

**EVIDENCE BRIEFING  
JANUARY 2019**

**Selumetinib for neurofibromatosis type 1**

<b>NIHRIO ID</b>	11060	<b>NICE ID</b>	10087
<b>Developer/Company</b>	AstraZeneca UK Ltd	<b>UKPS ID</b>	650145

<b>Licensing and market availability plans</b>	In phase II clinical trials.
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**SUMMARY**

Selumetinib is in clinical development for children with neurofibromatosis type 1 (NF1), also called von Recklinghausen's disease. NF1 is a rare genetic disorder characterized by the development of multiple benign tumours of nerves and skin and areas of abnormal skin colour. NF1 is caused by mutation in a gene that regulates the production of a protein known as neurofibromin which is thought to function as a tumour suppressor. At birth or early childhood, affected individuals may have relatively large, benign tumours that consist of bundles of nerves and other tissue. These are known as plexiform neurofibromas (PNs). PNs may cause ongoing pain, motor dysfunction and disfigurement. Surgery may be used to remove PNs, but at high patient risk with the possibility of re-growth.

Selumetinib blocks an enzyme that is part of a signalling pathway in cells which can cause cells to grow, divide and copy themselves in an uncontrolled manner and may result in tumour growth. This pathway is improperly activated in patients with NF1, leading to the growth of tumours. Early studies have demonstrated the ability of selumetinib to shrink large tumours through its action on this pathway. Selumetinib may also aid in the improvement of health problems associated with PNs such as pain and motion problems. If licensed, selumetinib taken orally may provide the first pharmacological treatment option for NF1 and inoperable PNs.

## PROPOSED INDICATION

Paediatric patients aged 3 years and above, with symptomatic and/or progressive neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN)<sup>a</sup>

## TECHNOLOGY

### DESCRIPTION

Selumetinib (AZD6244) is an orally active, highly potent adenosine triphosphate (ATP) independent inhibitor of the mitogen-activated kinase (MEK). 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.<sup>1,2</sup>

In the phase II clinical trial (SPRINT; NCT01362803) patients 2-18 years old with NF1, inoperable PN and  $\geq 1$  PN related morbidity received selumetinib at the recommended dose (25 mg/m<sup>2</sup> PO BID) every 12 hours with continuous dosing (1 cycle = 28 days) until unacceptable toxicity, patient withdrawal or pharmacodynamics (PD).<sup>3,4</sup>

### INNOVATION AND/OR ADVANTAGES

There is currently no cure for NF1, and treatment options are limited.

Preliminary results from the phase II clinical trial confirmed earlier phase I development that demonstrated the novel ability of selumetinib to shrink large tumours. Surgery to remove even small tumours is often not feasible, as many tumours are intertwined with healthy nerves and tissue. In addition, tumours that have been partially removed by surgery tend to grow back, notably in young children.

Selumetinib may also help to improve health problems associated with tumours. After a year of treatment, most patients in the phase II trial (or their parents) reported improved pain scores, strength, and range of motion.<sup>1,3,5</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Selumetinib is not currently licensed for any indication in the EU/UK.

Selumetinib was granted an orphan drug designation in the EU in 2018 for NF1.<sup>6</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

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, also known as von Recklinghausen's disease, is the most common type of NF, and accounts for about 90% of all

<sup>a</sup> Information provided by AstraZeneca

cases. NF1 is an autosomal dominant disease caused by a spectrum of mutations that affect the *NF1* gene.<sup>7</sup> 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. NF1 has one of the highest rates of spontaneous mutation among genetic diseases in humans. Only 50% of the NF1 patients have a positive family history of the disease.<sup>7,8</sup>

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. Plexiform neurofibromas (PNs) are a neurological manifestation of NF1 and arise from nerve fascicles that tend to grow along the length of the nerve. PNs occur in approximately 20-50% of NF1 patients causing pain, motor dysfunction and disfigurement.<sup>9</sup>

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.<sup>10</sup>

## CLINICAL NEED AND BURDEN OF DISEASE

As of 2013, NHS England estimated the birth incidence of NF1 as 1 in 3,000 and a prevalence of approximately 1 in 4,500.<sup>11</sup>

At the time of the 2011 Census, approximately 21% of the overall population of England and Wales was aged under 18 years (11.78 million of 56.1 million). If the 2013 prevalence figures are applied to the 2011 Census estimate of 11.78 million, there are approximately 2,600 individuals aged under 18 years with NF1 in England and Wales.<sup>12,13</sup> It is estimated that up to 50% or 1,300 of these individuals exhibit PNs, 72% or 935 of which are symptomatic. It is further projected that approximately 80% or 750 of such symptomatic PNs are inoperable.<sup>b</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

NF1 is diagnosed according to standardized clinical criteria established by the National Institutes of Health. According to these criteria, NF1 can be diagnosed if any two features on this list are present:<sup>14,15,16</sup>

- café-au-lait spots – more than six larger than 5 mm before puberty or 15 mm after puberty
- freckling under the arms, in the groin, or other skin folds
- iris Lisch nodules (tan bumps on the iris of the eye that do not affect vision)
- optic glioma
- two or more neurofibromas or one plexiform neurofibroma
- characteristic bone disorder involving shin bone or eye socket
- presence of NF1 in a parent, child, or sibling (first-degree relative)

Once the diagnosis is considered, referral should be made to any clinician skilled in the diagnosis of NF1, including geneticists, paediatricians, neurologists or dermatologists. The mainstay of

<sup>b</sup> Information provided by AstraZeneca

management is age specific monitoring of disease manifestations and patient education.<sup>16</sup> Treatment for NF1 may include physiotherapy, psychological support and pain management.<sup>17</sup>

Most PNs are diagnosed in early childhood and grow most rapidly during this period. Complete surgical resection of these tumours is often not feasible, and regrowth of the tumour after incomplete surgical resection has been observed.<sup>18</sup>

## CURRENT TREATMENT OPTIONS

Effective medical therapies are lacking for the treatment of NF1 related PNs.<sup>18</sup> As of 2018 there were no treatments authorised in the EU for NF1, exclusive of surgical removal of tumours.<sup>19</sup>

## PLACE OF TECHNOLOGY

If licensed, selumetinib will provide the first pharmacological treatment option for symptomatic and/or progressive NF1 inoperable PNs.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	SPRINT, <a href="#">NCT01362803</a> , 110161, 11-C-0161; children aged 2-18 years; phase II
<b>Sponsor</b>	AstraZeneca UK Ltd
<b>Status</b>	Ongoing
<b>Source of Information</b>	abstract <sup>3</sup> , trial registry <sup>4</sup>
<b>Location</b>	USA
<b>Design</b>	Non-randomised, single group assignment, open label
<b>Participants</b>	n=50; children aged 2-18 years; NF1; inoperable PN and ≥ 1 PN related morbidity
<b>Schedule</b>	Selumetinib (25 mg/m <sup>2</sup> PO BID) every 12 hours with continuous dosing (1 cycle = 28 days) until unacceptable toxicity, patient withdrawal or PD.
<b>Follow-up</b>	Not reported.
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>Determine MTD and extended tolerability [Time Frame: 3 treatment cycles]</li> <li>Evaluate the confirmed partial and complete response rate of selumetinib in children and young adults with NF1 and inoperable PN [Time Frame: prior to cycles 5, 6, 13, 17, 21, 25 and then every 6 cycles]</li> </ul>
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>Determine effect on growth rate of PN [Time Frame: At time of PD]</li> <li>Study PK [Time Frame: First course]</li> <li>Measure adherence of chronic dosing [Time Frame: At each response evaluation]</li> <li>Define toxicities [Time Frame: At each response evaluation]</li> <li>Evaluate confirmed partial and complete response rate, and duration of response [Time Frame: at each response evaluation]</li> <li>Determine long term tolerability and safety [Time Frame: at each response rate]</li> <li>Evaluate effect of selumetinib on bone mineral density, pain, quality of life and physical functioning [Time Frame: before cycles 3, 5, 9, 13, and then every 12 cycles]</li> </ul>

<b>Key Results</b>	50 children (30 male, median age 10.2 years, range 3.5, 17.4) enrolled. Disfigurement (n=44), motor dysfunction (n=33) and pain (n=28) were the most frequent PN-related morbidities. As of November 5, 2017: median cycle number 19.5 (range 0, 29); median change in PN volume -27.7% (range -50.6%, 2.2%). Best response PR (36 patients, 72%), stable disease (12 patients, 24%); 2 (4%) had no re-staging evaluations. Of the 36 PR, 32 were confirmed on $\geq$ two consecutive restaging studies. Pain intensity and interference scores improved significantly ( $p < 0.01$ ) over one year, as did strength (0-5 scale) and range of motion (degrees) ( $p < 0.01$ ).
<b>Adverse effects (AEs)</b>	The most frequent toxicities were nausea/vomiting, diarrhoea, asymptomatic creatine kinase increase, acneiform rash and paronychia. Selumetinib dose was reduced in 12 pts, of which 5 were removed from treatment.
<b>Expected reporting date</b>	Estimated primary completion date Sep 2020.

## ESTIMATED COST

The cost of selumetinib is not yet known.

## ADDITIONAL INFORMATION

AstraZeneca UK Ltd

## RELEVANT GUIDANCE

### NICE GUIDANCE

- No relevant 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

- Ferner RE et al (United Kingdom Neurofibromatosis Association Clinical Advisory Board). Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. 2007<sup>16</sup>

## REFERENCES

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<sup>2</sup> National Cancer Institute: Drug Dictionary. *Selumetinib*. Available from: <https://www.cancer.gov/publications/dictionaries/cancer-drug/def/selumetinib> [Accessed 18 December 2018]

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<sup>8</sup> Cunha KS, Barboza EP et al. Neurofibromatosis type I with periodontal manifestation. A case report and literature review. *British Dental Journal*. 2004 April 24; 196(6): 457-60. Available from: <https://doi.org/10.1038/sj.bdj.4811175>

<sup>9</sup> AstraZeneca. *Selumetinib granted Orphan Drug Designation by the US FDA for neurofibromatosis type 1*. Available from: <https://www.astrazeneca.com/media-centre/press-releases/2018/selumetinib-granted-orphan-drug-designation-by-the-us-fda-for-neurofibromatosis-type-1-15022018.html> [Accessed 7 January 2019]

<sup>10</sup> Wolkenstein P, Zeller J, Revuz J et al. Quality-of-Life Impairment in Neurofibromatosis Type 1A Cross-sectional Study of 128 Cases. *Archives of Dermatology*. 2001; 137(11): 1421-1425. Available from: <http://dx.doi.org/10.1001/archderm.137.11.1421>

<sup>11</sup> NHS England. *2013/14 NHS Standard Contract For Complex Neurofibromatosis Type 1 Service (All Ages – B13/S(HSS)/a)*. Available from: <https://www.england.nhs.uk/wp-content/uploads/2013/06/b13-comp-neurofib-1.pdf> [Accessed 18 December 2018]

<sup>12</sup> Office for National Statistics. *Census 2011 – Age Groups*. Available from: <https://www.ethnicity-facts-figures.service.gov.uk/british-population/demographics/age-groups/latest> [Accessed 19 January 2019]

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