Health Technology Briefing
December 2023

Vorasidenib for treating residual or recurrent grade 2 glioma

Company/Developer	Servier Laboratories Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28716	NICE ID: Not available	UKPS ID: 665090

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Vorasidenib is in clinical development for the treatment of residual or recurrent grade 2 glioma. Glioma is a type of brain tumour that begins in glial cells (the cells that surround and support nerve cells). There are three main types of gliomas: astrocytoma, oligodendroglioma, and glioblastoma. These are categorised by the isocitrate dehydrogenase (IDH) gene mutation status. Patients with astrocytoma and oligodendroglioma often have mutations in the IDH gene. The IDH gene produces the IDH enzyme, but mutations lead to the production of an abnormal IDH enzyme, which produces a chemical, 2-hydroxyglutarate, that causes cells to become cancerous. General symptoms include headache, anorexia, nausea, vomiting, seizures, drowsiness, personality changes, and cognitive slowing. More focal symptoms could include difficulties with hearing, speech, ambulation, dexterity, visual difficulties, and mood disturbances. Surgery is recommended for initial treatment, if possible, followed by either the active monitoring or radiotherapy/chemotherapy. However, options for further treatment for gliomas that recur locally after initial treatment are limited and palliative.

Vorasidenib is a brain-penetrant inhibitor which is administered via oral film-coated tablets. It is expected to block the activity of the abnormal IDH enzyme, reduce the production of 2-hydroxyglutarate and prevent the formation of cancer cells. If licensed, vorasidenib would offer a novel treatment option for patients with grade 2 glioma.

Proposed Indication

Treatment of residual or recurrent grade 2 glioma with an IDH1 R132 mutation or IDH2 R172 mutation, in patients aged 12 years and older, who have had one prior surgery.[1]

Technology

Description

Vorasidenib (AG-881) is a potent, oral, brain-penetrant dual inhibitor of both mutant IDH1 and mutant IDH2 enzymes.[2] Patients with glioma often have mutations in a gene producing the isocitrate dehydrogenase (IDH) enzyme. These mutations lead to the production of an abnormal IDH enzyme, which produces a chemical, 2-hydroxyglutarate (2-HG), that causes cells to become cancerous. Vorasidenib is expected to block the activity of the abnormal IDH enzyme, reduce the production of 2-hydroxyglutarate and prevent the formation of cancer cells.[3]

Vorasidenib is in clinical development for the treatment of residual or recurrent grade 2 glioma with an IDH1 or IDH2 mutation. In the phase III clinical trial (INDIGO; NCT04164901) vorasidenib is administered daily as 40mg oral film-coated tablets.[1]

Key Innovation

Vorasidenib is a first-in-class dual mutant IDH1/2 inhibitor with increased brain penetration.[2] Therapeutic progress for low-grade glioma has been slow-moving for decades, and so the development of vorasidenib presents an opportunity to shift the treatment paradigm for patients with IDH mutant low-grade glioma by potentially delivering the first targeted therapy.[4] In the UK, about 30% of patients receive only supportive care with steroids, with or without anticonvulsants. However, options for further treatment for gliomas that recur locally after initial treatment are limited and palliative. For a patient whose tumour recurs or progresses post-surgery/radiotherapy, the chemotherapy options are limited as available treatments have little efficacy. Current UK practice is to give first line chemotherapy to less than one third of patients whose tumour recurs after initial treatment, or about 15% of all diagnosed cases of brain tumour. This represents about 500 to 600 new cases per year.[5]

Vorasidenib has shown promising clinical activity in early clinical trials and was reported to reduce 2-HG levels by >90% in mutant IDH gliomas in humans.[2] If licensed, vorasidenib would offer a novel treatment option for patients with grade 2 glioma.

Regulatory & Development Status

Vorasidenib does not currently have Marketing Authorisation in the EU/UK for any indication.

Vorasidenib has the following regulatory designations/awards:[3,4]

- An orphan drug designation in the EU in 2023 for the treatment of glioma
- An FDA fast track designation in the USA in 2023 for the treatment of glioma

Vorasidenib is not currently in any other phase II or III trials for the treatment of other indications.[6]

Patient Group

Disease Area and Clinical Need

Gliomas are tumours that arise from glial or precursor cells within the central nervous system (CNS). The 2021 World Health Organization (WHO) classification recognises four general groups of gliomas, one of which is adult-type diffuse gliomas. These diffuse gliomas are the most common primary malignant brain tumours in adults.[4] Gliomas are graded according to their likely rate of growth, from grade 1 (slowest growing) to grade 4 (fastest growing).[7] Grade 2 tumour, also called low-grade glioma, are defined as being infiltrative gliomas — the tumour cells penetrate into the surrounding normal brain, making surgical cure more difficult. Most patients with grade II glioma (oligodendrogliomas, astrocytomas, mixed oligoastrocytomas) are young people who often present with seizures.[8] Astrocytomas are glial cell tumours developed from connective tissue cells called astrocytes , and oligodendrogliomas form from oligodendrocytes, which are the supportive tissue cells of the brain and are usually found in the cerebrum.[9] The pathogenesis and prognosis of these tumours are tightly linked to mutations (or lack thereof) in the metabolic enzyme IDH, and molecular testing is required for proper diagnosis.[4] IDH mutant means you have changes (mutations) in the IDH gene, and IDH wildtype means you do not have changes in the IDH gene.[10] Non-enhancing glioma means when the abnormal tissue of a tumour on a magnetic resonance image (MRI) or computed tomography (CT) scan does not enhance with contrast and is not oedema.[11] As of 2021, adult-type diffuse gliomas are sub-divided into only three categories:[4,12]

- Astrocytoma, IDH-mutant (CNS WHO grades 2-4)
- Oligodendroglioma IDH-mutant, 1p19q-codeleted (CNS WHO grades 2-3)
- Glioblastoma IDH-wildtype (CNS WHO grade 4)

People with malignant glioma can suffer from a range of symptoms and impairments. Some symptoms may be general, and others may be specific to the area of brain where the tumour is located. General symptoms include headache, anorexia, nausea, vomiting, seizures, drowsiness, personality changes, and cognitive slowing. More focal symptoms could include difficulties with hearing, speech, ambulation, dexterity, visual difficulties, and mood disturbances. These symptoms can have a profound effect on the quality of life of the patient as well as their ability to work and to care for themselves. At least 70% of malignant gliomas recur locally after initial treatment (recurrent), usually with very disabling neurological deficit and poor and rapidly deteriorating quality of life.[5]

Although brain tumours account for only 1.5% of all primary cancers and 2% of cancer deaths, they result in 7% of life-years lost before the age of 70. About 55% of primary brain cancers occur in males. Approximately 29% of adult patients survive one year after diagnosis and 13% survive 5 years. Malignant glioma is the most common form of primary brain tumour. The incidence in England and Wales is 4 per 100,000 population. There are about 3,500 new cases in the UK each year. They represent 50% to 60% of all primary brain tumours, and about 0.8% of all malignant neoplasms in adults in England and Wales.[5] Astrocytomas account for nearly half of all primary brain tumours and 2-4% are oligodendrogliomas.[9] In England 2022-23, there were 21,491 finished consultant episodes (FCE) and 16,383 admissions for malignant neoplasm of the brain (ICD-10 code C71). This resulted in 81,336 FCE bed days and 8,037 day cases. 2,505 diagnoses for this indication were in children aged 10 – 17 years old.[13]

Recommended Treatment Options

After initial treatment via surgery for low-grade gliomas, NICE recommends radiotherapy followed by up to 6 cycles of PCV chemotherapy (procarbazine, CCNU [lomustine] and vincristine) for people who have a 1p/19q codeleted, IDH-mutated low-grade glioma (oligodendroglioma) or have a 1p/19q non-codeleted, IDH-mutated low-grade glioma (astrocytoma), and are aged around 40 or over, or have residual tumour on postoperative MRI. Active monitoring, also known as 'watch and wait' is considered for people aged around 40 or under with an IDH-mutated low-grade glioma and no residual tumour on postoperative MRI.[14]

Clinical Trial Information

Trial	**INDIGO;** NCT04164901, **EudraCT** 2019-002481-13; 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 **Phase III** – active, not recruiting **Location(s)**: 6 EU countries, UK, USA, Canada, and other countries **Primary completion date**: September 2022
Trial Design	Randomised, quadruple masked, parallel assignment
Population	N=331 (actual); Have grade 2 oligodendroglioma or astrocytoma; have had at least 1 prior surgery for glioma; have confirmed IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status disease; 12 years and older
Intervention(s)	Vorasidenib 40mg oral film-coated tablets administered daily
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Progression-Free Survival (PFS) [time frame: up to approximately 30 months] See trial record for full list of other outcomes.
Results (efficacy)	In patients with grade 2 recurrent or residual IDH-mutant gliomas, vorasidenib significantly improved progression-free survival and delayed the time to the next intervention.[15] The interim analysis, which was prespecified in the design of the INDIGO trial, demonstrated a statistically significant and clinically meaningful improvement in both PFS and time to next intervention in patients randomised to vorasidenib monotherapy compared to patients randomised to placebo.[4]
Results (safety)	Adverse events of grade 3 or higher occurred in 22.8% of the patients who received vorasidenib and in 13.5% of those who received placebo. An increased alanine aminotransferase level of grade 3 or higher occurred in 9.6% of the patients who received vorasidenib and in no patients who received placebo.[15]

Estimated Cost

The cost of vorasidenib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23). March 2016.
- NICE guideline. Suspected neurological conditions: recognition and referral (NG127). Updated October 2023.
- NICE quality standard. Brain tumours (primary) and brain metastases in over 16s (QS203). December 2021.
- NICE guideline. Brain tumours (primary) and brain metastases in over 16s (NG99). January 2021.

- NICE quality standard. Suspected neurological conditions: recognition and referral (QS198). January 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract. For cancer: brain/central nervous system (adult). B13/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- European Association of Neuro-Oncology (EANO). EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. December 2020.[16]
- SIOPE Brain tumour group. SIOP-E-BTG and GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low Grade Glioma. May 2019.[17]
- Spanish Society of Medical Oncology (SEOM). SEOM clinical guideline of diagnosis and management of low-grade glioma. November 2017.[18]

Additional Information

References

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