to next intervention (TTNI), objective response rate (ORR), duration of response (DOR), tumor growth rate, and overall survival (OS). The investigators' analysis of the INDIGO trial has been publicly presented and published.[19] FDA's independent analyses of data submitted by the Applicant are presented below.

Demographics, Disease Characteristics and Prior Treatment: The primary efficacy analysis population included 331 patients with a confirmed diagnosis of Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria as detected by central laboratory testing (prospectively determined by the Life Technologies Corporation Oncomine Dx Target Test) and 1p19q status was determined by local testing (e.g., fluorescence in situ hybridization, comparative genomic hybridization array, sequencing) using an accredited laboratory. Patients were IDH inhibitor naïve, had at least 1 prior disease related surgical procedure, had not received prior radiation or chemotherapy, and had at least one measurable target lesion; in the ITT population, the median age was 40 years (range: 16 to 71); 57% were male; 78% were White, 4% were Asian, 1% were Black or African American and 16% had race not reported; 78% were not Hispanic or Latino, refer to Table 1 for population characteristics by treatment arm. In the ITT population, there was similar enrollment of patients with astrocytoma (48%) and oligodendroglioma (52%), Table 2.

Most patients had IDH1 mutations (95%) and the majority of IDH1 mutations were R132H (86%). The other alterations were reported as follows: R132C (4.5%), R132G (1.8%), R132L (1.8%), and R132S (1.2%). IDH2 mutations included R172K (4%) and R172G (0.6%). Most patients had one prior surgery (79%) and 21% had ≥2 prior surgeries, refer to Table 2 for by treatment group information. In the vorasidenib arm, 14% of patients had a biopsy, 48% had sub-total resection and 51% had gross-total resection, compared to 12%, 41%, and 58% in the placebo arm, respectively. Among the 80 study sites, patients were largely enrolled in the US and Western Europe (53% and 29%, respectively). Although there is limited knowledge regarding the specific incidence of *IDH*-mutation by sex, race, and ethnicity, there appears to be a slight White and male predominance in patients with *IDH*-mutant LGG[2] and the demographic and baseline disease characteristics of the primary efficacy population are generally representative of US patients.[20]

Efficacy results: The primary endpoint of PFS as assessed by BICR per modified RANO-LGG demonstrated a statistically significant improvement with a hazard ratio (HR) for PFS of 0.39 (95% CI: 0.27, 0.56; p-value <0.0001), favoring the vorasidenib arm (Table 3). PFS results were consistent across prespecified subgroups, including histology (astrocytoma or oligodendroglioma) and type of surgery (biopsy, subtotal, or gross total resection). The median PFS estimate in the vorasidenib arm may not be robust, given that a plateau was observed at 50% in the KM curve for the vorasidenib arm (Figure 1). Furthermore, 69% of patients were in follow-up without an event.

The key secondary endpoint of TTNI also demonstrated a statistically significant and clinically meaningful improvement in patients treated with vorasidenib, with a HR of 0.26 (95% CI: 0.15, 0.43; p-value of < 0.0001). Median TTNI was not reached for the treatment

arm and was 17.8 months for patients on the placebo arm. Forty-eight percent of patients in the placebo arm had a TTNI event of subsequent anticancer therapy, which was more often compared to 17% of patients in the vorasidenib arm. The frequency and type of next intervention, included in the TTNI calculation for the 19 patients who received vorasidenib followed by a subsequent therapy, are as follows: surgery (n=8, 42.1%), radiotherapy (n=7, 36.8%), and antineoplastic therapy (n=4, 21.1%). Consistent with the indolent nature of this disease, no deaths had occurred on either arm at the time of NDA submission.

Safety Results: The safety review evaluated primary safety data from a pooled safety population consisting of 244 patients with *IDH*-mutant glioma who received the recommended dose of vorasidenib in the INDIGO, AG881-C-002, and AG120-881-001 studies. A focused safety evaluation was performed in 167 patients who received single agent vorasidenib in the INDIGO trial. There were similar characteristics and rates of common and serious adverse events (AEs) between the pooled and focused safety populations.

There were no Grade 5 (fatal) treatment emergent adverse events (TEAEs). The rate of serious adverse events (SAEs) was similar between arms of the INDIGO trial with slightly more patients experiencing an SAE in the vorasidenib arm compared to the placebo arm (7% vs. 4.9%). Permanent discontinuation of vorasidenib was required in 3.3% of patients; of discontinuation events occurring in ≥ 2% of patients, permanent discontinuations were due to increased alanine aminotransferase (ALT). Dosage interruptions were required in 27% of patients; of interruption events occurring in ≥ 2% of patients, dose interruptions were due to increased ALT, COVID-19, and increased aspartate aminotransferase (AST). Dose reductions were required in 9% of patients; of reduction events occurring in ≥ 2% of patients, dose reductions were due to increased ALT. The most common adverse reactions (≥15%) observed in the INDIGO trial are summarized in Table 4, and notably there were few Grade 3 or higher adverse events noted.

There were no significant safety concerns identified during application review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Warnings and Precautions include risks of hepatotoxicity and fetal harm when administered to a pregnant woman (based on preclinical embryo-fetal development studies).

Regulatory Insights

FDA's approval of vorasidenib for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible *IDH1* or *IDH2* mutation following surgery including biopsy, sub-total resection, or gross total resection, represents the first approval of a dual *IDH* inhibitor where evidence of efficacy for both *IDH1*- and *IDH2*-mutant populations is included in the U.S. prescribing information. Key considerations in the review of the application included the clinical benefit of delaying progression for this population, limiting the indicated population to Grade 2 IDH-mutant astrocytoma or oligodendroglioma, and the inclusion of adolescent patients.

Magnitude of PFS and Supportive Efficacy Results: The magnitude of PFS benefit in INDIGO (HR 0.39), was large, clinically meaningful, and statistically significant. PFS was considered an acceptable endpoint for this disease with a long natural history and for which a trial with an OS endpoint would be infeasible. The delay in progression was felt to have additional clinical relevance given the disease can transform to a more aggressive phenotype, and progression increases the risk of known sequelae of the natural history of the disease and its treatment including seizures, weakness, language impairment, and delayed neurocognitive complications. The improvement in TTNI (HR 0.26) observed in INDIGO further supports the PFS benefit by demonstration of delay in subsequent anticancer therapies including systemic cytotoxic chemotherapy, surgery, and radiation therapies, given the manageable side effect profile of vorasidenib with very few patients reporting Grade 3 or higher adverse events (Table 4). Exploratory patient reported outcome (PRO) results also supported acceptable tolerability of vorasidenib. The INDIGO trial is an example of a successful randomized study in a rare disease with a long natural history.

Limiting the indicated population to patients with Grade 2 LGG: The Applicant initially proposed an expanded indication encompassing patients with "predominantly non-enhancing glioma," which could include patients with higher grade tumors who were not enrolled in the INDIGO trial.[21] FDA considered data from the vorasidenib arm of INDIGO, other trials in the vorasidenib and ivosidenib development programs, and expanded access data to assess the adequacy of the evidence to support the proposed indication. FDA reviewed a small population of patients with Grade 3 *IDH*-mutant glioma who were treated with an IDH inhibitor across the vorasidenib development program, however, the majority of these patients received treatment prior to vorasidenib (e.g. radiation and systemic therapy), consistent with standard of care for patients with higher grade glioma. Given that vorasidenib was not formally studied in a randomized controlled trial of patients with higher grade tumors for whom observation is not a standard approach to therapy, FDA determined that there was insufficient evidence to broaden the indication.

Inclusion of adolescent patients in the indicated population: The inclusion of patients 12 years of age and older in the indicated population is primarily based on extrapolation of the effectiveness of vorasidenib observed in INDIGO to adolescents. Although the eligibility criteria for the INDIGO trial allowed for enrollment of patients 12 years of age and older, only one patient under 18 years of age enrolled; this patient was randomized to the placebo arm. Inclusion of adolescent patients in the indication was supported by FDA's assessment of the similarity of disease across age ranges, available weight-based modeling that applies weight allometry to extrapolate PK in the adolescent population which has a significant overlap in body weight with adults, supportive non-clinical investigations, and clinical experience through the expanded access program. Oligodendrogliomas and astrocytomas that harbor *IDH1* or *IDH2* mutations in the pediatric population present similarly to those in adults and follow a similar clinicopathological path including indolent growth, and the targeted mechanism of vorasidenib is expected to act similarly in IDH-mutant tumors irrespective of patient age.[22,23,24] Consistent with FDA guidance, extrapolation may be considered for cases in which the disease has a similar

course and pathophysiologic basis in adult and pediatric populations and where similar pharmacologic activity of the drug is expected in adults and children.[25]

Although there is limited adolescent safety experience, given the similarity between adolescent and adult Grade 2 IDH-mutant astrocytomas and oligodendrogliomas in the context of the substantial magnitude of clinical benefit observed with vorasidenib in the INDIGO trial, FDA considered it appropriate to include adolescents 12 years of age and older in the indicated population. However, since the dataset for adolescent safety is limited, FDA issued a post-marketing requirement (PMR) to further characterize risk in a larger pediatric population, particularly since vorasidenib is intended for long-term use. Although this approval represents successful use of extrapolation of adult data to adolescents, the inclusion of a larger number of adolescent patients on INDIGO would have been the strongly preferred approach to a risk:benefit assessment in this population. Sponsors should solicit advice from key pediatric opinion leaders and involve pediatric oncology trial consortia as early as possible in any development program that is intended to support labeling for pediatric and adolescent patients.

Conclusion

Vorasidenib is the first approval of a targeted therapy specifically for patients with Grade 2, *IDH*-mutant glioma and the first IDH inhibitor that includes an assessment of *IDH1* and *IDH2* mutations. Traditional approval was granted based on a statistically significant and clinically meaningful magnitude of improvement in PFS supported by an extended time to next intervention in the context of an acceptable safety profile in this rare and life-threating disease (Table 5). A post-marketing commitment (PMC) was issued to complete survival follow-up of patients in the INDIGO trial to further characterize its clinical benefit. Two safety PMRs were issued: one to characterize hepatotoxicity and a second to characterize baseline risk factors and safety outcomes on effects on growth and development in pediatric patients following exposure to vorasidenib.

The vorasidenib approval provides an important treatment option for patients with Grade 2 *IDH1* or *IDH2* mutant astrocytoma or oligodendroglioma who had prior surgery including biopsy, sub-total resection, or gross total resection. The approval addresses a significant unmet medical need and provides a successful example of the feasibility of a randomized controlled trial using PFS in a rare disease population.

References

1. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro Oncol. 2017;19(suppl_5):v1–v88. [PubMed: 29117289]
2. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med. 2015;372(26):2481–2498. [PubMed: 26061751]
3. De Carli E, Wang X, Puget S. *IDH*1 and *IDH*2 mutations in gliomas. N Engl J Med. 2009 May 21;360(21):2248; author reply 2249. doi: 10.1056/NEJMc090593.
4. Yeo KK, Alexandrescu S, Cotter JA, Vogelzang J, Bhave V, Li MM, Ji J, Benhamida JK, Rosenblum MK, Bale TA, Bouvier N, Kaneva K, Rosenberg T, Lim-Fat MJ, Ghosh H, Martinez M, Aguilera D,

Smith A, Goldman S, Diamond EL, Gavrilovic I, MacDonald TJ, Wood MD, Nazemi KJ, Truong A, Cluster A, Ligon KL, Cole K, Bi WL, Margol AS, Karajannis MA, Wright KD. Multi-institutional study of the frequency, genomic landscape, and outcome of *IDH*-mutant glioma in pediatrics. Neuro Oncol. 2023 Jan 5;25(1):199–210. doi: 10.1093/neuonc/noac132. [PubMed: 35604410]

5. Tork CA, Atkinson C. Oligodendroglioma. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Accessed September 25, 2024.
6. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803–820. [PubMed: 27157931]
7. Murphy ES, Leyrer CM, Parsons M, Suh JH, Chao ST, Yu JS, Kotecha R, Jia X, Peereboom DM, Prayson RA, Stevens GHJ, Barnett GH, Vogelbaum MA, Ahluwalia MS. Risk Factors for Malignant Transformation of Low-Grade Glioma. Int J Radiat Oncol Biol Phys. 2018 Mar 15;100(4):965–971. doi: 10.1016/j.ijrobp.2017.12.258. Epub 2017 Dec 21. [PubMed: 29485076]
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Disorders V.1.2023. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed [July 8, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org.
9. Quinn JA, Reardon DA, Friedman AH, Rich JN, Sampson JH, Provenzale JM, McLendon RE, Gururangan S, Bigner DD, Herndon JE 2nd, Avgeropoulos N, Finlay J, Tourt-Uhlig S, Affronti ML, Evans B, Stafford-Fox V, Zaknoen S, Friedman HS. Phase II trial of temozolomide in patients with progressive low-grade glioma. J Clin Oncol. 2003 Feb 15;21(4):646–51. doi: 10.1200/JCO.2003.01.009. [PubMed: 12586801]
10. Tosoni A, Franceschi E, Ermani M, Bertorelle R, Bonaldi L, Blatt V, Brandes AA. Temozolomide three weeks on and one week off as first line therapy for patients with recurrent or progressive low grade gliomas. J Neurooncol. 2008 Sep;89(2):179–85. doi: 10.1007/s11060-008-9600-y. Epub 2008 Apr 23. [PubMed: 18431544]
11. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet. 2005;366(9490):985–990. [PubMed: 16168780]
12. U.S. Food and Drug Administration. Orphan Drug Designation. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products.
13. U.S. Food and Drug Administration. New Drug Application. https://www.fda.gov/drugs/types-applications/new-drug-application-nda
14. U.S. Food and Drug Administration. New Molecular Entity. https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products
15. U.S. Food and Drug Administration. Assessment aid. Available from: https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid
16. Food and Drug Administration. Priority Review. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review
17. U.S. Food and Drug Administration. Project Orbis. https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis
18. U.S. Food and Drug Administration. Drugs@FDA [database on the internet]. Vorasidenib USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218784s000lbl.pdf
19. Mellinghoff Ingo K. et al. , INDIGO: A global, randomized, double-blinded, phase 3 study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation. JCO 41, LBA1-LBA1(2023). DOI:10.1200/JCO.2023.41.17_suppl.LBA1
20. U.S. Food and Drug Administration. Drugs@FDA [database on the internet]. Vorasidenib Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/218784Orig1s000TOC.cfm
21. Mellinghoff IK, van den Bent MJ, Blumenthal DT, Touat M, Peters KB, Clarke J, Mendez J, Yust-Katz S, Welsh L, Mason WP, Ducray F, Umemura Y, Nabors B, Holdhoff M, Hottinger AF, Arakawa Y, Sepulveda JM, Wick W, Soffietti R, Perry JR, Giglio P, de la Fuente M, Maher EA,

Schoenfeld S, Zhao D, Pandya SS, Steelman L, Hassan I, Wen PY, Cloughesy TF; INDIGO Trial Investigators. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. N Engl J Med. 2023 Aug 17;389(7):589–601. doi: 10.1056/NEJMoa2304194. Epub 2023 Jun 4. [PubMed: 37272516]

22. Packer RJ, Pfister S, Bouffet E, et al. Pediatric low-grade gliomas: implications of the biologic era. Neuro Oncol. 2017;19(6):750–761. [PubMed: 27683733]
23. Ryall S, Tabori U, Hawkins C. A comprehensive review of paediatric low-grade diffuse glioma: pathology, molecular genetics and treatment. Brain Tumor Pathol. 2017;34(2):51–61. [PubMed: 28342104]
24. Sturm D, Pfister SM, Jones DTW. Pediatric gliomas: current concepts on diagnosis, biology, and clinical management. J Clin Oncol. 2017;35(21):2370–2377. [PubMed: 28640698]
25. U.S. Food and Drug Administration. Change in Pediatric Extrapolation of Efficacy from Adults. https://www.fda.gov/science-research/fda-stem-outreach-education-and-engagement/change-pediatric-extrapolation-efficacy-adults#:~:text=In%201994%20the%20FDA%20introduced,a%20more%20evidence%2Dbased%20approach.

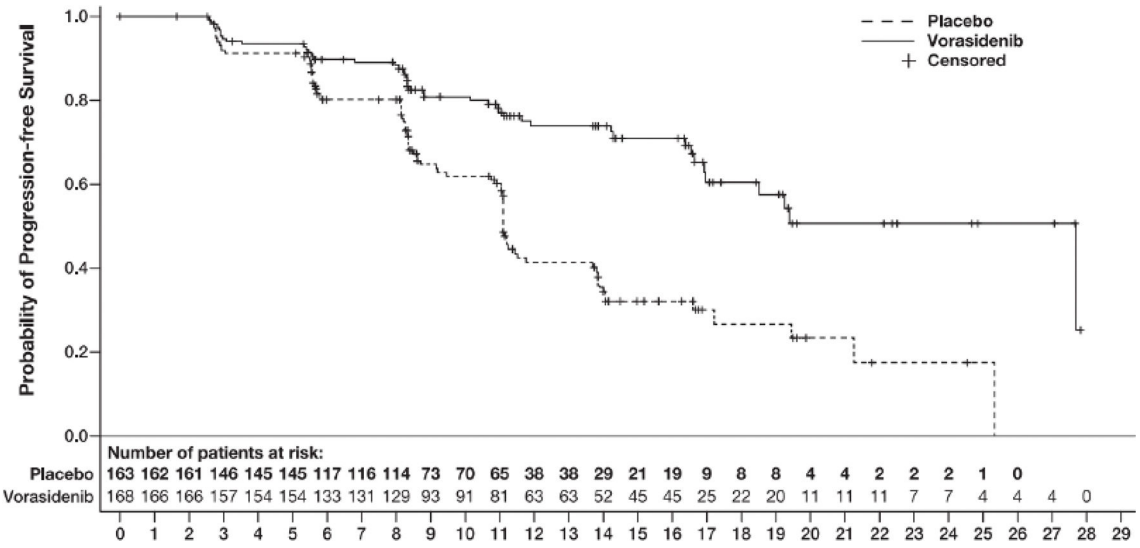

Figure 1. Kaplan-Meier Curve for Progression-free Survival per BIRC for the INDIGO Trial
Source: U.S. Food and Drug Administration. USPI vorasidenib.[18]

Table 1:

Demographics and Baseline Characteristics

	Placebo (N=163) n (%)	Vorasidenib (N=168) n (%)
Age (years)		
Median	39	40.5
Min, max	16, 65	21, 71
Sex, n (%)		
Male	86 (53)	101 (60)
Female	77 (47)	67 (40)
Race, n (%)		
American Indian or Alaska Native	0	1 (0.6)
Asian	8 (4.9)	5 (3.0)
Black or African American	1 (0.6)	2 (1.2)
Native Hawaiian or other Pacific Islander	0	0
White	132 (81)	125 (74)
Other	1 (0.6)	2 (1.2)
Not reported	21 (13)	33 (20)
Ethnicity, n (%)		
Hispanic or Latino	9 (6)	9 (5)
Not Hispanic or Latino	135 (83)	122 (73)
Not Reported	19 (12)	37 (22)

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation and Approval packages, vorasidenib.[20]

Table 2:

Pathology and Disease Characteristics

	Placebo (N=163) n (%)	Vorasidenib (N=168) n (%)
Histological subtype, n (%)		
Oligodendroglioma	84 (52)	88 (52)
Astrocytoma	79 (48)	80 (48)
Chromosome 1p19q co-deletion status		
Co-deleted	84 (52)	88 (52)
Not co-deleted	79 (48)	80 (48)
CDKN2A homozygous deletion	93 (57.1)	109 (64.9)
Present	2 (1.2)	0
Absent	91 (56)	109 (65)
Tumor size at baseline (cm)		
Longest diameter of ≥2 cm	137 (84)	139 (83)
Longest diameter of <2 cm	26 (16)	29 (17)
IDH1 positive	152 (93.3)	163 (97.0)
R132C	7 (4.3)	8 (4.8)
R132G	1 (0.6)	5 (3.0)
R132H	138 (85)	146 (87)
R132L	4 (2.5)	2 (1.2)
R132S	2 (1.2)	2 (1.2)
IDH2 positive	11 (7)	5 (3.0)
R172G	0	2 (1.2)
R172K	10 (6)	3 (1.8)
R172M	0	0
R172S	0	0
R172W	1 (0.6)	0

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation and Approval packages, vorasidenib.[20]

Table 3:

Efficacy Results Based on Independent Review of the INDIGO Study

Efficacy Parameter	**VORANIGO 40 mg daily (n=168)**	**Placebo (n=163)**
Progression-Free Survival (PFS)		
Number of Events, n (%) Progressive disease Death	47 (28) 0	88 (54) 0
Hazard ratio (95% CI) [a]	0.39 (0.27, 0.56)	
p-value [b]	<0.0001	

CI = Confidence Interval

[a] Stratified Cox proportional hazard model, stratified by 1p19q status and baseline tumor size.

[b] Based on one-sided stratified log-rank test compared to the pre-specified α of 0.000359 (one-sided).

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation and Approval packages, vorasidenib.[20]

Table 4:

Adverse Reactions (≥5%) in Patients with Grade 2 IDH1/2 Mutant Glioma Who Received Vorasidenib Compared with Placebo in the INDIGO Trial

	VORANIGO 40 mg daily (n=167)		Placebo (n=163)	
Adverse Reaction[a]	**All Grades (%)**	**Grades 3 or 4 (%)**	**All Grades (%)**	**Grades 3 or 4 (%)**
Nervous System Disorders				
Headache[b]	28	0	29	0.6
Dizziness[c]	16	0	18	0
Seizure[d]	16	4.2	15	3.7
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[e]	26	0	25	1.8
Gastrointestinal Disorders				
Nausea	22	0	23	0
Diarrhea[f]	25	0.6	17	0.6
Vomiting	7	0	10	0
Decreased appetite	9	0	3.7	0
Constipation	13	0	12	0
Abdominal Pain[g]	13	0	12	0
Infections And Infestations				
COVID-19	33	0	29	0
General Disorders				
Fatigue[h]	37	0.6	36	1.2

[a] Adverse reactions are based on NCI CTCAE v5.0.

[b] Grouped term includes sinus headache, migraine, migraine with aura, postictal headache, ophthalmic migraine, and tension headache.

[c] Grouped term includes vertigo.

[d] Grouped term includes partial seizures, generalized tonic-clonic seizure, epilepsy, clonic convulsion, and simple partial seizures.

[e] Grouped term includes arthralgia, back pain, non-cardiac chest pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, arthritis, and musculoskeletal stiffness.

[f] Grouped term includes feces soft and frequent bowel movements.

[g] Grouped term includes abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and epigastric discomfort.

[h] Grouped term includes asthenia.

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation and Approval packages, vorasidenib.[20]

Note: Some events (headache, dizziness, nausea, and vomiting) were excluded from the product labeling per FDA labeling guidelines, because they occurred more commonly in the placebo arm.

Table 5:

FDA Benefit-Risk Analysis

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 3,500 new cases of Grade 2 low-grade glioma [LGG]) occur annually in the United States.[2] • *IDH*-mutation frequency in Grade 2 gliomas ranges from 70% to 80% for *IDH1* and 3% to 5% for *IDH2*.[4] • The clinicopathologic characteristics of patients with Grade 2 *IDH*-mutant glioma include a peak incidence range from 35 to 44 years of age with a slight White male predominance.[3] • Reported median OS is 10 to12 years. • LGGs can undergo malignant transformation into high-grade gliomas adopting an aggressive clinical course and shortened survival.[7]	*IDH1* and *IDH2* mutated Grade 2 astrocytoma and oligodendroglioma are serious and life-threatening diseases that can transform into high grade tumors with poor survival.
Current Treatment Options	• There are no approved therapies specifically for patients with *IDH*-mutant LGG. • For WHO Grade 2 LGG conventional therapy consists of the following: • For patients with low-risk disease: surgery followed by observation or a clinical trial.[9] • For patients with high-risk disease: surgery followed by clinical trial or systemic therapy is preferred. With systemic therapy, reported ORRs range from 30% to 69% with adjuvant PCV or TMZ.[10,11,12] • For recurrent disease, treatment options include multimodal treatment including radiation therapy; off-label use of targeted therapy for *IDH*-mutated tumors is an option.	There is an unmet medical need for patients with *IDH*-mutant LGGs. There are no approved therapies specifically for patients with *IDH*-mutant LGG; observation following maximal surgical resection is considered a reasonable approach for low-risk patients to delay more toxic treatment options. High-risk patients are typically treated with systemic chemotherapy (e.g., the PCV regimen or TMZ) following surgery, associated with myelosuppression and neurotoxicity. Patients with recurrent disease are often treated with radiation therapy which is associated with substantial short- and long-term morbidity.
Benefit	• The primary efficacy data supporting this NDA is derived from the INDIGO trial, a randomized, multicenter, double-blind, placebo-controlled study of vorasidenib in patients with Grade 2, *IDH1* or *IDH2* mutant astrocytoma or oligodendroglioma who have had prior surgery including biopsy, sub-total resection, or gross total resection. • Among the 168 patients randomized to receive vorasidenib on the treatment arm of the INDIGO trial, there was a 16-month improvement in the median PFS reported as 27.7 months (95% CI: 17, NE) vs 11.1 months (95% CI: 11, 13.7) for the placebo arm. The HR for PFS was 0.39 (95% CI: 0.27, 0.56; p-value <0.0001) and there was a statistically significant improvement in TTNI for patients receiving vorasidenib vs placebo with a HR of 0.26 (95% CI: 0.15, 0.43; p-value< 0.0001).	The submitted evidence meets the statutory evidentiary standard for traditional approval. The magnitude of PFS improvement observed with vorasidenib is clinically meaningful for patients with *IDH*-mutant Grade 2 astrocytoma and oligodendroglioma. A PMC was issued to assess survival follow-up of patients in the INDIGO trial.
Risk and Risk Management	• The pooled safety population included 244 patients with glioma who received at least 1 dose of vorasidenib at the recommended dose on the INDIGO, AG881-C-002, and AG120-881-001 studies. • The warnings and precautions in the product label for vorasidenib include hepatotoxicity and embryo-fetal toxicity. • In the pooled safety population, n=244, serious adverse reactions occurred in 9% of patients receiving the recommended dose of vorasidenib. • The most common (≥ 15%) adverse reactions were fatigue (33%), headache (28%), COVID-19 (28%), musculoskeletal pain (24%), diarrhea (21%), nausea (20%), seizure (16%), and dizziness (14%). • The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased ALT (9%), increased AST (4.8%), increased GGT (2.2%), and decreased neutrophils (2.2%).	Although vorasidenib can cause serious adverse reactions, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Three PMRs were issued to address safety in adolescents and adults under FDAAA. Two PMRs were issued to assess carcinogenicity in mice and rats and one PMR was issued to assess the safety of vorasidenib in patients with severe hepatic impairment. The clinical review team determined that it is in the best interest of U.S. patients to approve vorasidenib before a companion diagnostic assay was available. Since the review of an application for an in vitro companion diagnostic device could not be completed in time for contemporaneous approval with this NDA, the approved labeling states that there is no FDA-approved test for selecting patients for treatment with vorasidenib. A companion diagnostic test to detect *IDH*-mutations for identifying patients who may benefit from vorasidenib has been approved as of the time of this publication. Review of the analytical and clinical validation results from clinical trial data

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		to support labeling of the companion diagnostic was ongoing at the time of this publication.

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation and Approval packages, vorasidenib.[20]