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Newcastle University

Health Technology Briefing
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Alpelisib for treating PIK3CA-related overgrowth spectrum

Company/Developer	Novartis Pharmaceuticals UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30732	NICE ID: 10680	UKPS ID: 664545

Licensing and Market Availability Plans

Currently in phase II clinical trials

Summary

Alpelisib is in development for the treatment of the rare disease PIK3CA-related overgrowth spectrum (PROS). PROS is a group of genetic conditions where parts of the body become abnormally overgrown and can affect anywhere from the limbs to the brain, resulting in a wide range of symptoms which can include: pain, fatigue, or seizures depending on the affected areas. PIK3CA is a gene that affects the growth and movement of cells and is mutated (genetically altered) to be overactive in PROS. PROS usually occurs early in development and sometimes stops after childhood, but cases have high variability. Currently, there are no treatments that address that cause of the disease, and patients only receive supportive care dependent on symptoms.

Alpelisib targets the PI3K pathway, stopping the overactivation of this pathway, resulting in cells multiplying normally. This is expected to reduce the abnormal growths seen in patients and prevent new ones occurring. Alpelisib is administered once daily, orally. If licensed alpelisib will be the first treatment option available for patients aged 2 years and older with PROS.

Proposed Indication

Treatment of adult and paediatric patients with PIK3CA-related overgrowth spectrum (PROS).[1]

Technology

Description

Alpelisib (Piqray) is a novel therapy that selectively inhibits the PI3K pathway which is important in many cell activities such as: growth, proliferation, movement of cells; transport of materials within cells; and cell survival.[2] Inhibition of the PI3K pathway by alpelisib is expected to restore normal multiplication of the cells, reducing overgrowths and improving symptoms of disease.[1,3]

Alpelisib is currently in development for the treatment of PROS. In the phase II clinical trial (NCT04589650), alpelisib will be delivered via oral administration once daily at a dose of 50mg-125mg (age dependent dosing), to patients with PROS aged 2 years and older.[1]

Key Innovation

Currently there are no medicinal products approved for the treatment of PROS and patients rely on supportive care.[4] Alpelisib is the first potential treatment to specifically address the underlying mechanism of PROS pathophysiology conditions by targeting the PI3K pathway. Initial results from trial EPIK-P1 (NCT04285723) show that 38% of patients achieved ≥20% reduction in growth lesion volume and no patients experienced disease progression or death during the 24-week trial period. Patients who received alpelisib also experienced a reduction in pain and fatigue, showing improvements to quality of life.[5] If licensed, alpelisib will offer a new treatment option for patients with PROS who currently have no effective therapies available.

Regulatory & Development Status

Alpelisib currently has Marketing Authorisation in the EU/UK for:[6]

- Treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced, or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-based therapy (in combination with fulvestrant)

Alpelisib has the following regulatory designations/ awards:[3,5]

- An orphan drug in the EU in March 2021 for the treatment of PIK3CA-related PROS
- A breakthrough therapy designation by the US FDA for PIK3CA-related PROS in November 2019

Alpelisib is also in phase III/ II trials for:[7]

- Ovarian cancer
- Breast cancer
- Endometrial cancer
- PIK3CA mutated solid tumours
- Colorectal cancer
- Head and neck cancer
- Oropharyngeal cancer
- Lung cancer

Patient Group

Disease Area and Clinical Need

PROS disorders are a group of genetic disorders that are driven by somatic, gain-of-function mutations in the PIK3CA gene that result in hyperactivation of the phosphatidylinositol-3-kinase (PI3K) signalling pathway, which leads to overgrowth of various body parts. These syndromes are typically diagnosed at birth or in early childhood.[8,9] PIK3CA gene is involved in making a protein that helps regulate cell growth, division, and survival. A broad array of disorders falls within this spectrum, with some overlap of symptoms between the different disorders. Syndromes within the spectrum may also overlap genetically, meaning they may share specific PIK3CA gene mutations in cells in the areas of the body that are affected.[9] The predominant areas of overgrowth include the brain, limbs (including fingers and toes), trunk (including abdomen and chest), and face, all usually in an asymmetric distribution. Generalised brain overgrowth may be accompanied by secondary overgrowth of specific brain structures. The degree of intellectual disability appears to be mostly related to the presence and severity of seizures, cortical dysplasia, and hydrocephalus which can result from brain overgrowth.[10] Mutations in certain 'hot spots' on the PIK3CA gene (p.E542, p.E545, and p.H1047) have been associated with foetal mortality when present more diffusely in the brain and other somatic tissues as they activate PI3K kinase activity the most.[10]

PROS includes several different syndromes making the incidence and prevalence rates difficult to estimate.[10] Mortality and survival rates are dependent on levels of gene activation and site of mutation so cannot be fully categorised.[11]

Recommended Treatment Options

There are currently no NICE recommended treatments for PROS.[12] Management of symptoms can include treatments such as surgical interventions, orthopaedic care, or pain management.[10]

Clinical Trial Information

Trial	**EPIK-P2; NCT04589650, 2020-000561-16;** A Phase II Double-blind Study With an Upfront, 16-week Randomized, Placebo-controlled Period, to Assess the Efficacy, Safety and Pharmacokinetics of Alpelisib (BYL719) in Paediatric and Adult Patients With PIK3CA-related Overgrowth Spectrum (PROS) **Phase II –** Recruiting **Primary completion date:** June 2023 **Location(s):** 8 EU countries, UK, USA, and other countries
Trial Design	Randomised, parallel assignment, quadruple-masked, placebo-controlled
Population	N=189 (estimated) patients with PIK3CA-related PROS who have symptomatic and/or progressive overgrowth; aged 2 years and older
Intervention(s)	Alpelisib, oral once daily (50mg/day for ages 2-17 years, 125mg/day for ages 18 years and older)
Comparator(s)	Matched placebo for 16 weeks then switched to active treatment with alpelisib
Outcome(s)	Primary outcome measure: - Proportion of participants randomised to alpelisib with a response at week 24 in group 1 (ages 18 years and above), and group 2 (ages 6-17 years)

	See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**EPIK-P3; NCT04980833; 2020-005896-12;** A Phase II Study to Evaluate the Long-term Safety and Efficacy of Alpelisib in Patients With PIK3CA-Related Overgrowth Spectrum (PROS) Who Previously Participated in Study CBYL719F12002 (EPIK-P1) **Phase II –** Active, not recruiting **Primary completion date:** August 2027 **Location(s):** 3 EU countries and USA
Trial Design	Single group assignment, open label
Population	N= 39 patients with PIK3CA-related PROS who previously participated in study NCT04285723; aged 2 years and older
Intervention(s)	Alpelisib, oral once daily (50-250mg, dose determined by physician)
Comparator(s)	No comparator used
Outcome(s)	Primary outcome measure: • Prospective period only: proportion of participants with new or worsening grade ≥3 treatment emergent adverse events (AEs) [Time frame: from date of first interventional dose administration in the prospective period (day 1) to 30 days after last dose of study drug, assessed up to 5 years See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT04285723; Retrospective Chart Review Study of Patients With PIK3CA-Related Overgrowth Spectrum (PROS) Who Have Received Alpelisib as Part of a Compassionate Use Program (EPIK-P1) **Observational study** **Study completion date:** April 2021 **Location(s):** 3 EU countries, USA, and Australia
Trial Design	Case-only, retrospective
Population	N= 59; patients with PIK3CA-related PROS who have received alpelisib as part of a compassionate use program (EPIK-P1); aged 2 years and older
Intervention(s)	-
Comparator(s)	-

Outcome(s)	Primary outcome measure: - Proportion of patients with response (yes/no) at week 24 (+/- 4 weeks) [Time frame: 24 weeks (+/- 4 weeks)] See trial record for full list of other outcomes
Results (efficacy)	In the primary endpoint analysis at week 24, 37.5% (95% CI, 21.1-56.3%) of patients (12/32 of the complete cases) responded; sensitivity analysis showed similar results. Of the 12 responders, 0 experienced disease progression or death by data cut-off. 23 out of 31 patients (74.2%) reported reduction in sum of target lesion volume with mean reduction of 13.7%. At week 24, proportion of patients with improvement in the most frequent (in the full-study population) PROS-related symptoms/signs was pain 90.9% (20/22), fatigue 76.2% (32/42), vascular malformation 78.9% (30/38), limb asymmetry 69.0% (20/29), and disseminated intravascular coagulation 55.2% (16/29). In the first 24 weeks, there were no surgeries due to disease progression.[13]
Results (safety)	AEs and therapeutic-related AEs were experienced by 82.5% (n=47) and 38.6% (n=22) of patients, respectively; no deaths were reported. The most common therapeutic-related AEs were hyperglycaemia (n=7, 12.3%), aphthous ulcer (n=6, 10.5%), and stomatitis (n=3, 5.3%).[13]

Estimated Cost

The NHS hospital indicative price of alpelisib (28 x 200mg tablets) is £4,082.14.[14]

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Oxford academic. PIK3CA-related overgrowth spectrum. 2019.[15]
- American Journal of Medical Genetics. PIK3CA-related overgrowth spectrum (PROS): Diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. 2015.[16]

Additional Information

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