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Health Technology Briefing
July 2024

Selumetinib (granule formulation) for treating neurofibromas type 1-related symptomatic, inoperable plexiform in children

Company/Developer	Alexion Pharmaceuticals Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35024	NICE ID: Not available	UKPS ID: 671618

Licensing and Market Availability Plans

Currently in phase I/II clinical trials

Summary

Selumetinib granule formulation is currently in clinical development for the treatment of symptomatic and inoperable plexiform neurofibromas (PN) associated with type 1 neurofibromatosis (NF1) in children. NF1 is a genetic condition that causes tumours to grow along the nerves. The tumours are usually non-cancerous but may cause a range of symptoms. Some children have a special kind of neurofibroma called PN. These often develop early in childhood involve swelling to the whole section of a nerve and its branches. There is currently no cure for NF1. Surgery carries several risks and a proportion of PN are considered inoperable. Children with NF1-associated PNs experience substantial disease burden with significant unmet needs and increased risk of developing other tumours. These tumours are typically located in challenging areas such as the head, neck, chest, and spine. In most cases, the skin is affected, causing symptoms such as birthmarks but the most severe symptoms include pain, disfigurement, and difficulties with movement.

Selumetinib, blocks enzymes called MEK1 and MEK 2 which are involved in stimulating cells to grow. MEK1/2 are overactive in NF1, making tumour cells grow uncontrollably. By blocking these enzymes, selumetinib helps slow down growth of the tumour cells. Selumetinib is currently available as a capsule taken twice daily for those aged 3 years and older but presents a potential choking hazard or difficulty in administering as directed due to patient age. If licensed selumetinib granule formulation will provide a new treatment option for children aged 1-2 and a new administration option for children aged 3-7 years with NF1 related symptomatic inoperable PN.

Proposed Indication

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

Technology

Description

Selumetinib (AZD6244) is a selective inhibitor of mitogen activated protein kinase kinases 1 and 2 (MEK-1/2). Selumetinib blocks MEK activity and the rapidly accelerated fibrosarcoma kinase (RAF)-MEK-extracellular signal-related kinase (ERK) pathway. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.[2] The NF1 gene, a tumour suppressor gene, translates neurofibromin, a negative regulator of the RAS/MAPK pathway controlling cell growth, differentiation, and survival. Mutations in the NF1 gene result in dysregulations in RAS/RAF/MEK/ERK signalling, which can lead to uncontrolled cell division and may result in tumour growth.[3,4]

In a phase I/II clinical trial SPRINKLE (NCT05309668), participants will receive selumetinib for 25 cycles (or until they meet discontinuation criteria). Selumetinib granule formulation will be administered using body surface area (BSA)-based dosing. At enrolment participants must have a BSA within the range 0.40 to 1.09 m^2; once participants attain a BSA between 1.10 and 1.29 m^2 they will be encouraged to transition to the capsule formulation.[1]

Key Innovation

NF-1 is a rare disease with increased morbidity and mortality in children with associated PNs. Surgical outcomes for PNs are often poor.[5] Oral administration of selumetinib inhibited ERK phosphorylation, and reduced the number, volume, and proliferation of neurofibromas. Results from a phase II clinical study (NCT01362803) showed that treatment with selumetinib was associated with durable tumour shrinkage and clinical benefit in paediatric patients (2-18 years of age) with NF1 and inoperable PNs.[3] Selumetinib is currently available as a capsule which must be swallowed whole. Some patients, in particular children < 6 years of age, may be at risk of choking on a capsule formulation due to developmental, anatomical, or psychological reasons.[2] An alternative age-appropriate granule formulation (selumetinib granules) is now being developed to provide dose flexibility and easier swallowing for patients ≥1 years and <7 years of age. The bioavailability of the granule formulation has been shown to be the same as the capsules version in NCT03649165.[6]

If licenced, selumetinib granules formulation will provide a novel treatment option for paediatric patients aged 1-2 with NF1-related symptomatic, inoperable PN, and a novel method of administration for children aged 3-7.

Regulatory & Development Status

Selumetinib capsule 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.[2]

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

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

- NF1 adults who have symptomatic, inoperable plexiform neurofibromas.

- Gliomas
- NF2 related tumours

Patient Group

Disease Area and Clinical Need

NF1 is a genetic condition that affects the skin, the skeleton and the part of the nervous system outside the brain and spinal cord (peripheral nervous system).[9] NF1 is caused by a faulty gene, which leads to the production of a non-functional version of neurofibromin that cannot regulate cell growth and division. As a result, tumours such as neurofibromas can form along nerves throughout the body.[10] Inoperable tumours are PNs that cannot be completely surgically removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN.[11] The main signs and symptoms of NF1 include dark-coloured spots on the skin (café-au-lait spots), benign growths along the nerves (neurofibromas), and freckles in the underarm and groin. Other symptoms may include coloured spots in the eye (Lisch nodules), curvature of the spine, learning disabilities, and an increased risk for cancer.[9] Most PN associated with NF1 are symptomatic, and can cause pain, disfigurement and difficulties with physical functioning.[12] A study indicated that paediatric patients with NF1-PN experience diminished overall health-related quality of life (HRQoL) and functional impairment across four domains (educational, emotional, social, and physical).[13]

While NF-1 is a rare disease, up to around one-third of patients have PNs, and these tumours can cause high morbidity.[5] This is because, large PNFs can compress vital organs and can result in severe morbidity and even death.[14] NF1 is associated with substantial morbidity and mortality and in a recent study it was shown that patients with NF1 seem to have a decrease in life expectancy of about 15 years compared with the general population.[15,16] 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 there are approximately 11,267 individuals with NF1 in England (2013/14).[17] In England (2022-23) there were 1,245 finished consultant episodes (FCEs) and 1,191 admissions for neurofibromatosis (ICD10 code Q85.0), which resulted in 1,007-day cases and 1,430 FCE bed days.[18]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends selumetinib for treating symptomatic and inoperable PN associated with NF1 in children aged 3 years and above.[12] There are no NICE recommended treatment for children under 3 years.

Clinical Trial Information

Trial	**SPRINKLE; NCT05309668; 2020-005608-20.** A Phase I/II, Single-Arm, Open Label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥1 to <7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN) (SPRINKLE) **Phase I/II** – Active, not recruiting. **Location(s):** 4 EU countries, USA, Russia, and Japan **Primary completion date:** May 2024

Trial Design	Open label, single group assignment
Population	**N**=36 (actual); children aged ≥ 1 to < 7 years with NF1 related symptomatic, inoperable PN.
Intervention(s)	Selumetinib granule formulation
Comparator(s)	No comparator
Outcome(s)	Primary outcome: - Selumetinib AUC0-12 derived after single dose administration [Time frame: Pre-dose and 1, 2, 3, 4, 6, 8 and 10-12 hours after selumetinib single dose on the first day of study treatment (cycle 1 day 1) (each cycle is 28 days)] - Adverse Events graded by CTCAE Ver 5.0 [Time Frame: from screening until 30 days after last dose] 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.[12,19] The cost of selumetinib granule is unknown.

Relevant Guidance

NICE Guidance

No relevant NICE guidance identified.

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

- Bruce et al. Neurofibromatosis type 1 (NF1): Management and prognosis. September 2023

Additional Information

References

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.