For patients with Grade 2 m*IDH1/2* astrocytoma or oligodendroglioma

INDIGO long-term follow-up analysis for VORANIGO: PFS, ORR, and seizure rate

Primary analysis: progression-free survival (major efficacy outcome)
61% reduced risk of disease progression or death vs placebo
(HR = 0.39; 95% CI, 0.27-0.56; *P*<0.0001)[1]

Median follow-up: 14.2 months[2]

Primary analysis
September 2022

Median follow-up: 20.1 months[2]

Extended analysis
March 2023

Median follow-up: 41.6 months[2,a]

Long-term follow-up analysis[b]
January 2025

44.1 months mPFS
with VORANIGO
(95% CI, 27.7-NE)
vs 11.4 months with placebo
(95% CI, 11.1-14.0)[2]

The long-term follow-up analysis for PFS was not controlled for multiplicity.

[a]Median follow-up is for VORANIGO arm only.[2]

[b]The long-term follow-up analysis includes an additional 28 months of data beyond the primary analysis data cutoff date of September 6, 2022, to January 17, 2025. The trial was unblinded on March 7, 2023.[2]

CI, confidence interval; HR, hazard ratio; m*IDH*, mutant isocitrate dehydrogenase; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; PFS, progression-free survival.

View data from the long-term follow-up inside

INDICATION

VORANIGO (40 mg tablets) is indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation, as detected by an FDA-approved test, following surgery including biopsy, sub-total resection, or gross total resection.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hepatotoxicity: VORANIGO can cause hepatic transaminase elevations, which can lead to hepatic failure, hepatic necrosis, and autoimmune hepatitis. Monitor liver laboratory tests (AST, ALT, GGT, total bilirubin, and alkaline phosphatase) prior to the start of VORANIGO, every 2 weeks during the first 2 months of treatment, then monthly for the first 2 years of treatment, and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue VORANIGO based on severity.

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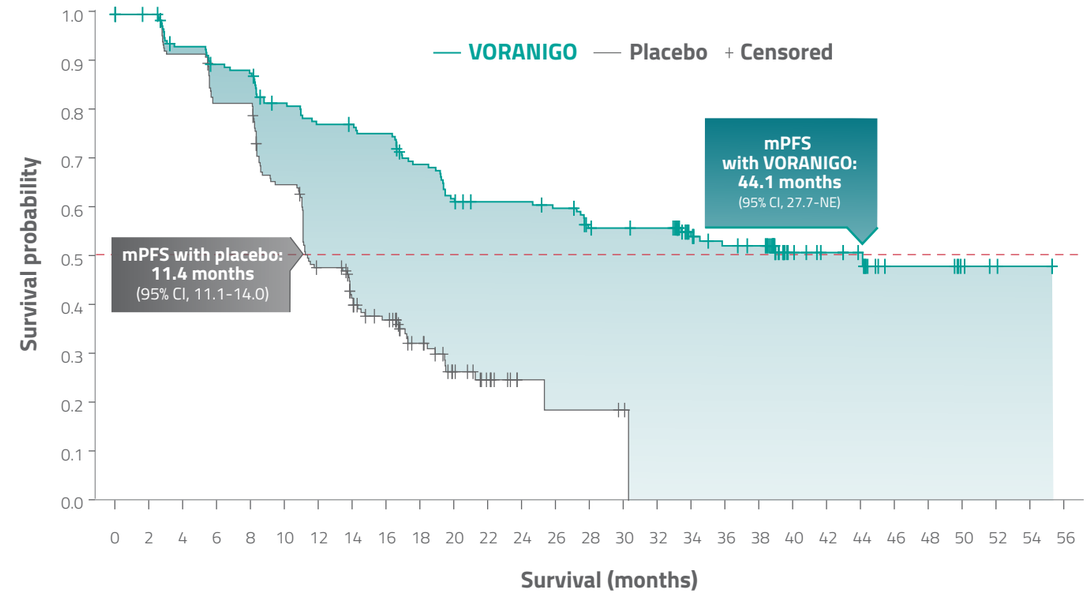
Major efficacy outcome: Progression-free survival[a,b]

VORANIGO significantly extended PFS, giving patients with Grade 2 m*IDH* glioma more time without disease progression vs placebo[1]

- **Primary analysis (14.2 months median follow-up): 61% reduced risk of disease progression or death vs placebo** (HR = 0.39; 95% CI, 0.27-0.56; *P*<0.0001)[1,2]
- **Long-term follow-up analysis (41.6 months median follow-up[c]): 44.1 months mPFS with VORANIGO** (95% CI, 27.7-NE) vs 11.4 months with placebo (95% CI, 11.1-14.0)[2]

Kaplan-Meier Curve for PFS per BIRC in the INDIGO trial: long-term follow-up analysis[2]



Number of patients at risk:

VORANIGO	168	166	154	147	144	131	124	123	120	108	97	93	93	90	81	80	79	60	54	52	25	21	18	9	9	5	3	2	0
Placebo	163	161	146	129	129	100	72	58	47	31	19	12	4	3	3	2	0												

The long-term follow-up analysis for PFS was not controlled for multiplicity.

BIRC, blinded independent review committee.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS (cont'd)

Embryo-Fetal Toxicity: Based on findings from animal studies, VORANIGO can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with VORANIGO and for 3 months after the last dose, since VORANIGO can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with VORANIGO and for 3 months after the last dose.

PFS in the INDIGO long-term follow-up analysis

PFS in patients with Grade 2 m*IDH* glioma[2,3]

	VORANIGO (N = 168)	Placebo (N = 163)
Events[d], n (%)	76 (45.2)	109 (66.9)
mPFS, months (95% CI)	44.1 (27.7-NE)	11.4 (11.1-14.0)
Median follow-up, months	41.6	20.2

PFS rates[2]

	VORANIGO (N = 168)	Placebo (N = 163)	PFS rate difference
12-month PFS rate, %	77.4	47.9	29.5
18-month PFS rate, %	69.2	32.4	36.8
24-month PFS rate, %	61.5	24.9	36.6
36-month PFS rate, %	52.4	NE	-

[a]VORANIGO was studied in the INDIGO trial—a phase 3, randomized (1:1), multicenter, double-blind, placebo-controlled trial for patients with Grade 2 m*IDH1/2* astrocytoma or oligodendroglioma (N = 331). Patients were aged ≥12 years, had prior surgery for glioma, presented with measurable, nonenhancing disease, and had not received prior anticancer treatment, including chemotherapy or radiotherapy. Crossover from placebo to VORANIGO was permitted after documented radiographic disease progression. Patients were randomized to receive VORANIGO 40 mg orally once daily or placebo orally once daily until radiographic disease progression or unacceptable toxicity.[1,4]

[b]The major efficacy outcome was PFS, evaluated by a BIRC per RANO-LGG criteria. PFS is defined as the time from randomization to the date of the first documented disease progression or death due to any cause. The RANO criteria for LGGs define progressive disease as either a radiographic disease response (a ≥25% increase in the sum of the products of perpendicular diameters of T2-weighted or T2-weighted FLAIR hyperintense nonenhancing lesions), or the presence of a new lesion as a newly measurable or increased enhancement.[1,5]

[c]Median follow-up is for VORANIGO arm only.[2]

[d]Number of events includes progressive disease and death.[1]

FLAIR, fluid-attenuated inversion recovery; RANO-LGG, Response Assessment in Neuro-Oncology for Low Grade Glioma.

IMPORTANT SAFETY INFORMATION (cont'd)
ADVERSE REACTIONS

The most common (≥15%) adverse reactions included fatigue, headache, COVID-19, musculoskeletal pain, diarrhea, nausea, and seizure. Grade 3 or 4 (≥2%) laboratory abnormalities were ALT increased, AST increased, GGT increased, and neutrophils decreased.

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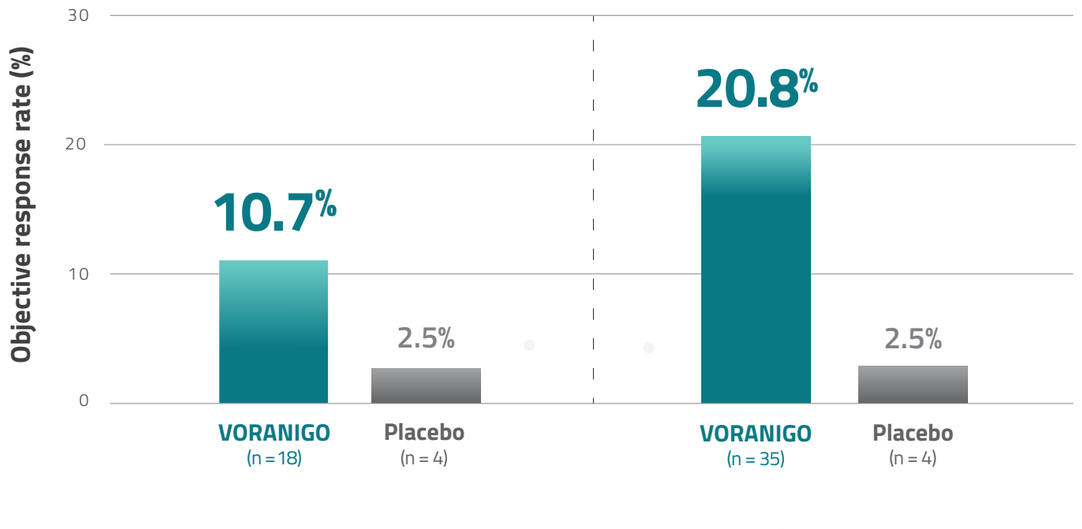
Secondary outcome: Objective response rate[a]

- **Primary analysis:** ORR with VORANIGO was 10.7% vs 2.5% with placebo[6]
- **Long-term follow-up analysis:** ORR with VORANIGO was 20.8% vs 2.5% with placebo[2]

ORR per BIRC in the INDIGO trial: primary and long-term follow-up analyses[2,6]



	Primary analysis		Long-term follow-up analysis	
	VORANIGO (N = 168)	**Placebo (N = 163)**	**VORANIGO (N = 168)**	**Placebo (N = 163)**
CR, n (%)[2,6]	0 (0)	0 (0)	0 (0)	0 (0)
PR, n (%)[2,6]	2 (1.2)	0 (0)	6 (3.6)	0 (0)
MR, n (%)[2,6]	16 (9.5)	4 (2.5)	29 (17.3)	4 (2.5)
Median follow-up, months[2-4]	14.0	14.3	41.6	20.2

A rigorous statistical conclusion cannot be made and the results should be interpreted with caution.

[a] Objective response rate is defined as the proportion of subjects with a best overall response being complete response (CR), partial response (PR), or minor response (MR) as assessed by the BIRC per modified RANO-LGG criteria. CR: disappearance of all lesions; PR: ≥50% decrease from baseline in the SPD of all measurable nonenhancing lesions; MR: ≥25% to <50% decrease from baseline in the SPD of all measurable nonenhancing lesions.[5]

SPD, sum of products of perpendicular diameters.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

Avoid concomitant use of VORANIGO with strong and moderate CYP1A2 inhibitors. Avoid concomitant use with moderate CYP1A2 inducers and smoking tobacco. Avoid concomitant use with CYP3A substrates, where a minimal concentration change can reduce efficacy. If concomitant use of hormonal contraception cannot be avoided, use nonhormonal contraception methods.

Exploratory outcome: Seizure activity[b,c]

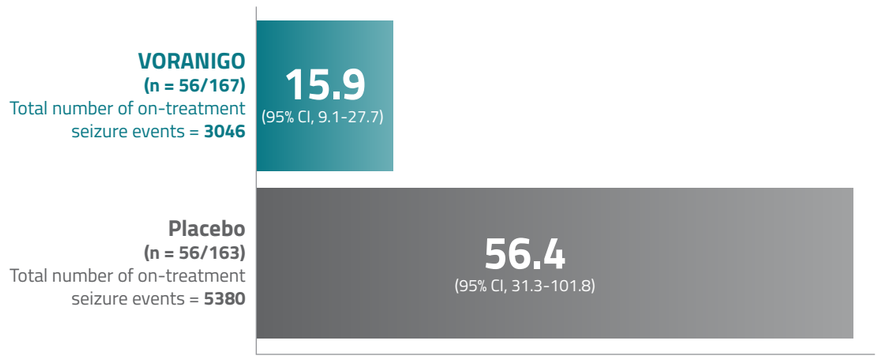
In the INDIGO trial, investigators reported seizures as an adverse event for all grades in 16% of patients treated with VORANIGO and 15% of patients treated with placebo[1]

Seizure AEs were assessed and reported in the Prescribing Information if qualified as an AE.

Data based on patient self-reported diary that captured the number and severity of seizures during each cycle[3]

- Only patients with controlled seizures were included in the INDIGO trial[3,d]
- Antiseizure medication was prescribed at the investigator's discretion[3]

Subgroup analysis in patients who reported ≥1 seizure while on treatment: long-term follow-up analysis[1,2]



The seizure rate for VORANIGO was **72% LOWER** compared to placebo[e]

A rigorous statistical conclusion cannot be made because seizure activity was an exploratory outcome, and the results should be interpreted with caution. This outcome was not controlled for multiplicity.

[b] Grouped term includes partial seizures, generalized tonic-clonic seizure, epilepsy, clonic convulsion, and simple partial seizures.[1]

[c] On-treatment seizure activity was calculated using a negative binomial regression model, adjusted for number of baseline seizures and stratification factors.[3]

[d] Uncontrolled seizures were defined as persistent seizures interfering with daily life and unresponsive to three antiepileptic drug regimens, including at least 1 combination regimen.[3]

[e] Ratio of rates for VORANIGO vs placebo was 0.28 (95% CI, 0.14-0.55).[2]

AE, adverse event.

IMPORTANT SAFETY INFORMATION (cont'd)

LACTATION

Advise women not to breastfeed during VORANIGO treatment and for 2 months after the last dose.

IMPAIRED FERTILITY

VORANIGO may impair fertility of females and males of reproductive potential.

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For patients with Grade 2 m*IDH1/2* astrocytoma or oligodendroglioma

Discover additional VORANIGO long-term follow-up data from the INDIGO trial

Progression-free survival (major efficacy outcome)

Primary analysis:

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(HR = 0.39; 95% CI, 0.27-0.56; *P*<0.0001)[1]

Long-term follow-up analysis:

44.1 months mPFS with VORANIGO

(95% CI, 27.7-NE) vs 11.4 months with placebo (95% CI, 11.1-14.0)[2]

The long-term follow-up analysis for PFS was not controlled for multiplicity.

Safety profile:

- **The most common (≥15%) ARs in patients treated with VORANIGO were fatigue (37%), COVID-19 (33%), musculoskeletal pain (26%), diarrhea (25%), and seizure (16%)[1]**
- **Grade 3 or 4 (≥2%) laboratory abnormalities were ALT increased (10%), AST increased (4.8%), GGT increased (3%), and neutrophils decreased (2.4%)[1]**
- **Permanent discontinuation due to ARs occurred in 3.6% of patients treated with VORANIGO[1]**

With nearly 3x the length of follow-up, no new safety signals were observed with VORANIGO vs the primary analysis[2,4]

ALT, alanine aminotransferase; AR, adverse reaction; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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References: 1. Voranigo. Package insert. Servier Pharmaceuticals LLC; 2025. **2.** Data on file. Servier Pharmaceuticals LLC. **3.** Cloughesy TF, van den Bent MJ, Touat M, et al. Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2025;26(12):1665-1675. doi:10.1016/s1470-2045(25)00472-3 **4.** 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(7):589-601. doi:10.1056/nejmoa2304194 **5.** Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. Protocol. *N Engl J Med.* 2023;389(7):589-601. doi:10.1056/nejmoa2304194 **6.** 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(7):589-601. Supplementary appendix. doi:10.1056/nejmoa2304194

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