Health Technology Briefing
September 2023

Selumetinib for treating symptomatic, inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in adults

Company/Developer	Alexion Pharmaceuticals

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33516	NICE TSID: N/A	UKPS ID: 671617

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Selumetinib is currently in clinical development for the treatment of symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in adults. Neurofibromatosis type 1 (NF1), caused by changes in NF1 gene, is a type of genetic disorders that primarily affects the cell growth of neural substance. Due to these changes, the gene is unable to carry out its regulatory function, thereby leading to rapid cell multiplication and development of tumours. Plexiform neurofibromas (PNs) develop along the nerve fibres and can infiltrate into surrounding tissues, casing both neurological and space-occupying symptoms. 30-50% of patients with NF1 will develop PN. Inoperable PNs are those that cannot be completely removed surgically, without affecting adjacent critical structures, such as surrounding nerves and vascular architecture, which can lead to further damage. PNs are typically located in challenging areas such as the head, neck, chest and spine) and can affect large and irregularly shaped. Most PN associated with NF1 are symptomatic and can cause pain, disfigurement, and difficulties with physical functioning.

Selumetinib is administered orally and blocks the action of a protein called the mitogen-activated kinase (MEK), an enzyme vital for cell growth. Selumetinib's inhibition of the MEK enzyme potentially inhibits tumour growth. If licenced, selumetinib may provide a new treatment option for adult patients with symptomatic and inoperable PN associated with NF1.

Proposed Indication

Treatment of adults with symptomatic, inoperable plexiform neurofibromas (PN) associated with neurofibromatosis type 1 (NF1).[1]

Technology

Description

Selumetinib (AZD6244) is an orally active selective inhibitor of mitogen-activated protein kinase, kinases 1 and (MEK 1/2). The NF1 gene provides instructions for making a protein called neurofibromin, which negatively regulates the RAS/MAPK pathway, helping to control cell growth, differentiation, and survival. Mutations in the NF1 gene may result in dysregulations in RAS/RAF/MEK/ERK signalling, which can cause cells to grow, divide and copy themselves in an uncontrolled manner and may result in tumour growth. Selumetinib inhibits the MEK enzyme in this pathway, potentially leading to inhibition of tumour growth.[2,3]

Selumetinib is currently in clinical development for the treatment of symptomatic and inoperable PN associated with NF1 in adults. In a phase III clinical trial (NCT04924608), participants received 10mg and 25 mg oral capsules of selumetinib for three years.[1]

Key Innovation

There is no cure for NF1, and the treatment options are limited.[2] In patients with the disorder, dysfunction of the guanosine triphosphatase–activating protein neurofibromin leads to overactivation of the RAS pathway. Therefore, targeted inhibition of the RAS pathway with mitogen-activated protein kinase (MAPK) kinase (MEK) inhibition is a logical treatment approach that has been successful in a preclinical model of NF1. Preliminary results from the phase II clinical trial confirmed earlier phase I development that demonstrated the novel ability of selumetinib to shrink large tumours. Selumetinib may also help to improve health problems associated with tumours. After a year of treatment, most patients in the phase II trial reported improved pain scores, strength, and range of motion.[4,5]

If licenced, selumetinib may provide a new treatment option for adult patients with symptomatic and inoperable PN associated with NF1.

Regulatory & Development Status

Selumetinib currently has conditional Marketing Authorisation in the UK for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.[6]

Selumetinib was granted an orphan drug designation in the EU in 2018 for NF1.[7]

Selumetinib is also in phase II/III clinical development for the following indications:[8]

- Malignant peripheral nerve sheath tumour (MPNST)
- Sarcoma
- Non-small cell lung cancer (NSCLC)
- Optic nerve glioma
- Meningioma
- Non-hodgkin lymphoma
- Thyroid gland carcinoma

Patient Group

Disease Area and Clinical Need

The term neurofibromatosis (NF) refers to a group of genetic disorders that primarily affect the cell growth of neural tissues. There are two forms of NF: type 1 (NF1) and type 2 (NF2). NF1 is an autosomal dominant disease caused by a spectrum of mutations that affect the NF1 gene.[9,10] This gene is a tumour suppressor located on the long arm of chromosome 17 (17q11.2). Loss of this gene's function due to a mutation leads to an increase in cell proliferation and development of tumours.[10] NF1 is an incurable condition with highly variable symptoms, including cutaneous (skin), neurological (nervous system) and orthopaedic (skeletal) manifestations. NF1 can cause secondary complications including learning difficulties, visual impairment, pain, disfigurement, twisting and curvature of the spine, high blood pressure and epilepsy. PN are a neurological manifestation of NF1 and arise from nerve fascicles that tend to grow along the length of the nerve.[11,12] Inoperable PN means that surgical intervention would not completely remove the tumour without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN.[6] Most PN associated with NF1 are symptomatic, and can cause pain, disfigurement and difficulties with physical functioning.[13] NF1 has a major adverse effect on patients' lives through severe complications, adverse effects on cosmetic features, and the uncertainty of the effects of the disorder. Although the morbidity and the mortality caused by NF1 are dictated by the occurrence of these complications, which may involve any of the body systems, patients were found to perceive cosmetic disfigurement as the major clinical problem.[14]

As of 2013, NF1 has a birth incidence of 1 in 3,000 and a prevalence of approximately 1 in 4,500. Based on a population of 50.7 million then, there were 11,267 individuals with NF1 in England.[15] Recently, about 25,000 people have been estimated to live with neurofibromatosis in the UK.[16] In England (2021-22) there were 1,110 finished consultant episodes (FCEs) and 1,089 admissions for neurofibromatosis (ICD10 code Q85.0), which resulted in 946 day cases and 940 FCE bed days.[17]

Recommended Treatment Options

There is currently no recommended treatment by National Institute for Health and Care Excellence (NICE) for this patient group.

Clinical Trial Information

Trial	**KOMET,** NCT04924608, 2020-005607-39; A phase III, multicentre, international study with a parallel, randomised, double-blind, placebo-controlled, 2 arm design to assess the efficacy and safety of selumetinib in adult participants with NF1 who have symptomatic, inoperable plexiform neurofibromas. **Phase III** - Active, not recruiting. **Location(s):** Five EU countries, UK, US, Canada, Australia, and other countries **Primary completion date:** October 2024
Trial Design	Randomised, parallel assignment, quadruple-masked
Population	N=146 (actual), adults with diagnosis of NF1 with symptomatic, inoperable PN
Intervention(s)	Selumetinib oral capsules 10mg and 25mg
Comparator(s)	Oral placebo capsules 10mg and 25mg

Outcome(s)	**Primary outcome measure:** Confirmed Objective Response Rate (ORR) for Arm A versus Arm B [Time frame: Approximately 3 years]. ORR will be defined as the proportion of patients who have a confirmed complete response or confirmed partial response as determined by ICR per REiNS criteria. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The price for selumetinib is £4,223.59 for a 10-mg 60-capsule pack and £10,560.00 for a 25-mg 60-capsule pack (excluding VAT). The company has a commercial arrangement that makes selumetinib available to the NHS with a discount. This discounted price is unknown.[13]

Relevant Guidance

NICE Guidance

- No relevant NICE guidance for this patient group.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (All Ages). E01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Complex Neurofibromatosis Type 1 Service (All Ages). B13/S(HSS)/a.

Other Guidance

No other guidance found from available published sources.

Additional Information

References

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